Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal product, animal species and marketing authorisation holders in the Member States

Member State EU/EEA	Marketing authorisation holder	Invented name	Strength	Pharmaceutical form	Animal species
Austria	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS - Emulsion zur Injektion für Rinder	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Belgium	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Czech Republic	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS Injekční emulze pro skot	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Denmark	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age

Member State EU/EEA	**Marketing authorisation holder**	**Invented name**	**Strength**	**Pharmaceutical form**	**Animal species**
France	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS EMULSION INJECTABLE POUR BOVINS	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Germany	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Greece	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Hungary	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS vakcina A.U.V.	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age

Member State EU/EEA	Marketing authorisation holder	Invented name	Strength	Pharmaceutical form	Animal species
Ireland	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS Emulsion for injection for cattle	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Italy	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS Emulsion for injection for cattle	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Poland	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS emulsja do wstrzykiwań dla bydła	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Portugal	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS Emulsão para injecção para bovinos	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age

Member State EU/EEA	Marketing authorisation holder	Invented name	Strength	Pharmaceutical form	Animal species
Slovak Republic	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS injekčná emulzia pre dobytok	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
Spain	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
The Netherlands	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age
United Kingdom	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170- AMER (Girona) SPAIN	HIPRABOVIS PNEUMOS Emulsion for Injection for Cattle	*Mannheimia haemolytica* Biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. Inactivated *Histophilus somni* Bailie strain	Emulsion for injection	Cattle from 2 months of age

Annex II

Scientific conclusions and grounds for suspension of the marketing authorisation(s)

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF HIPRABOVIS PNEUMOS EMULSION FOR INJECTION FOR CATTLE AND ASSOCIATED NAMES

1. Introduction

HIPRABOVIS PNEUMOS Emulsion for injection for cattle is an inactivated vaccine for reduction of the clinical signs and lung lesions caused by *Mannheimia haemolytica* serotype A1 and *Histophilus somni* in calves from 2 months of age.

Since October 2010, the number of reports resembling anaphylactic events, some of which were fatal, has increased, (from 12 to 24), most notably in four of the 16 European Union (EU) Member States where the product is authorised. These reports raised concern over a potential association with the use of HIPRABOVIS PNEUMOS Emulsion for injection for cattle. Although it was not clear whether such events represented 'true' anaphylactic reactions or resulted from similar clinical signs due to anaphylactoid or endotoxin-related events, the term 'anaphylactic-type' is used hereafter to describe the adverse events reported. The greatest number of adverse events was reported in France. Following the initial placing on the market in France in 2009, the frequency of adverse events reported in relation to the amount of product sold was estimated to be approximately one affected animal for 860 animals treated (nine adverse event reports involving 69 affected animals, 18 of which died). After evaluation of the adverse events, the French competent authority considered that the benefit-risk balance for the product was unfavourable and suspended the marketing authorisation in France as a precautionary measure until the cause of the adverse events could be identified and corrective measures implemented.

The marketing authorisation holder voluntarily stopped the sales of the product in March 2011, initially in France and subsequently in all other concerned EU Member States. The marketing authorisations in Spain and Italy were suspended by the national competent authorities on 11 and 20 April 2011, respectively.

2. Discussion of data available

Adverse events concerning anaphylactic-type reactions, some of which were fatal, have been reported in four EU Member States. To date no adverse events have been reported in the remaining 12 concerned Member States. The frequency of events reported varies across Member States and does not appear to directly reflect the amount of product sold. Anaphylactic-type adverse events have been reported most frequently in three of the 16 Member States where the product is authorised, Belgium, France and Italy. Additionally, in Spain where approximately half of the total EU-product sales are recorded, two adverse events have been reported to date. In France, the incidence of anaphylactic-type events reported was estimated to be 0.177% or 1 affected animal for 560 treated animals. Between 1 April 2010 and 28 February 2011, the overall incidence of adverse events in the EU was estimated to be approximately 0.048% (or 'rare') and the incidence of fatalities was estimated as approximately 0.0087% (or 'very rare').

The Committee for Medicinal Products for Veterinary Use (CVMP) considered that the pharmacovigilance data (adverse event reports) indicated that the frequency of reported events of anaphylactic-type reactions varied across the EU. The Committee considered the possible role of additional contributory factors in relation to the adverse events reported, such as quality (batch)-related effects, animal related effects (e.g. breed, age sensitivity); interactions; and/or geographical factors. The potential relation between the adverse events reported and possible endotoxin effects

associated with the product was considered. However, from the data evaluated, a definitive conclusion could not be drawn concerning these hypotheses. Following the evaluation of the data presented by the marketing authorisation holder, it was considered that there was insufficient information to identify the underlying mechanism for anaphylactic-type events following administration of HIPRABOVIS PNEUMOS Emulsion for injection for cattle, or potential factors that may contribute to such events.

