# ANNEX I

# SCIENTIFIC CONCLUSIONS AND GROUNDS TO VARY THE MARKETING AUTHORISATIONS PRESENTED BY THE EMEA.

## SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA

*OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION*

In the beginning of 1999 field problems in cattle accompanied with high mortality were reported by The Netherlands. The cases were, in the first instance, suspected to relate to Bayovac IBR Marker Vivum and later also to Rhinobovin Marker Vivum. Both products have different names because of co-marketing, but are equal in composition. On 9 March 1999 a rapid alert was sent by the Netherlands to all the Member States. Also one Italian field case was reported which was suspected to relate to Rhinobovin Marker Vivum.

The first official reported Dutch field cases (12-13 herds) were related to 1 batch of Bayovac IBR Marker Vivum (WG4622) and this batch was the only batch of Bayovac IBR Marker Vivum marketed in the Netherlands at that time. The only reported field case concerned in another EU-country (Italy) was suspected to relate to 1 batch of Rhinobovin Marker Vivum (02U056). Both batches were originated from the same bulk of vaccine (77/V4392).

Later Dutch field cases ('case 2') were suspected to be related to other batches of Bayovac IBR-Marker Vivum and Rhinobovin Marker Vivum, which did not originate from this bulk of vaccine. The CVMP concluded however on 9 November 1999, that evidence linking these 'case 2' complaints with the subject of the original referral was equivocal and that the Opinion of the CVMP will be confined to the original referral.

## OVERVIEW OF ANALYTICAL ASPECTS

**The Polymerase Chain Reaction (PCR) for testing of raw materials is well-described in a Standard Operation Procedure (SOP). The PCR method validation (sensitivity, specificity and reproducibility) was provided. The original Immuno Peroxidase Linked Assay (IPLA) is well-described in an SOP and sufficiently validated.**

Due to limited availability* of Master Seed Virus (MSV) and Master Cell Seed (MCS), only the Working Seed Virus (WSV) and Working Cell Seed (WCS) of Bayovac IBR Marker Vivum and Rhinobovin Marker Vivum were retested for the absence of BVD virus, using IPLA and PCR.

No contamination of the working seeds WSV ELR522M1D and WCS-ELR510A125 / WCS-ELR510A127 with BVD-virus was found. The MSV, WSV, MCS and WCS were excluded as the source of the vaccine contamination with BVD virus.

The ingredients of biological origin used in the manufacturing of Bayovac IBR Marker Vivum and Rhinobovin Marker Vivum are foetal calf serum, and trypsin. The trypsin used in the manufacturing is incubated below pH 2 and additionally gamma-irradiated. Data on investigation of batches of foetal calf serum were presented.

Batch of calf serum HyClone AFA4774 was formerly tested and certified as BVD virus free according to the EU Guidelines and USA Federal Regulations. However, re-evaluation revealed that the presence of a rather high level of BVD antibodies in this serum masked the presence of contaminating BVD-virus and limited its multiplication. Using FPLC preparation and ultrafiltration to concentrate virus and to eliminate antibodies, viable BVD virus types 1

* A great part of the master cell seed, working cell seed and master seed virus were used in a research project.

and 2 was detected in this batch. This batch of serum was used to establish 2 batches of Production Seed Virus (PSV), V4602 and P1641, as well as 6 batches of Production Cell Seed (PCS): all are employed for the production of the vaccines.

In the production of vaccine bulk 77/V4392 from which batch WG4622, its sister-batches of Bayovac IBR-Marker Vivum and Rhinobovin Marker Attenuato batch 02U056 are originated, the PSV P1641 and PCS V4028 were used.
No other serum than foetal calf serum is used in the manufacturing.

Flow charts of the production and testing of Bayovac IBR-Marker Vivum batch WG4622 and vaccine bulk 77/V4392 were presented. Original batch documentation was supplied.

The possibility of BVD cross-contamination in general was investigated, but was estimated highly unlikely. However, there was a timely coincidence of production of IBR Marker Vivum and BVD-vaccine virus type 2, although in different, closely situated units with different personnel. The sequence of the BVD-vaccine virus type 2 appeared to be different from those of Bayovac IBR Marker Vivum BVD contaminant type 2, a BVD virus type 2 from a first Dutch field case and a reference BVD virus.

