Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, applicant / marketing authorisation holder in the Member States

Member State EU / EEA	Applicant / marketing authorisation holder	Name	Strength	Pharmaceutical form	Animal species	Route of administration
Belgium	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use
Bulgaria	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use
Croatia	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use

Member State EU / EEA	Applicant / marketing authorisation holder	Name	Strength	Pharmaceutical form	Animal species	Route of administration
France	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use
Germany	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use
Ireland	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use

Member State EU / EEA	Applicant / marketing authorisation holder	Name	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use
The Netherlands	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use
Poland	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use

Member State EU / EEA	Applicant / marketing authorisation holder	Name	Strength	Pharmaceutical form	Animal species	Route of administration
Portugal	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use
Romania	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use
Slovenia	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use

Member State EU / EEA	Applicant / marketing authorisation holder	Name	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use
United Kingdom	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	CattleMarker IBR Inactivated emulsion for injection for cattle	Each 2 ml dose contains: Inactivated gE Bovine Herpes Virus type 1 (BoHV-1), strain Difivac, to induce a geometric mean seroneutralising titre ≥5.5 $\log_2$	Emulsion for injection	Cattle	Subcutaneous use

Annex II

Scientific conclusions and grounds for the granting of the marketing authorisations

Overall summary of the scientific evaluation of CattleMarker IBR Inactivated (see Annex I)

1. Introduction

CattleMarker IBR Inactivated emulsion for injection for cattle (thereafter called CattleMarker IBR Inactivated) is an inactivated infectious bovine rhinotracheitis (IBR) vaccine which contains glycoprotein E (gE) negative bovine herpes virus 1 (BoHV-1), strain Difivac. The product is indicated for active immunisation of seronegative cattle from 2 weeks of age to reduce the clinical signs (pyrexia and depression) of IBR and the duration of virus shedding caused by BoHV-1 infection. Active immunisation of female cattle from 6 months of age is also indicated:

- to reduce the clinical signs (pyrexia and duration of dyspnoea) of infectious bovine rhinotracheitis (IBR) and virus shedding caused by BoHV-1 infection;
- to reduce the incidence of abortions associated with BoHV-1 infections as demonstrated during the second trimester of gestation following challenge.

Onset and duration of protection for the seronegative cattle form 2 weeks of age is 2 weeks and 6 months respectively after completion of the primary vaccination

Onset of protection for female cattle is 2 weeks or 19 days prior to breeding or insemination and duration is 12 months post primary vaccination.

The marketing authorisation holder (MAH), Zoetis Belgium SA, submitted an application for mutual recognition of the marketing authorisation granted by Belgium in accordance with Article 32 of Directive 2001/82/EC. For the mutual recognition procedure (MRP), Belgium acted as a reference Member State and Bulgaria, Croatia, France, Germany, Ireland, Italy, the Netherlands, Poland, Portugal, Romania, Slovenia, Spain and the United Kingdom were concerned Member States.

During the MRP Germany raised a concern about the immunological safety of CattleMarker IBR Inactivated, as the composition of this product is similar to PregSure BVD, a vaccine which has been shown to induce a long-lasting allogeneic antibody response which has been associated with Bovine Neonatal Pancytopenia (BNP), a neonatal alloimmune disease, in the progeny of vaccinated dams. CattleMarker IBR Inactivated is produced on the same bovine cell line and is adjuvanted with the same highly potent adjuvant, Procision-A, as PregSure BVD.

The potential risk of recurrence of BNP linked to the use of this vaccine in pregnant cows has been addressed by the MAH; however Germany considered that the proposed handling of the risks was inadequate and that a large scale post authorisation study should be initiated by the MAH. These issues remained unresolved and therefore a referral under Article 33(1) of Directive 2001/82/EC to the Coordination group for Mutual recognition and Decentralised procedures (veterinary) (CMD(v)) was started. Since the issues raised by Germany remained unresolved, the Member States concerned failed to reach agreement regarding the marketing authorisation CattleMarker IBR Inactivated and consequently the matter was referred to the CVMP on 29 September 2015 under Article 33(4) of Directive 2001/82/EC.