The Committee reviewed the ongoing and planned studies supported by the marketing authorisation holder to investigate the potential relation between HIPRABOVIS PNEUMOS Emulsion for injection for cattle and anaphylactic-type adverse events. One clinical trial investigated the potential role of bovine respiratory syncytial virus vaccines as a potential predisposing factor to the adverse events after use of HIPRABOVIS PNEUMOS Emulsion for injection for cattle. It was considered that the conditions under which the study was conducted and the limited number of animals enrolled were insufficient to draw definitive conclusions to explain the increase in anaphylactic-type events observed in the field or to recommend measures to reduce the risk of such events. A second study, also investigating the potential role of bovine respiratory syncytial virus vaccines as a predisposing factor, was ongoing and results are expected by the end of July 2011. The emphasis placed by the marketing authorisation holder on investigation of the role of bovine respiratory syncytial virus infection or vaccination was considered to be pursued to the exclusion of other possible risk factors which may contribute to the adverse events. It was recommended that further investigation of all potential contributory factors be explored further by the marketing authorisation holder.

The Committee considered the measures proposed by the marketing authorisation holder to mitigate the risk of anaphylactic-type events following use of the product. In the absence of an identified underlying cause for the adverse events observed at the time, the changes proposed to the summary of product characteristics (SPC) and product literature were, on the whole, not considered sufficient to minimise the risk of anaphylactic-type events following administration of HIPRABOVIS PNEUMOS Emulsion for injection for cattle under authorised conditions of use. Although it was considered that it may be useful to revise the SPC text in future to more accurately reflect the frequency and severity of adverse events reported, such a change was not considered to be an adequate measure to address the issue concerning anaphylactic-type events. It was noted that since March 2011 the marketing authorisation holder voluntarily stopped sales of the product in all concerned EU Member States where the product is authorised.

Whilst acknowledging the inherent limitations of the pharmacovigilance data and the limited size of the clinical study conducted by the marketing authorisation holder, having evaluated the data available, the CVMP concluded that the above-mentioned findings provide evidence to suggest an association between the anaphylactic-type events observed and administration of HIPRABOVIS PNEUMOS Emulsion for injection for cattle. The underlying mechanism and potential contributory factors associated with the events have yet to be elucidated. A laboratory trial is currently ongoing, however further investigations will be required to determine the underlying cause(s) of the anaphylactic-type events reported.

3. Benefit-risk evaluation

HIPRABOVIS PNEUMOS Emulsion for injection for cattle is the only vaccine currently authorised in the EU with the combination of active components, *Mannheimia haemolytica* and *Histophilus somni*. It increases the range of available vaccine options. The vaccine is expected to benefit herd health and welfare by reducing the clinical signs and lung lesions caused by *Mannheimia haemolytica* serotype A1 and *Histophilus somni* in cattle. Whilst the animal health and welfare and economic and benefits of vaccination against bovine respiratory disease are acknowledged, HIPRABOVIS PNEUMOS Emulsion for injection for cattle is not an essential vaccine for cattle. There are valid alternative therapeutic and

management tools available on the EU market to control the diseases caused by *Mannheimia haemolytica* and *Histophilus somni*.

The principal risks associated with the product relate to the potential for anaphylactic-type events in treated animals, some of which have been fatal. In France, the incidence of anaphylactic-type events reported was estimated to be 0.177% or 1 affected animal for 560 treated animals. Between 1 April 2010 and 28 February 2011, the overall EU incidence for adverse events reported following use of the product was estimated to be 0.048% (or 'rare') between 1 April 2010 and 28 February 2011 and the incidence of fatalities was 0.0087% (or 'very rare'). The frequency of anaphylactic-type events reported following use of the product increased markedly since October 2010 in Belgium, France and Italy compared with other concerned Member States. Based on post-authorisation safety data, there is no evidence that the product poses a risk to the user, the consumer or the environment.

The data evaluated indicate an association between vaccination of cattle with HIPRABOVIS PNEUMOS Emulsion for injection for cattle and the occurrence of anaphylactic-type events, which has increased recently in some EU Member States. The underlying mechanism for the events observed and potential contributory factors are unknown at present and subject to ongoing research. As the underlying cause(s) has not yet been determined, appropriate corrective measures to minimise the risk of such adverse events could not be identified. The marketing authorisation holder has taken precautionary measures to stop sales of the product in the EU.

As no corrective measures can be implemented at present, it cannot be excluded that the serious adverse events reported in some Member States could also occur in others which to date have been unaffected. The potential risk of such events following use of the product was considered to be not acceptable in comparison to the benefits provided. The CVMP concluded that the overall benefit-risk balance of the product is unfavourable under the authorised conditions of use.

Grounds for suspension of the marketing authorisations

Whereas

- anaphylactic-type adverse events, some of which were fatal, reported after the use of HIPRABOVIS PNEUMOS Emulsion for injection for cattle indicates an association with the product;
- the underlying cause of the adverse events observed has yet to be determined and consequently no specific measures could be recommended to ensure that the product is not associated with an unacceptable risk of anaphylactic-type events, some of which were fatal, under the authorised conditions of use;
- the CVMP concluded that the benefit-risk balance for HIPRABOVIS PNEUMOS Emulsion for injection for cattle is unfavourable under the authorised conditions of use;

therefore, in accordance with Article 83 (1)(a) of Directive 2001/82/EC, the CVMP recommends the suspension of the marketing authorisations for the veterinary medicinal products referred to in Annex I of the CVMP Opinion.

Conditions for lifting the suspension

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 should investigate the qualitative nature of the adverse events observed; investigate the potential factors that may explain the regional differences observed concerning the adverse events; and propose appropriate measures to mitigate the risk of occurrence of such adverse events to demonstrate a favourable benefit-risk balance for the product when used according to the recommendations of the summary of product characteristics.