Furthermore, only other inactivated products are made at the manufacturing site: Bayovac IBR Marker inactivatum/Rhinobovin Marker inactivatum, Baypamune and Foot and Mouth disease vaccines. The same inactivation procedure is used for all these products as for Bayovac IBR Marker Vivum / Rhinobovin Marker Vivum and this procedure was evaluated regarding BVD virus.

The SOPs describing the isolation and hygienic measures regarding the manufacturing units at the manufacturing site to avoid BVD virus cross-contamination of the products were supplied.

The full report of the last official GMP-inspection (13.7.1998) was presented. The recommendations of the Inspectors were followed: immediately or according to an agreed timetable.

The full reports of the external consultant (15.4.1999 / 4.6.1999) were provided. The recommendations of the external consultant were also implemented.

Original documentation regarding the quality control testing of Bayovac IBR Marker Vivum, batch WG4622 and vaccine bulk 77/V4392 was supplied.

The SOPs of the quality control testing of batches of vaccine were provided.

The results of tests on the presence of BVD virus contaminants of all batches of vaccine of Bayovac IBR Marker Vivum and Rhinobovin Marker Vivum were supplied.

The following batches of Bayovac IBR Marker vivum and the corresponding Rhinobovin Marker vivum were contaminated with BVD virus:

| **Bayer Batch No.** | **Hoechst Roussel Vet Batch No.** | **Contamination** | **Approx. amount of BVD virus per dose as determined by:** | |
|---|---|---|---|---|
| | | | PCR | IPLA |
| Bulk 77/V4392 | | | | |
| WG4622 | | BVD virus type 2 | $10^{4,9}$ | $10^{2}$ |
| VE4456 | U056 | BVD virus type 2 | $10^{5,2}$ | n.d. |

| | | | | |
|---|---|---|---|---|
| Other Bulks | | | | |
| TV 3294 | | BVD virus type 1 | $10^{1,6}$ | 1* |
| TW3391 | B045 | BVD virus type 1 | $10^{1,6}$ | 1* |
| TX3607 | | BVD virus type 1 | $10^{0,6}$ | 1* |
| VB3914 | U050 | BVD virus type 1 | $10^{1,6}$ | 1* |
| VB3915 | | BVD virus type 1 | $10^{1,6}$ | 1* |
| VB4046 | | BVD virus type 1 | $10^{1}$ | 1* |
| VD4331 | | BVD virus type 1 | Less than 1 | 1* |
| VE4422 | | BVD virus type 1 | $10^{1,6}$ | 1* |

* virus only isolated from concentrated samples.

**The calves used in the safety test originated from a certified IBR-free cattle herd and this herd was routinely vaccinated against BVD. The European Pharmacopoeia does not require testing for BVD virus or antibodies of the animals used in safety testing of the finished product of live IBR-vaccines.**

The use of cattle with low level of antibodies against BVD virus in the safety testing of the finished product of Bayovac IBR Marker Vivum and Rhinobovin Marker Vivum was justified. Experience has shown that calves having no ELISA-titre of antibodies against BVD-virus may have a low ($\leq$ 1:16) titre of virus-neutralising antibodies against BVD virus. Nevertheless, such calves are considered to be fully susceptible for BVD virus infection.

In conclusion, the CVMP agrees that the safety problems in the field originated most probably from contaminated foetal calf serum used in the manufacture which may have arisen from the inadequacy of the applied inactivation used which therefore merit particular attention. The present quality control appears to be insufficient to detect BVD virus. Therefore, additional quality control testing using PCR and IPLA regarding BVD virus is deemed essential.

The manufacturer proposes the following main modifications:

- The implementation of the recommendations of an external inspecting consultant.
- The addition of PCR and IPLA for detecting BVD virus (as described respectively in attachment 40 (SO D-127) and attachment 35 (SO D-076) to the answers to the outstanding issues sent to the EMEA on 28 September 1999).
- In addition the screening of foetal calf serum on BVD virus and antibodies before gamma-irradiation to be used in the manufacturing (as described in attachment 47 (SP-017) and attachment 33 (SO D-020) to the answers to the outstanding issues sent to the EMEA on 28 September 1999).
- The establishment of new Production Seed Virus and Production Cell Seed free of BVD virus.
- The extension and intensification of the quality control on the absence of BVD virus on different levels of manufacturing (production virus, production cells, bulk vaccine, finished product) (as described in attachment 37 (SO D-107) and in accordance with attachment 44 (FC-IBML) to the answers to the outstanding issues sent to the EMEA on 28 September 1999).
- The use of BVD-susceptible cattle in the batch safety-test (as described in attachment 39 (SO D-123) to the answers to the outstanding issues sent to the EMEA on 28 September 1999).

