Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Divence Tri Lyophilisate and Solvent for Emulsion for Injection

Date Created: February 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Divence Tri Lyophilisate and Solvent for Emulsion for Injection
Applicant	Laboratorios Hipra SA, Avda La Selva 135, 17170 Amer (Girona), Spain
Active substance(s)	Live attenuated bovine respiratory syncytial virus (BRSV), strain Lym-56 $10^{5.2}$ - $10^{6.5}$ $CCID_{50}$* Live gE- tk- double-gene deleted bovine herpesvirus type 1 (BoHV-1), strain CEDDEL $10^{6.3}$ - $10^{7.6}$ $CCID_{50}$* Inactivated bovine parainfluenza 3 virus (PI-3), s SF4 ≥ 206.2 EU** gE- : deleted glycoprotein E; tk- : deleted thymidine kinase * Cell Culture Infectious Dose 50 % ** ELISA Units
ATC Vetcode	QI02AH
Target species	Cattle
Indication for use	Active immunisation of cattle from 10 weeks of age: BRSV and PI-3: to reduce virus shedding, hyperthermia, clinical signs and lung lesions. BoHV-1: to reduce virus shedding, hyperthermia and clinical signs of IBR (infectious bovine rhinotracheitis).

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	Full application in accordance with Article 8 of VMRs 2013 (Schedule 1, Part 1) as amended.
Date of conclusion of the procedure	05/12/24

I. SCIENTIFIC OVERVIEW

This is a full application for Divence Tri Lyophilisate and Solvent for Emulsion for Injection.

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 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 live attenuated bovine respiratory syncytial virus (BRSV), strain Lym-56; live gE- tk- double-gene deleted bovine herpesvirus type 1 (BoHV-1), strain CEDDEL; inactivated bovine parainfluenza 3 virus (PI-3), strain SF4, the adjuvant Montanide IMS and the excipients, dipotassium phosphate, gelatin, glycine, potassium dihydrogen phosphate, sorbitol, sucrose, disodium phosphate dodecahydrate, potassium chloride, potassium dihydrogen phosphate, sodium chloride and water for injections.

The container/closure system consists of Type 1 glass vials and PET containers with bromobutyl stoppers. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvant and vaccine strain are justified.

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

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

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.

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

II.C. Control of Starting Materials

The active substances are live attenuated bovine respiratory syncytial virus (BRSV), strain Lym-56; live gE- tk- double-gene deleted bovine herpesvirus type 1 (BoHV-1), strain CEDDEL; inactivated bovine parainfluenza 3 virus (PI-3), strain SF4, an established active substance described in the European Pharmacopoeia. 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 Ph. Eur.

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

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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

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

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

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable regulatory 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 regulatory 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

Shelf life of the veterinary medicinal product as packaged for sale: 30 months.
Shelf life of the solvent as packaged for sale: 3 years.
Shelf life after reconstitution according to directions: 2 hours
Store and transport refrigerated (2 ºC - 8 ºC).
Do not freeze.
Protect from light.

III. SAFETY ASSESSMENT

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. The investigation was performed according to the recommendations of Article 8 of VMRs 2013 as amended and the relevant guidelines.

Effects on reproductive performance were examined, and it was concluded that the vaccine can be used during lactation and pregnancy.

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.

Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strains.

The adjuvant and excipients used are out of scope. 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.

Field studies

Two multi-centre, randomised, double blinded and placebo-controlled clinical trials investigating safety and efficacy were conducted. Calves, heifers and cows were included in these trials. From the results provided in the study, it can be concluded that the vaccine is safe in target species.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. No warnings are therefore required.

IV. CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements. A challenge model study was provided for each strain of the vaccine. The studies proved the vaccine compliant and efficacious for each antigen for each claim relevant to that antigen.

Onset of Immunity

Onset of immunity was established to be 21 days after the conclusion of the basic vaccination scheme as demonstrated by separate challenge studies for each antigen.

Duration of Immunity

Duration of immunity following the basic vaccination scheme was studied in separate challenge studies. The challenge was given at 6 months after the conclusion of the basic vaccination scheme. It was determined that 6 months was the duration of immunity after completion of the basic scheme and 1 year after completion of the re-vaccination scheme for IBR.

Field Trials

Two blinded GCP field trials were performed to assess safety and efficacy of the parent vaccine.

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.

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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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