IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

DIVENCE TRI

PRODUCT SUMMARY

EU Procedure number	IE/V/0562/001/DC
Name, strength and pharmaceutical form	DIVENCE TRI
Active substances(s)	Bovine respiratory syncytial virus, strain LYM-56, Live,Infectious bovine rhinotracheitis virus, strain CEDDEL, gE- tk- double-gene deleted, Live,Bovine parainfluenza virus 3, strain SF-4, Inactivated
Applicant	Laboratorios Hipra S.A. Avda. La Selva 135 17170 - Amer (Girona) Spain
Legal basis of application	Full application - known active substance (Article 8 of Regulation (EU) 2019/6)
Date of completion of procedure	30/10/2024
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). Onset of immunity: 3 weeks after completion of the basic vaccination scheme. Duration of immunity: 6 months after completion of the basic vaccination scheme. 1 year after completion of the re-vaccination scheme.
ATCvet code	QI02AH
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 the relevant articles of Regulation (EU) 2019/6. 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

The quality part of the dossier complies with the Annex to Regulation (EU) 2019/6. General and, where relevant, specific Ph. Eur. monographs have been followed, and the data is adequate in support of a consistent and well controlled manufacturing process.

The composition of the product including the adjuvant is described in sufficient detail. The development of the product has been adequately described and justified. DIVENCE TRI is identical with respect to composition and manufacturing process to the DIVENCE PENTA vaccine, however, does not contain the E2 recombinant proteins from BVDV-1 and BVDV-2. Reasonable justification is given regarding the relevance of the chosen vaccine strains within the EU. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

The manufacturing process consists of seven main steps: manufacturing of the three active substances, the freeze drying excipient, the finished product and the solvent. The manufacturing process has been described in adequate detail with adequate validation data provided to support the hold-times for the antigens.

Starting materials have been listed and shown to comply with Pharmacopoeial or in-house requirements. The extraneous agents and TSE risk assessments provided are considered sufficient. A satisfactory risk assessment has been provided with regard to the potential tumorigenicity of Master Cell Seeds in accordance with Ph. Eur. 5.2.4.

Control tests performed during the manufacturing process have been adequately described and appropriately validated. The validation data were generated for the DIVENCE PENTA dossier, which is considered acceptable considering the manufacturing process and composition is identical with the exception of the presence of the E2 recombinant proteins from BVDV-1 and BVDV-2 in DIVENCE PENTA. The range of control tests is considered to provide adequate control of the consistency of the manufacturing process and critical points. Results of testing of production scale batches of lyophilisate and solvent support the consistency of the manufacturing process.

Finished product control tests have generally been adequately described and appropriately validated. The range of tests is considered to provide adequate control of the quality of the final product with respect to its critical attributes.

Data on stability of the active substances as well as the finished product and solvent have been provided. These data were generated for the DIVENCE PENTA dossier, which is considered acceptable. The results of testing give no indication of a reduction in potency or change in composition of the lyophilisate or the solvent. The data provided are considered adequate to support a shelf life of 21 months for the lyophilisate and 3 years for the solvent.

III. SAFETY ASSESSMENT

A full safety file in accordance with Article 8(1)(b) has been provided. Safety data were provided in accordance with the requirements of Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament. Studies were performed with a larger combination vaccine, Divence Penta, which contains the same three antigenic components as Divence Tri but also contains E2 recombinant proteins of bovine viral diarrhoea virus type 1 (BVDV-1) and bovine viral diarrhoea virus type 2 (BVDV-2). The safety data generated with the larger multi-component vaccine Divence Penta are considered acceptable for the demonstration of safety of Divence Tri, since this represents a worst-case scenario for safety evaluation, in accordance with current guidance. Divence Tri contains 3 antigens; live attenuated bovine respiratory syncytial virus (BRSV), strain Lym-56, live gE- tk- double-gene deleted bovine herpesvirus type 1 (BoHV-1), strain CEDDEL, and inactivated bovine parainfluenza-3 virus (PI-3), strain SF4. The lyophilisate fraction includes all the antigens together with a well-known freeze-drying excipient intended to provide cryoprotection as well as stability to the antigens. The solvent contains phosphate buffered saline (PBS) and the adjuvant Montanide IMS.