Three representative batches of vaccine of Bayovac IBR-Marker Vivum including the Working Seed Virus, the new Production Seed Virus, the Working Cell Seed, the new Production Cell Seed as well as the foetal calf serum were manufactured and tested according to the proposed modifications. The results of the quality control testing complied with the requirements. No BVD virus was detected at any stage of the production. The BVD virus genome content showed a clear decline over the production process as required. So, no indication for multiplication of BVD virus was found.

Test results:

| **Fetal Calf Serum γ-irradiated (25 – 42 kGy)** | | | |
|---|---|---|---|
| **serum EMEA/CVMP/768/99/Final** | **Results** | | |
| **test parameters** | **limits** | **lot No: V3852** | **lot No: P2233** |
| sterility | no microbial growth | no microbial growth | no microbial growth |
| extraneous agents | no extr. agents detectable | no extr. agents detectable | no extr. agents detectable |
| cytopathic effect (cpe) | no cpe detectable | no cpe detectable | no cpe detectable |
| hemadsorption (ha) | no ha detectable | no ha detectable | no ha detectable |
| BVD virus/IPLA | negative | negative | negative |
| BVD virus/PCR | last positive at dilution $10^{-3}$ | last positive at $10^{-3}$ | last positive at $10^{-3}$ |
| mycoplasma | no mycoplasma detectable | no mycoplasma detectable | no mycoplasma detectable |
| growth promotion | must comply | complies | complies |
| BVD virus type 1 antibodies | < 1:16 | < 1:2 | < 1:2 |
| BVD virus type 2 antibodies | < 1:16 | < 1:3,5 | < 1:2 |

| **Production Cell Stock (PCS)** | | | | |
|---|---|---|---|---|
| test parameters | limits | lot No: X5737 | lot No: X5883 | lot No: X5958 |
| microscopical inspection | typical for MDBK-cells | complies | NA | |
| **sterility** | no microbial growth | no microbial growth | no microbial growth | no microbial growth |
| mycoplasma | no mycoplasma detectable | no mycoplasma detectable | no mycoplasma detectable | no mycoplasma detectable |
| extraneous agents | no extr. agents detectable | no extr. agents detectable | no extr. agents detectable | no extr. agents detectable |
| *cytopathic effect (cpe)* | *no cpe detectable* | *no cpe detectable* | no cpe detectable | no cpe detectable |
| *hemadsorption (ha)* | *no ha detectable* | *no ha detectable* | *no ha detectable* | *no ha detectable* |
| *BVD virus/IPLA* | *negative* | *negative* | *negative* | *negative* |
| *BVD virus/PCR* | *last positive at dilution $10^{-4}$* | *last positive at $10^{-4}$* | *last positive at $10^{-1}$* | *last positive at $10^{-1}$* |
| *virus titre (lg $TCID_{50}$/ml)* | *≥ 7.0* | *NA* | *8.45* | 8.4 |