The CVMP was asked to consider the issues raised by Germany and conclude whether marketing authorisations for CattleMarker IBR Inactivated should be granted.

2. Assessment of the data submitted

According to the definition of BNP, for a calf to be diagnosed with the disease, the following three criteria need to be associated: 1.) The calf should be younger than 1 month old, 2.) the calf should have a blood pancytopenia consecutive to bone marrow aplasia, 3.) other non-immune diseases/conditions with similar clinical signs included in the differential diagnosis (such as BVD, nitrofuran treatment) should be excluded. In the past initially epidemiological information and then rapidly increasing pharmacovigilance data documented an increase of the frequency of this alloimmune reaction between the dam and the foetus and finally a close relationship between the occurrences of BNP and the repeated vaccination of dams with PregSure BVD was established. In 2010, due to these concerns, a procedure under Article 78 of Directive 2001/82/EC was initiated in which the CVMP concluded that although the aetiology of BNP had yet to be determined there was evidence to suggest that PregSure BVD may be associated with BNP and that the benefit-risk balance for the product was unfavourable. With Commission Decisions 5694 of 10/08/2010 and 7077 of 07/10/2010 the marketing authorisations for PregSure BVD were suspended. Later the marketing authorisations for PregSure BVD were withdrawn by the MAH Pfizer (now Zoetis) from all EU and in 2011 even from non-EU countries after reports about BNP cases in PregSure BVD-vaccinated herds in New Zealand became public.

Nonetheless in the assessment in the frame of this procedure under Article 78 of Directive 2001/82/EC the frequency of the BNP caused by PregSure BVD was approximated to be around 0.01% by the CVMP. The epidemiology of the disease is difficult to describe as a number of potential biases may have influenced the results. There have been great variations in pharmacovigilance reporting and it is difficult to conclude whether they are related to genuine variations of frequency of BNP occurrence or because of the differences of the information gathered on the condition.

The potential risk deriving from the intended use of CattleMarker IBR Inactivated to trigger BNP is associated with the composition and manufacture of the vaccine and more specifically with the amount of Antigens Not related to the Active Substance (ANAS) and is also linked to the use of the vaccine in female cattle subject to repeated vaccinations. CattleMarker IBR Inactivated has the same highly potent adjuvant, Procision-A, and is grown on the same bovine-derived kidney cell line (MDBK) as PregSure BVD.

However the manufacturing process of CattleMarker IBR Inactivated leads to an amount of remnant of ANAS (e.g. MDBK cell debris) lower than the one of PregSure BVD. A filtration step using three filtration membranes has been integrated into the production process for clarification of the antigen preparations. Data have been provided to demonstrate the efficiency of the filtration step. These results show that the overall protein content per ml is higher in BVDV-1 antigen batches than in BoHV-1 antigen batches. In a hyperimmunisation study it has been demonstrated that these remaining ANAS from the manufacturing process of CattleMarker IBR Inactivated did not trigger the production of alloantibodies at a level similar to this of animals hyperimmunised with PregSure BVD.

Furthermore, the MAH has made post authorisation commitments to set a maximum level of total proteins for batch release and to perform two additional studies in order to investigate possible interactions of vaccinations with CattleMarker IBR Inactivated in animals previously vaccinated with PregSure BVD or other vaccines. Additionally, a surveillance and monitoring strategy has been proposed, which together with the suggested studies is deemed adequate and proportionate to the identified risk. A large scale post-marketing prospective survey is deemed less effective to identify whether the level of BNP is acceptable when compared with the surveillance and monitoring strategy proposed, because the number of animals to be enrolled in such a study would exceed several thousands of animals (due to the estimated BNP frequency of around 0.01%) and the time span anticipated for BNP cases to occur consecutive to vaccination would not be shorter. The proposed

measures, which will be included in a risk management plan, are considered proportionate and the most efficient way to tackle the BNP risk.