The vaccine is intended for the active immunisation of cattle from 10 weeks of age. The recommended vaccination programme includes a basic vaccination scheme, which consists of the administration of two intramuscular injections (2 ml each), the first dose administered to calves from 10 weeks of age, and the second dose three weeks later. Re-vaccination is recommended at an interval not longer than 6 months after completion of the basic vaccination scheme by the administration of a single dose. Afterwards, subsequent re-vaccinations are recommended at an interval not longer than 12 months.

The laboratory and field safety studies were conducted in accordance with GLP and GCP, respectively.

Laboratory Trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in calves of the minimum age was demonstrated in a study investigating the safety of an overdose. The investigation was performed according to the recommendations of Regulation (EU) 2019/6 and the relevant guidelines. In this study, a vaccine batch representative of maximum potency for the antigens included in the vaccine (study performed using Divence Penta) was administered to seronegative calves. The calves received a 10-fold overdose followed by three single maximum doses at appropriate intervals. 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.
Overall, the vaccine was shown to be well tolerated in the target species. The adverse events were considered acceptable for this type of vaccine and were limited to rectal temperature increases and local reactions at the site of administration. The local and systemic reactions observed are described in the SPC and package leaflet.

The examination of effects on reproductive performance was investigated in pregnant cows in accordance with guidelines. The safety of basic vaccination in pregnant cows, seronegative or with low levels of antibodies at time of vaccination, followed by one booster vaccination 6 months later was investigated. The data supported the safety of vaccination during pregnancy when used in accordance with recommendations. Another study was performed in accordance with Ph. Eur. 0696 "Infectious bovine rhinotracheitis vaccine (live)", which supported the safe use of the vaccine during pregnancy. It was concluded that vaccination with Divence Penta, and therefore the smaller fall-out vaccine, Divence Tri, does not have negative effects on reproductive performance. Safety during lactation was not investigated in pre-clinical studies, however data from the use of Divence Penta under field conditions supported the safety of use in lactating cows. The SPC states that Divence Tri can be used during pregnancy and lactation.

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.

Special requirements for live vaccines are applicable for each of the live strains included in the vaccine; BRSV and BoHV-1. Spread of the live vaccine strains was investigated in two separate studies. The results support absence of spreading of the BRSV and BoHV-1 vaccine strains.
Considering the dissemination of the vaccine strains in the target animals, with respect to the BRSV component of the vaccine, a study performed for the single BRSV Lym56 vaccine was presented. The results supported that the vaccine virus does not disseminate beyond the upper airways. For BoHV-1, the study provided supports the conclusion that the BoHV-1 vaccine virus does not disseminate to any significant degree.
Reversion to virulence was investigated in accordance with the Ph. Eur. requirements. On the basis of the data presented, it is concluded that there is no evidence of reversion to virulence of the BRSV or BoHV-1 vaccine strains included in Divence Tri.
No specific studies have been conducted to determine the intrinsic biological properties of the vaccine strains, this is considered acceptable based on the data provided.
Regarding the genomic reassortment or recombination/redistribution of the strains with other strains of BRSV virus or BoHV-1 virus, no specific trials have been performed. The chances of recombination occurring are considered very small. Any potential recombination is not expected to increase the virulence to more than the virulence of circulating wild-type strains.
The excipients, including adjuvants, of Divence Tri 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 are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product. Based on this information, no withdrawal period is proposed, and considered acceptable.

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

Field Studies

The safety of vaccination was evaluated under field conditions in two field trials conducted in two EU Member States; the first clinical study was performed in calves of the youngest age recommended for vaccination, the second clinical study was performed in female cattle, including pregnant cows and heifers. The vaccine was administered according to the recommended schedule. In addition, in the second clinical study the safety of the administration of the first re-vaccination and subsequent re-vaccination was investigated. All animals were observed for adverse reactions during each study and reproductive parameters and milk production were evaluated in the second study. It is accepted that the safety of use under field conditions has been adequately supported; local reactions and rectal temperature increases were comparable to those reported in the pre-clinical studies, apart from in the first trial in calves in which two anaphylactic-type reactions were reported. An appropriate warning is included in the SPC. In the second field study, there was no adverse effect on reproductive performance or milk yield after vaccination.