| **PRODUCT BATCH RESULTS** |
|---|

| | Limits | Batch No. 990811 | Batch No. 990801 | Batch No. 990810 |
|---|---|---|---|---|
| Safety | 2/2 calves well | complies | complies | complies |
| Identity | Complete neutralisation | complies | complies | complies |
| Extraneous agents | No cpe detectable<br>No haemadsorption<br>No live BVD virus detectable | complies<br>complies<br>No live BVD virus detectable | complies<br>complies<br>No live BVD virus detectable | complies<br>complies<br>No live BVD virus detectable |
| BVD virus PCR | Last positive at dilution $10^{-2}$ | Last positive at dilution $10^{-1}$ | last positive at dilution $10^{-1}$ | Last positive at dilution $10^{-1}$ |
| Mycoplasma | No mycoplasma detectable | No mycoplasma detectable | No mycoplasma detectable | No mycoplasma detectable |
| Sterility | No microbial growth | No microbial growth | No microbial growth | No microbial growth |
| Virus titre ($TCID_{50}$/vial) for potency* | *10 dose vial<br>$10^{6.5} – 10^{8.0}$<br>*50 dose vial<br>$10^{7.2} – 10^{8.7}$ | $10^{7.0}$ | $10^{7.8}$ | $10^{6.9}$ |
| Virus titre ($TCID_{50}$/dose) | $10^{5.5} – 10^{7.0}$ | $10^{6.0}$ | $10^{6.8}$ | $10^{5.9}$ |
| Moisture content | 1 % - 3 % | 2.15 % | 1.9 % | 1.8 % |

**The proposed modifications of production and quality control are fully assessed and considered sufficiently validated.**

## OVERVIEW OF SAFETY ASPECTS

The sequences of a BVD-virus type 2 contaminant of Bayovac IBR-Marker Vivum and a BVD virus type 2 of the first Dutch field cases were found to match fully.

Striking clinical signs of disease were in the most typical and severe field cases: anorexia, drop in lactation, fever, nasal discharge, diarrhoea and mortality. At post-mortem, macroscopic lesions were not reported or not specific and in other cases indicative for Bovine Viral Diarrhoea (BVD).

Clinical features of the first field cases could be reproduced by vaccination of susceptible cattle with the contaminated (BVD virus type 2) batch of vaccine concerned.

The Dutch Agricultural and Horticultural Organisation (Land- en Tuinbouw-Organisatie, LTO) has asked approx. 45.000 cattle farmers to report any health problems occurring after IBR-vaccination to

the GD. The number of reported cases increased to approx. 7,000. Of these cases, so far only 6 were handed from LTO to Bayer or Hoechst.

**No BVD-virus isolate from the last mentioned alleged field cases is available. Seven out of 40 investigated batches of Bayovac IBR Marker Vivum originating from bulk of vaccine other than bulk 77/V4392 are mentioned, using IPLA, to be contaminated with BVD virus (< 10 virus particles per vial: only after a second passage on cell culture). These batches are suspected to relate to the later Dutch field cases ('case 2'). Vaccination with 50 doses of such a contaminated batch of vaccine concerned did not result in an infection of susceptible cattle.**

**Serious adverse drug reactions were reported in 451 Dutch field cases. Only about 5% of these cases were evaluated as 'probable/possible related' to Bayovac IBR Marker Vivum or Rhinobovin Marker Vivum. The other cases were classified as "unlikely related". Evaluation by veterinarians at farms concerned demonstrated that often no data were available to support a relation with the vaccines or the farmers were not willing to give them.**

**An independent expert evaluated the animal health situation in farms vaccinated with Bayovac IBR Marker Vivum and Rhinobovin Marker Vivum and comparable non-IBR-vaccinated cattle farms. The disease problems occurring on both groups of farms were comparable .**

**According to an independent commission of international BVD experts it is difficult to assess the probability that cattle vaccinated with IBR-vaccine contaminated with a small amount of live BVD virus become diseased, because various factors are involved that determine whether or not BVD emerges.**

The CVMP concluded on 9 November 1999, that evidence linking these 'case 2' cases with the subject of the original referral was equivocal and that the Opinion of the CVMP will be confined to the original referral.

## GROUNDS FOR RECOMMENDING THE VARIATIONS OF THE MARKETING AUTHORISATIONS:

Whereas

- the Committee considered the referral made under article 23 a (2) of Council Directive 81/851/EEC as amended regarding safety issues related to the use of the products listed in Annex II of the Opinion;

- the Committee agreed that the safety problems were originated most probably from contaminated foetal calf serum used in the manufacture;

- the Committee agreed that particular attention needs to be given to the inactivation used in irradiating foetal calf serum and that therefore additional guarantees are required to ensure that γ-irradiation of foetal calf serum will be performed in line with the European requirements.