3. Benefit-risk assessment

Benefit assessment

Vaccines are important tools to combat Bovine Herpesvirus Type 1 Infection which is a notifiable disease in several Member States, e.g. Austria, Denmark, Germany. gE deleted IBR vaccines such as CattleMarker IBR Inactivated are “DIVA vaccines”, differentiating infected from vaccinated animals. Several live and inactivated IBR marker vaccines are authorised and successfully used throughout the EU. Due to the efficiency and safety of the gE deleted IBR vaccines currently on the market the eradication of IBR is making good progress and several European countries are on the way towards freedom from BoHV-1.

CattleMarker IBR Inactivated fulfils the criteria for an effective IBR marker vaccine and provides the full therapeutic benefit.

Risk assessment

BNP is a disease which can be fatal in neonatal calves and which has been experimentally reproduced by the intake of colostrum from dams which have alloantibodies. The frequency of this condition had been dramatically exacerbated by PregSure BVD vaccination in the 2000’s leading to the characterisation of a strong association between the occurrence of BNP and the use of Pregsure BVD; however the frequency of BNP disease caused by PregSure BVD vaccination has not been solidly determined, varying from 5% to 0.004% according to the source; the CVMP approximated this frequency to be around 0.01% during the Article 78 procedure. CattleMarker IBR Inactivated contains the same adjuvant Procision-A as PregSure BVD and the virus production also utilises a bovine-derived kidney cell line (MDBK). An association between BNP and alloimune reaction to Antigens Not related to the Active Substance (ANAS) (e.g. bovine kidney cell line derived antigens and all antigenic substances remaining from the manufacturing process) is widely accepted. Data has been provided to demonstrate that CattleMarker IBR Inactivated, unlike PregSure BVD, has a reduced amount of immunologically significant amount of ANAS remaining from its manufacturing process on the bovine derived kidney cell line in the final product. In a hyperimmunisation study, repeated injections of CattleMarker IBR Inactivated did not trigger the production of alloantibodies at a level similar to this of animals hyperimmunised with PregSure BVD. However, a concern remains and the MAH committed to further investigate this result in two additional similar studies. Finally, by comparison with published data on alloantibody response triggered by other marketed vaccines, the BNP risk for CattleMarker IBR Inactivated appears to be significantly lower than this for PregSure BVD.

No other concern was notified by the reference Member State.

Risk management measures

The MAH proposed a post-marketing pharmacovigilance surveillance program utilising its usual pharmacovigilance system for the monitoring of animals vaccinated with CattleMarker IBR Inactivated. The MAH committed to conducting thorough investigations for any unexplained mortality in the offspring of vaccinated animals following documented use of vaccinesThese measures are proportionate to the BNP risk and include all the current knowledge on BNP gathered from the PregSure BVD incident. Considering that the frequency of BNP is anticipated to be much lower than 0.01% (PregSure BVD BNP frequency) these measures, which will be included in a RMP, are considered the most efficient way to tackle this risk.

Evaluation of the overall benefit-risk balance

Overall, the benefit-risk balance for CattleMarker IBR Inactivated emulsion for injection is considered positive, subject to the conduct of additional studies and the implementation of further measures specified in a RMP.

Grounds for the granting of the marketing authorisations

Whereas

- The MAH has provided data demonstrating that the risk that repeated injections with the vaccine CattleMarker IBR Inactivated could induce BNP is significantly lower than this for PregSure BVD;
- A range of quality and risk mitigation and surveillance measures has been proposed by the MAH which will be included in a risk management plan and are deemed adequate and proportionate to the identified risk of development of BNP;

the CVMP has recommended the granting of the marketing authorisation for CattleMarker IBR Inactivated emulsion for injection for cattle subject to conditions affecting the marketing authorisations as set out in Annex IV.

Annex III

Summary of product characteristics, labelling and package leaflet

The valid summary of product characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.