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. The assessment concluded that Divence Tri is expected to pose a negligible risk to the environment when used as recommended. 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

IV.B Clinical Studies

Divence Tri is intended for the active immunisation of cattle from 10 weeks of age to reduce virus shedding, hyperthermia, clinical signs and lung lesions due to BRSV and PI-3, and to reduce virus shedding, hyperthermia and clinical signs of IBR (infectious bovine rhinotracheitis) caused by BoHV-1. As stated in Part 3, the recommended vaccination programme includes a basic vaccination scheme, which consists of the administration of two intramuscular injections (2 ml each), the first dose administered to calves from 10 weeks of age, and the second dose three weeks later. The onset of immunity is 3 weeks after completion of the basic vaccination scheme and the duration of immunity is 6 months after completion of the basic vaccination scheme. Re-vaccination with a single dose is recommended at an interval not longer than 6 months after completion of the basic vaccination scheme, thereafter subsequent re-vaccination is recommended at an interval not longer than 12 months later. The duration of immunity is 1 year after completion of the re-vaccination scheme.

Laboratory Trials

The efficacy of the product has been demonstrated in pre-clinical studies in target animals of the minimum age recommended for vaccination, in accordance with the relevant requirements, including the specific European Pharmacopoeia (Ph. Eur.) monographs for Bovine Respiratory Syncytial virus vaccine (live) (Ph. Eur. 1177), Infectious Bovine Rhinotracheitis vaccine (live) (Ph. Eur. 0696) and whilst a specific Ph. Eur. Monograph is not available for inactivated PI-3 vaccines, the requirements for Bovine Parainfluenza virus vaccine (live) (Ph. Eur. 1176) were taken into account.

Studies were conducted using the larger combination vaccine, Divence Penta. An additional study was provided to support comparability of immune response to vaccination in animals to the antigenic agents included in Divence Tri compared to that in animals vaccinated with Divence Penta. Therefore, the approach to extrapolate the efficacy data obtained following vaccination with the larger combination vaccine to support the efficacy of Divence Tri is acceptable, in accordance with current guidelines.

The vaccine batches used in the laboratory efficacy studies were at minimum potency for all antigens.

Onset of immunity:

The efficacy in the target species was demonstrated by means of challenge trials. The onset of immunity at 3 weeks post vaccination has been satisfactorily demonstrated in seronegative calves for the claimed protection against BRSV, BoHV-1 and PI-3.

BRSV

A study was performed to assess onset of immunity (OOI) and the effects of maternally derived antibodies (MDA) on the efficacy of vaccination against BRSV challenge. The study was blinded, randomised and placebo controlled and investigated the OOI to BRSV in MDA+ and MDA- calves following vaccination in accordance with recommendations. Different groups of calves were included in the study with MDA representative of levels comparable to what is observed in the field. A control group received PBS. All groups were challenged with virulent BRSV three weeks after completion of the basic vaccination scheme. The results demonstrated that vaccinated calves showed significantly lower virus excretion, clinical signs, hyperthermia and lung lesions than the control group calves. No difference in level of protection was observed between MDA- and MDA+ vaccinated groups. The results support the claimed onset of immunity at 3 weeks.

BoHV-1

A study was performed to investigate the OOI to BoHV-1. The study was blinded, randomised and placebo controlled. One group of calves was vaccinated in accordance with recommendations, another control group of calves received PBS. After challenge at three weeks post-vaccination, a significant reduction of virus shedding was observed in vaccinates compared to controls and the duration of shedding was significantly shorter in vaccinates. Clinical signs and increases in rectal temperature significantly decreased in vaccinates compared to controls. The results support the claimed onset of immunity at 3 weeks.