- the Committee agreed that the present quality control has been insufficient to detect BVD virus;

- the Committee agreed that modifications of BVD virus testing are required;

- the Committee agreed with the proposed modifications of the MAHs to decrease the risk of contamination and to increase the likelihood for detection of any possible contamination with BVD virus;

- the Committee assessed the quality control data of three representative batches manufactured according to the proposed measures and considered the new quality control tests being sufficiently validated;

- The Committee agreed that the proposed modifications provide the necessary assurance that the risk for BVD virus contamination of the finished products is negligible:

- the Committee considered the lack of data regarding the secondly reported alleged Serious Adverse Drug reaction reports in The Netherlands ('case 2') and decided that evidence linking these 'cases with the subject of the original referral was equivocal and that the Opinion of the CVMP will be confined to the original referral.

**the CVMP has recommended the variations of the Marketing Authorisations for all products listed in Annex II to include the new fully evaluated Polymerase Chain Reaction and Immuno Peroxidase Linked Assay, the additional screening of foetal calf serum on BVD virus and antibodies, the extension and intensification of the quality control on the absence of BVD virus on different levels of manufacture and the use of BVD-susceptible cattle in the batch safety-test.**

**The Marketing Authorisation Holders are required to send to the National Competent Authorities exactly the same documentation (in particular SP-017, SO D-20, SO D-107, SO D-076, SO D-127, SO D-123 and FC-IBM which were fully assessed and considered sufficiently validated by the CVMP to support the recommended changes) in order to initiate the corresponding variations to the National Marketing Authorisations.**

In addition the manufacturer is required to guarantee that the inactivation methods of all foetal calf serum used for the manufacture of virus seeds, cell seeds and finished products, for all vaccines listed in Annex II fully comply with the requirements of the European Pharmacopoeia and the EU Guideline 'General requirements for the production and control of live mammalian bacterial and viral vaccines for veterinary use' (Volume 7 of The Rules Governing Medicinal Products in the European Union). Therefore the manufacturer is required to provide to the CVMP before 15 April 2000 the data of validation studies of γ-irradiation of foetal calf serum used in the manufacture; 1) showing the reduction of Bovine Viral Diarrhoea virus by at least $10^6$ and 2) establishing the exact dose of irradiation received by the serum.

**ANNEX II**

LIST OF NAMES OF THE MEDICINAL PRODUCTS, MARKETING AUTHORISATION HOLDERS, PHARMACEUTICAL FORMS, STRENGTHS, ROUTE OF ADMINISTRATION, PACKING AND PACKAGE SIZES IN THE MEMBER STATES.

| **Member State** | **Marketing Authorisation Holder**<br>**Company name & address** | **Authorisation year + number** | **Product name** | Strength (mg)/ **pharmaceutical form** | **Administration route** | **Pack size/ nature of container** |
|---|---|---|---|---|---|---|
| UK | Bayer AG<br>Entwicklund PZII<br>D-51368<br>Leverkusen<br>Germany<br>Tel no +49 2173 38 42 44<br>Fax no +49 2173 38 34 79 | 1999<br>10.2.99<br>Vm04895/4001 | Bayovac IBR – Marker Vivum | Bovine Herpes Type I $10^5$ $TCID_{50}$<br>IBR Marker Virus gE Neg<br>$10^2$ $TCID_{50}$<br>Freeze-dried live virus vaccine with diluent for reconstitution | Intra-nasal or/and intra-muscular | 10 or 50 dose glass bottles + glass bottles containing 20 ml and 100 ml sterile water for injection. |
| DE | Bayer AG<br>Geschäftsbereich<br>Tiergesundheit<br>51368 Leverkusen<br>Tel no 02173-38 42 44<br>Fax no 02173-38 34 79 | 1994<br>496a/93 | Bayovac IBR – Marker Vivum | Powder for injection (lyophilized) + suspension | intra-muscular or Intra-nasal | Glass vials<br>10 doses, 50 doses |
| DE | Hoechst Roussel Vet Vertriebs GmbH<br>Feldstraße 1a<br>85716 Unterschleißheim<br>Tel no 089-31 00 60<br>Fax no 089-31 00 62 28 | 1995<br>37a/95 | Rhinobovin Marker lebend | Powder for injection (lyophilized) + suspension | intra-muscular or Intra-nasal | Glass vials<br>10 doses, 50 doses |
| NL | Bayer B.V. Animal Health<br>Energieweg 1 - Postbox 80<br>3641 RT Mijdrecht<br>The Netherlands<br>Tel no 0297-280666<br>Fax no 0297-284165 | 1995<br>13 February<br>REGNL 8427 | Bayovac IBR – Marker Vivum | | | 20 ml and 100 ml (respectively 50 doses) |