Annex IV

Conditions of the marketing authorisations

The national competent authorities, coordinated by the reference Member State, shall ensure that the following conditions are fulfilled by the marketing authorisation holder:

- The marketing authorisation holder shall conduct a controlled laboratory study to confirm that hyperimmunisation of cattle with CattleMarker IBR Inactivated does not induce a significant alloantibody response to MHC-I and MDBK cells and also to assess if vaccination with other cattle vaccines produced on bovine cell lines and with high amount of ANAS followed by booster with CattleMarker IBR Inactivated leads to a significant increase in alloantibody titres against MHC-I and MDBK cells. As lack of alloantibody response would be anticipated leading to negative results they should be compared with the available data on Pregsure BVD and with an appropriate internal positive control. To address the concerns on alloantibody response the marketing authorisation holder should ensure that the results of the study can be reliably interpreted. Prior to placing CattleMarker IBR Inactivated on the EU market the results should be submitted to the national competent authorities to be assessed by the authorities to their satisfaction.
- The marketing authorisation holder shall conduct a study to assess the potential booster of CattleMarker IBR Inactivated on any MHC-I or opsonizing alloantibody responses in cattle previously vaccinated using PregSure BVD. Prior to placing CattleMarker IBR Inactivated on the EU market the results should be submitted to the national competent authorities to be assessed by the authorities to their satisfaction.
- The marketing authorisation holder shall include a new specification in the finished product of a maximum total protein content. To set this specification the marketing authorisation holder shall:
  - Clinically validate the upper limit for total protein content. The limit should be equal to or below the quantity of total protein of the CattleMarker IBR vaccine used in hyperimmunisation study 9134R-08-11-457.
  - Show that there is no impact of the scaling-up (considering a worst-case scenario, i.e. the maximum commercial batch) on the efficiency of consistently decreasing the total protein content.
  - The marketing authorisation holder should consider the development a method for assaying the protein content in the finished product.
- The marketing authorisation holder shall implement a single risk management plan addressing the following risk mitigation and surveillance measures:
  - Prior to launch of the vaccine on the market and annually thereafter, provide specific training to the bovine sales and technical teams on the CattleMarker IBR Inactivated product safety profile, BNP and pharmacovigilance obligations.
  - Send out a letter to all customers receiving the CattleMarker IBR Inactivated for the first time with additional information to raise awareness for possible BNP cases.
  - In addition to the usual pharmacovigilance system for the monitoring of animals vaccinated with CattleMarker IBR Inactivated, to conduct thorough investigations for any unexplained mortality in the offspring of vaccinated animals following documented use of CattleMarker IBR Inactivated. Any confirmed BNP calves will also be assessed for MHC-I alloantibodies.

This thorough investigations includes:

1. Exclusion of infectious, toxic or any other cause in live animals, to be further detailed in the risk management plan.

2. If dead, bone marrow histopathology shows trilineage hypoplasia.

3. If alive, profound thrombocytopenia (with or without neutropenia, lymphopenia and non-regenerative anaemia).

- PSURs shall be provided every 6 months for the first 5 years of commercialisation.
- Provide a contingency plan in the unlikely circumstance that BNP reports occur that involve CattleMarker IBR Inactivated vaccinated dams.
- Utilise the existing GMP product/batch recall procedures. Should proposals for alternative immunisation schemes, indications, or contraindications be necessary, these regulatory measures should also be handled consistently with the normal operating practices for adverse event reports and variations associated with veterinary medicinal products.
- Utilise the existing colostrum practices in case of BNP cases and develop further mitigation measure for colostrum.

Updates to the risk management plan should be proposed as required as soon as any issues arise, otherwise the risk management plan should be reviewed on a yearly basis at least, in conjunction with the PSUR submission.

The abovementioned study results should be provided to the relevant national competent authorities for assessment prior to placing CattleMarker IBR Inactivated on the EU market and within 24 months of the Commission Decision. The risk management plan should be submitted to the national competent authorities within 6 months of the Commission Decision and maintained until such time as the concerned national competent authorities consider that the risk profile of the product has been sufficiently characterised and all appropriate risk mitigation and surveillance measures have been implemented.