Divergent position on a CVMP opinion on an Article 33(4) referral of Directive 2001/82/EC for

CattleMarker IBR Inactivated suspension for injection for cattle (EMEA/V/A/115)

We, the undersigned, have a divergent opinion on the marketing authorisation for CattleMarker IBR Inactivated suspension for injection for cattle.

CattleMarker IBR Inactivated is an inactivated infectious bovine rhinotracheitis (IBR) vaccine which contains 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 and of female cattle from 6 months of age. Duration of protection for seronegative cattle is 6 months and for female cattle 12 months after completion of the primary vaccination.

The composition and manufacture of the vaccine CattleMarker IBR Inactivated is very similar to PregSure BVD, a Zoetis vaccine against BVDV-1 infections. PregSure BVD has been shown to induce a long-lasting allogeneic antibody response which may cause Bovine Neonatal Pancytopenia (BNP) in the progeny of vaccinated dams. Epidemiological data indicate a strong association of the occurrence of BNP and the use of PregSure BVD. The disease only occurred in countries where PregSure BVD had been marketed for several years. In this context, CattleMarker IBR Inactivated bears a potential risk to induce BNP in cattle due to the production of the BoHV-1 antigen on the same homologous bovine cell line (MDBK-derived cells) and the use of the same highly potent adjuvant (Procision A). The combination of both components has been identified as key in the induction of BNP. In addition, the potential risk cannot be ignored for the progeny of female cattle subject to repeated vaccination with CattleMarker IBR Inactivated and also for booster vaccinations with CattleMarker IBR Inactivated of dams already primed with other vaccines produced on bovine kidney cell lines.

In our opinion the potential risk of CattleMarker IBR Inactivated to induce BNP in cattle has not been sufficiently investigated:

1. Even if there is lower amount of cell remnants in CattleMarker IBR Inactivated compared to PregSure BVD, a weak or non-detectable boost effect is anticipated on a subclinical alloreactivity to clinically relevant levels. To reduce the amount of remnant of the antigen production process (e.g. MDBK cell debris), filtration steps using consecutive filtration membranes have been integrated into the production process for CattleMarker IBR Inactivated for clarification of the antigen preparations. Data have been generated 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. However, the reduction of total protein content through the filtration process is 25% for experimental vaccine batches and only 12% for a single large scale production batch. These results give no assurance that scale-up does not impact on the efficiency of filtration in decreasing the total protein content as well as on the consistency of this decrease. In addition, the level of target antigen (BoHV-1) present is comparable to the amount of MHC-1. The effect of the filtration process on both antigens is equivalent. Filtration does not specifically deplete MHC-1. MHC-1 antigens are not absent and can still be detected in the final product. As the level of both antigens is similar, this indicates that the amount of alloantigens present in CattleMarker IBR Inactivated may be immunologically relevant. This means that as the immune response of animals is not dose-dependent, minute amounts of such remnant may boost sensitised animals. The natural life

expectancy of cattle is long and specific breeds could reach 10 and more years under rural farming conditions still in practice in several parts of Europe. According to the proposed annual vaccination scheme such animals could receive 10 and more vaccinations in their life. In the end, the use of the vaccine CattleMarker IBR Inactivated in cattle subject to repeated vaccination and/or vaccinated already with vaccines produced on bovine cell lines may strengthen the potential risk of BNP.

2. The experience with Pregsure BVD stresses the need for immediate and clear regulatory actions if such adverse events reappear. Proposals for post-authorisation studies and for surveillance and monitoring in the field that could mitigate and manage the risk for future cases of BNP developing from the use of the vaccine Cattle Master IBR Inactivated are discussed. The two additional laboratory studies and the surveillance and monitoring strategy proposed are acknowledged but the mitigation measures are not sufficient to lead to a negligible level of risk. The proposed strategy is unlikely to detect BNP early enough as it can impossibly reveal any clinical/subclinical effects. Surveillance and monitoring cannot be accepted as the only precautionary measure to avoid BNP because the actions only start when the first clinical cases in calves have been verified. It is likely that by this time the cattle population will already have reached a level of vaccination that results in additional cases becoming unavoidable unless a strict colostrum management is in place. Therefore the pharmacovigilance measures contribute to risk management but cannot contribute to risk mitigation. They have no immediate preventive character because the maternal alloimmune antibodies persist for five years and longer. However, the pharmacovigilance measures are useful to manage reports of clinical BNP in an efficient manner. A large post-marketing study based on blood testing would allow gathering of a lot more data on the safe use of the product and would also allow a timely stop of the marketing of CattleMarker IBR Inactivated, if necessary. The chance to intervene at a preclinical level before the full syndrome develops large scale would be more probable in this scenario. Due to the fact that PregSure BVD was strongly associated with BNP in calves, there is a potential risk that other vaccines grown on bovine kidney derived cells and formulated with a very potent adjuvant may also cause BNP in calves. Therefore any risk for re-emergence of BNP related to vaccination has to be minimised as far and as early as possible. It is the intended purpose of post-marketing studies to monitor adverse events of a low incidence and therefore to investigate possible risks which cannot be adequately addressed during a licensing procedure. The applicant's concerns that such a study is difficult to organise and to perform are strongly acknowledged. Nevertheless this seems to be the only way to mitigate the BNP risk adequately using current scientific knowledge. Therefore a large-scale post-marketing safety study is required as an appropriate measure to avoid a re-emerging of BNP.

Having considered all the overall submitted data the undersigned are not satisfied that all concerns relating to the risk of BNP have been sufficiently addressed.

Given the above mentioned points, the benefit-risk balance is therefore considered as not being in favour of granting a marketing authorisation to this vaccine.

London, 17 March 2016

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