| | | | | | | |
|---|---|---|---|---|---|---|
| NL (Co-licensee) | Hoechst Roussel Vet NV<br>Charleroisesteenweg 111-113<br>1060 Brussel<br>Belgium<br>Tel no 0032 2 533 42 43<br>Fax no 0032 2 533 43 55 | 1995 13 June<br>REGNL 8800 | Rhinobovin Marker live | | | 20 ml and 100 ml (respectively 50 doses) |

| | | | | | | |
|---|---|---|---|---|---|---|
| LUX | Bayer Belgium s.a.<br>143, av. Louise<br>B-1050 Bruxelles<br>Tel no 32-2-535 66 47<br>Fax no 32-2-537 36 61 | 1996<br>V/442/96/01/0476 | Bayovac IBR – Marker Vivum | Virus herpétique bovin type 1 (BHV-1), souche Difivac (Virus IBR - Marker, gE-négatif), virus vivant atténué | Injectable solution | 10 doses + solvent<br>50 doses + solvent |
| BE | Bayer NV<br>Division Animal Health<br>Contact Belgium:<br>Dr Gevaert<br>Regulatory Affairs<br>Manager Benelux<br>or Dr D'hoore<br>(Bayer Animal Health Belgium)<br>Tel no 32-2-5358837/32-2-5356647<br>Fax no 32-2-5373661 | 1995<br>187IS278F17 | Bayovac IBR – Marker Vivum | Live, gE-deleted vaccin against IBR infectious bovine rhinotracheitis | | 20 ml (10 doses)<br>100 ml (50 doses) |
| BE<br>(Co-licensee) | Hoechst Roussel Vet N.V. Benelux<br>Contact Germany:<br>Dr Kretzdorn<br>Tel no 49-2173384244<br>Fax no 49-2173383479<br><br>Contact Belgium:<br>Dr Lens<br>General Manager Hoechst Roussel Vet NV Benelux<br>Tel no 32-2-5334243<br>Fax no 32-2-5334355 | 1995<br>1293IS43F17 | Rhinobovin Marker live | Live, gE-deleted vaccin against IBR infectious bovine rhinotracheitis | | 20 ml (10 doses)<br>100 ml (50 doses) |

| | | | | | | |
|---|---|---|---|---|---|---|
| ES | Quimica<br>Farmaceutica<br>Bayer, S.A.<br>(Division TG)<br>C/Calabria, 268<br>Barcelona<br>08080<br>Tel no 0034-93-495 6500<br>Fax no 0034-93-322 5413 | 1994<br>9381 | Bayovac IBR – Marker Vivum | Powder and solvent for suspension for injection<br>$10^5$ $DICT_{50}$ (Min)<br>$10^7$ $DICT_{50}$ (Max)<br>per dose | Intramuscular<br>Intranasal | Vials with 10 and 50 dose |
| ES | Hoechst Roussel Vet.<br>Ronda General<br>Mitre, 72-74<br>08017 Barcelona<br>Tel no 0034-93-306 8113<br>Fax no 0034-93-414 5870 | 1996<br>9419 | Rhinobovin Marker Viva | Powder and solvent for suspension for injection<br>$10^5$ $DICT_{50}$ (Min)<br>$10^7$ $DICT_{50}$ (Max)<br>per dose | Intramuscular<br>Intranasal | Vials with 10 and 50 dose |
| IT | Bayer S.p.A.<br>Viale Certosa 126<br>20156 Milano<br>Tel no 0039-02-39781<br>Fax no 0039-02-3978 2303 | 1995<br>100401013<br>(10 doses)<br>100401025<br>(50 doses) | Bayovac IBR – Marker Vivum | Live, gE-deleted vaccin against IBR infectious bovine rhinotracheitis | Intranasal and/or intramuscolar inoculation | Glass bottles with 10 doses and 50 doses of freeze-dried product and glass bottles with 20 ml and 100 ml solvent, respectively |
| IT | Hoechst Roussel Vet S.r.l.<br>Piazzale Tur 5<br>20149 Milano<br>Tel no 0039-02-345 4981<br>Fax no 0039-02-345 49826 | 1996<br>102186018<br>(10 doses)<br>102186020<br>(50 doses) | Rhinobovin Marker Attenuato | Live, gE-deleted vaccin against IBR infectious bovine rhinotracheitis | Intranasal and/or intramuscolar inoculation | Glass bottles with 10 doses and 50 doses of freeze-dried product and glass bottles with 20 ml and 100 ml solvent, respectively |