PI-3

A study was performed to investigate the OOI to PI-3 virus. The study was blinded, randomised and placebo controlled. One group of calves was vaccinated in accordance with recommendations, another control group of calves received PBS. After challenge at three weeks post-vaccination, vaccinates did not shed virus but controls did. Vaccinates had significantly lower average rectal temperatures and overall clinical scores. Lung lesion scores were significantly lower in the vaccinates. The results support the claimed onset of immunity at 3 weeks.

It was concluded that the data support the claims for a reduction of virus shedding, hyperthermia, clinical signs and lung lesions due to BRSV and PI-3, and a reduction of virus shedding, hyperthermia and clinical signs of IBR (infectious bovine rhinotracheitis) caused by BoHV-1.

Duration of immunity
The duration of immunity against BRSV, BoHV-1 and PI-3 was studied in separate challenge studies in calves. Studies were performed in accordance with the specific Ph. Eur. monographs, in each case the studies were valid, and the vaccine was shown to meet the requirements. Protection was shown to last 6 months after the primary vaccination schedule. Re-vaccination at this point with a single booster dose has been demonstrated to provide immunity for one year, as demonstrated in a challenge study for BoHV-1, and as demonstrated by serology (seroneutralising antibodies) for BRSV and PI-3. The data are considered supportive of a DOI of 1 year after re-vaccination.

Maternally derived antibodies (MDA)
The influence of MDA on the onset of protection was appropriately investigated.
The influence of MDA on the onset of protection was studied for BRSV in the OOI study, as summarised above, and no differences in protection level between MDA+ and MDA- calves were observed.
For BoHV-1 a randomised, blinded, controlled study in MDA+ and MDA- calves of the youngest age for vaccination was performed. MDA+ and MDA- calves were vaccinated in accordance with recommendations, the remaining MDA+ control animals were treated with PBS. When MDA levels had dropped to undetectable levels all calves were challenged with virulent BoHV-1 and monitored for 3 weeks. The vaccine met the requirements of the Ph. Eur. 0696 monograph, both for MDA+ and MDA- animals. It was concluded there was no effect of MDA on protection against IBR in calves at the youngest age for vaccination.
For PI-3, a randomised, blinded, controlled study in MDA+ and MDA- calves of the youngest age for vaccination was performed. MDA+ and MDA- calves were vaccinated in accordance with recommendations. The remaining MDA+ control animals were treated with PBS. At three weeks post-vaccination, all calves were challenged with virulent PI-3 and monitored for 2 weeks. The vaccine met the requirements of the Ph. Eur. 1176 monograph (although these strictly do not apply for inactivated vaccines), both for MDA+ and MDA- animals. It was concluded there was no effect of MDA on protection against PI-3 in calves.
No differences in protection level between MDA+ and MDA- calves were observed for BRSV, BoHV-1 or PI-3.

As stated in Part 3, no specific studies have been carried out to investigate the possible interactions of Divence Tri with other veterinary medicinal products. A warning sentence to this extent has been included in the SPC. However, it should be noted that Divence Tri may be used for subsequent re-vaccinations after vaccination with Divence Penta if there is no further need for protection against BVDV. In addition, Divence IBR Marker Live may be used for subsequent re-vaccinations after vaccination with Divence Tri if there is no further need for protection against PI-3 and BRSV.

Field Trials

As discussed in Part 3, two field trials were performed in order to assess the safety and efficacy under field conditions of use, however the field trial performed in heifers and cows was designed to evaluate efficacy parameters linked to the BVDV antigenic components of Divence Penta and therefore is not relevant for Divence Tri. The first study performed in calves showed that vaccination reduced the incidence and severity of respiratory disease during an outbreak of BRSV, occurring in one farm at 23 days after the start of the vaccination program. The number of sporadic episodes of respiratory disease was reduced, as was the overall severity of respiratory disease. The results of the field trial do not provide any additional support for the results of pre-clinical studies with regard to protection against BoHV-1 or PI-3. However, in line with available guidance,

when pre-clinical studies fully support the claims made in the SPC, trials carried out in field conditions are not required. In this case, for each of the active substances included in Divence Tri, efficacy for the claimed indications was adequately demonstrated in pre-clinical 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

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.