| | | | | | | |
|---|---|---|---|---|---|---|
| PT | Hoechst Roussel Vet. Products<br>Para Saude<br>Animal Ldc.<br>Estrada Nacional<br>No. 249 Km 14,2<br>Apartado 144<br>2626 Mem Martins<br>Codex<br>Tel no 351-21-9269883/9269711<br>Fax no 351-21-9202231 | National authority<br>2.8.96<br>No. 552/96<br>Dev | Rhinobovin viva<br>Marcada | Herpes Virus<br>Bov Tipo 1<br>(Min) $10^5$<br>***DICT$_{50}$***<br>Estirpe<br>Dicivac do<br>Virus IBR<br>gE – (Max) $10^7$<br>$DICT_{50}$ | Intranasal<br>Intramuscular | Vials of 10 and 50 doses |
| IR | Bayer Ireland Ltd.,<br>Chapel Lane,<br>Swords,<br>Co. Dublin,<br>Ireland<br>Tel no 353-1-8132222<br>Fax no 353-1-8132288 | Licence No.<br>AR8/005/01+02<br>Issue Date<br>19/01/98<br>Expiry Date<br>27/09/99 | Bayovac IBR – Marker Vivum | Bovine Herpes Type I $10^5$ $TCID_{50}$<br>IBR Marker Virus<br>gE Neg<br>$10^2$ $TCID_{50}$<br>Freeze-dried live virus vaccine with diluent for reconstitution | Intra-nasal or/and intra-muscular | 10 or 50 dose glass bottles + glass bottles containing 20 ml and 100 ml sterile water for injection. |

# ANNEX III

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

*see Annex II*

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active substance(s)**

| | |
|---|---|
| Bovine Herpes Virus type 1 (BHV-1),<br>strain Difivac (IBR-Marker Virus, gE-negative),<br>modified live (attenuated) virus | min. $10^{5.0}$ $TCID_{50}$<br>max. $10^{7.0}$ $TCID_{50}$ |

**Adjuvant(s)**

not applicable

**List of excipients**

| | |
|---|---|
| Stabiliser: | |
| Dextran 60 | 4.8 mg |
| Glycin | 1.2 mg |
| | |
| pH-stabiliser: | |
| HEPES Na | 1 mg |

## 3. PHARMACEUTICAL FORM

Freeze-dried product, yellowish to white lyophilisate and solvent (aqua pro injectionem), clear colourless liquid for intranasal and/or intramuscular application

## 4. PHARMACOLOGICAL PROPERTIES

### 4.1 Properties of active ingredient

The Bovine Herpes Virus type 1 (BHV-1), strain Difivac (IBR-Marker Virus, gE-negative) was attenuated by multiple passages in bovine cell cultures. After further passages in bovine cell cultures a BHV-1 strain could be isolated by serial single plaque purifications that lacks the entire gene coding for the viral structural glycoprotein gE. Due to this gene deletion the glycoprotein gE is absent in virus particles of the IBR-Marker Vaccine MLV. Therefore the vaccine virus and the antibodies against it can be clearly differentiated from field strains or antibodies against the latter by its genomic profile and by serological methods, respectively. BHV-1 gE-deletion mutants are immunogenic but show a reduced virulence.

### 4.2 Immunological properties

The vaccine induces immunity in cattle against clinical respiratory symptoms caused by the Infectious Bovine Rhinotracheitis (IBR) virus. Following infection the intensity and duration of clinical symptoms as well as the titre and duration of virus shedding are significantly reduced. As with other vaccines, vaccination may not completely prevent but does reduce risk of infection. The product

induces in vaccinated cattle antibodies which are detected in the serumneutralisation test and in conventional ELISA tests. With the specific testkit .... these antibodies can be differentiated - due to the lack of antibodies against gE - from those of field virus infected animals or animals vaccinated with conventional vaccines.
Pharmacotherapeutic group: {group}, ATCvet code: {code}

## 5. CLINICAL PARTICULARS

### 5.0 Target species

Cattle

### 5.1 Indications for use

For active immunisation of cattle against the respiratory symptoms caused by Infectious Bovine Rhinotracheitis (IBR) virus. Vaccinated cattle can be differentiated from field virus infected animals due to the marker deletion, unless the cattle were previously vaccinated with a conventional vaccine or infected with field virus.

### 5.2 Contraindications

Diseased cattle and cattle infested heavily by parasites should be excluded from the vaccination.

### 5.3 Undesirable effects

When inoculated parenterally in very rare cases minor, transient swelling may occur at the injection site. Following intranasal inoculation slight transient, serous nasal discharge may occur in rare chases.

### 5.4 Special precaution(s) for use

None

### 5.5 Pregnancy and lactation

No precautions are required.

### 5.6 Interaction with other veterinary medicinal products and other forms of interaction

Immunosuppressive substances, i.e. cortcosteroids, should be avoided in a period of 7 days prior to and after vaccination as this may impair the development of the immunity.

Interferon sensitive products should not be applied intranasally following 5 days after intranasal vaccination.

### 5.7 Posology and method of administration

The dose for cattle, over 2 weeks of age, is 2 ml of the reconstituted vaccine for intranasal and/or intramuscular inoculation.

The freeze-dried product should be reconstituted just prior to use. To prepare the vaccine for inoculation, approximately a quarter of the solvent is transferred to the lyophilisate with a sterile syringe, then mixed and finally transferred back into the remaining solvent. The needles and syringes used for application of the vaccine must not be sterilised by chemical desinfectants as this may impair the efficacy of the vaccine.

The vaccine is applied aseptically via the intramuscular route (2 ml) or sprayed into the nostrils (1 ml per nostril during aspiration) with the spray canula supplied in the package. Once resuspended the vaccine remains potent for max. 8 hours when product is withdrawn sterily and the vaccine is refrigerated.

The vaccination scheme consists of basic immunisation and booster vaccinations.

Basic immunisation:
Two injections of 1 dose (2 ml) each 3-5 weeks apart.

Booster vaccinations:
1 dose (2 ml) 6 months apart.

**Calves** may be vaccinated beginning from their 3rd week of life, irrespective of the status of maternal antibodies. The first vaccination has to be applied intranasally, followed by the second vaccination intramuscularly. These calves must receive their first booster vaccination at the age of 6 months.

**Cattle over 3 months of age** - e.g. fattening bulls, beef cattle, including pregnant heifers or cows - are vaccinated by two intramuscular inoculations, 3-5 weeks apart. This will induce an immunity lasting for 6 months. Booster vaccinations are performed every 6 months. Beef cattle and fattening bulls are vaccinated preferably just prior to housing (crowding) or at transfer to new groups.

To stimulate local immunity IBR infected cattle or cattle under risk of infection - including pregnant cattle - receive their first vaccination intranasally, the revaccination intramuscular.

It is recommended to vaccinate all cattle of a herd."

### 5.8 Overdose

Not recorded.

### 5.9 Special warnings for each target species

None

### 5.10 Withdrawal period

None

### 5.11 Special precautions to be taken by the person administering the veterinary medicinal product to animals

None

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 Incompatibilities

Not recorded.

### 6.2 Shelf life

#### 6.2.1 Unopened product:

30 months

#### 6.2.2 Broached containers:

Following reconstitution the vaccine remains potent for max. 8 hours when the product is withdrawn aseptically and the vaccine is refrigerated.

### 6.3 Special precautions for storage

Store at +2°C to +8°C (refrigerated), protected from frost, heat or light.

### 6.4 Nature and contents of container

Glass bottles with 10 doses and 50 doses of freeze-dryed product and glass bottles with 20 ml and 100 ml solvent, respectively.

### 6.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from such veterinary medicinal products

Not recorded. Special requirements according to national prescriptions.

## 7. PROHIBITION OF SALE, SUPPLY AND/OR USE

## 8. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

## 9. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

## 10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 11. DATE OF REVISION OF THE TEXT