Annex I

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

Member State	Marketing Authorisation Holder	Product name	Pharmaceutical form	Strength	Target animal species	Route of administration
Belgium	Pfizer Animal Health Rue Laid Burniat 1 1348 - Louvain-la-Neuve BELGIUM	PREGSURE BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Bulgaria	Pfizer Animal Health MA EEIG Ramsgate Road Sandwich, Kent CT13 9NJ UNITED KINGDOM	PregSure BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Czech Republic	Pfizer, spol. s r.o. Stroupežnického 17 150 00 Praha CZECH REPUBLIC	PregSure BVD injekční emulze	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Estonia	Pfizer Animal Health Rue Laid Burniat 1 1348 - Louvain-la-Neuve BELGIUM	PregSure BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
France	PFIZER 23/25 Avenue du Docteur Lannelongue 75014 Paris FRANCE	PREGSURE BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Germany	Pfizer GmbH Linkstraße 10 D-10785 Berlin GERMANY	PregSure BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Greece	PFIZER HELLAS S.A 243 Messogeion Ave. Neo Psychiko GR-154 51 GREECE	PREGSURE BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous

Member State	Marketing Authorisation Holder	Product name	Pharmaceutical form	Strength	Target animal species	Route of administration
Hungary	Pfizer Kft. Alkotas u 53 MOM Park "F" Épület Budapest H-1123 HUNGARY	PregSure BVD vakcina A.U.V.	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Ireland	Pfizer Healthcare Ireland trading as Pfizer Animal Health Ringaskiddy County Cork IRELAND	PregSure BVD Emulsion for Injection	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Italy	Pfizer Italia Srl Via Isonzo 71 04100 – Latina ITALY	Pregsure BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Lithuania	Pfizer Animal Health S.A. Rue Laid Burniat 1 B-1348 - Louvain-la-Neuve BELGIUM	PREGSURE BVD, injekcinė emulsija	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Latvia	Pfizer Ltd Ramsgate Road Sandwich, Kent CT13 9NJ UNITED KINGDOM	PregSure BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Poland	Pfizer Trading Polska Sp. z o.o. ul. Rzymowskiego 34 02-697 Warszawa POLAND	PregSure BVD emulsja do wstrzykiwań	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Portugal	Laboratórios Pfizer Lda Lagoas Park – Edifício 10 2740-244 Porto Salvo PORTUGAL	Pregsure BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous

Member State	Marketing Authorisation Holder	Product name	Pharmaceutical form	Strength	Target animal species	Route of administration
Romania	Pfizer Animal Health MA EEIG Ramsgate Road, Sandwich, Kent CT 13 9NJ UNITED KINGDOM	Pregsure BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Slovenia	Pfizer Luxembourg SARL Gran Duchy of Luxembourg 51, Avenue J.F. Kennedy L-1855 - Luxembourg	Pregsure BVD emulzija za injiciranje	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Slovak republic	Pfizer Luxembourg SARL o.z. Pfizer AH Pribinova 25 81109 Bratislava SLOVAK REPUBLIC	Pregsure BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
Spain	Pfizer SA Avda. De Europa, 20 B Parque Empresarial la Moraleja (Alcobendas) 28108 SPAIN	PREGSURE BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
The Netherlands	Pfizer Animal Health BV Rivium Westlaan 142 2909 LD Capelle a/d Ijssel P.O. Box 37 2900 AA Capelle a/d Ijssel THE NETHERLANDS	PREGSURE BVD	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous
United Kingdom	Pfizer Ltd Ramsgate Road Sandwich, Kent CT13 9NJ UNITED KINGDOM	Pregsure BVD Emulsion for Injection	Emulsion for injection	to induce a geometric mean seroneutralizing titre in guinea pigs of at least 5.6 log2	Cattle at breeding age (cows and heifers)	Subcutaneous

Annex II

Scientific conclusions and grounds for suspension of the marketing authorisations

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF Pregsure BVD AND ASSOCIATED NAMES (SEE ANNEX I)

1. Introduction

Pregsure BVD is an inactivated vaccine for the immunisation of female cattle to prevent bovine viral diarrhoea virus (BVDV) type 1 (cytopathogenic strain 5960) transplacental infection and the birth of BVDV type 1 persistently infected calves.

Since March 2009, over 400 adverse events of bovine neonatal pancytopenia (involving over 2,000 animals) have been reported within eleven European Union (EU) Member States where the product is authorised. These reports raised concern over a potential association with the use of Pregsure BVD.

Germany is the Member State where most adverse events of bovine neonatal pancytopenia have been reported. Following the evaluation of adverse event reports of bovine neonatal pancytopenia after the use of Pregsure BVD, and epidemiological data and findings from research projects on bovine neonatal pancytopenia, the German authority (Paul-Ehrlich Institut (PEI)) questioned the benefit-risk balance for the product.

The marketing authorisation holder voluntarily stopped the sales of the product from the market in Germany in April 2010 and from all other concerned EU Member States in June 2010.

2. Discussion of data available

Evaluation of the potential association between the occurrence of bovine neonatal pancytopenia in calves and vaccination of dams using Pregsure BVD and associated names

Bovine neonatal pancytopenia has been reported in eleven EU Member States. The frequency of adverse event reports with signs typical of bovine neonatal pancytopenia in herds in which Pregsure BVD was one of the vaccines used varies across affected Member States and in some Member States, e.g. Germany and United Kingdom, has increased markedly since 2009. The overall incidence for bovine neonatal pancytopenia at EU level between 2004 and 2009 was estimated to be 0.016% based on a single dose. It was noted that in Member States where Pregsure BVD was not marketed or in herds where Pregsure BVD had not been used, bovine neonatal pancytopenia appears to be reported as isolated events and may be compatible with so-called idiopathic bovine neonatal pancytopenia.

The Committee for Medicinal Products for Veterinary Use (CVMP) considered that the pharmacovigilance data (adverse event reports) indicated a general trend between reported events of bovine neonatal pancytopenia and the temporal and geographical distribution of Pregsure BVD sales, including the number of doses sold in the different EU Member States.

In addition to the pharmacovigilance data, the CVMP also took into account epidemiological and experimental studies that provided further evidence to suggest an association between Pregsure BVD and bovine neonatal pancytopenia. A number of laboratory studies identified the ingestion of colostral antibodies from vaccinated dams as a potential risk factor. The possibility of the vaccine triggering the production of allo- or auto-antibodies cannot be excluded and may explain the rapid onset of the disorder in calves that have recently ingested colostrum from vaccinated dams. Preliminary epidemiological findings report an association between bovine neonatal pancytopenia calves and a vaccination history, at the herd level, involving Pregsure BVD. In addition, unpublished data from a study involving negative control farms to investigate management factors potentially associated with bovine neonatal pancytopenia identified a history of Pregsure BVD vaccination at the herd level as a potential risk factor for bovine neonatal pancytopenia.

The Committee reviewed the list of ongoing or planned research studies supported by the marketing authorisation holder to investigate bovine neonatal pancytopenia and the potential relation with Pregsure BVD. Although considered by the marketing authorisation holder, an association between the occurrence of bovine neonatal pancytopenia and the release of particular batch(es) of the product has not been found nor any indication for circovirus contamination of the product. Whilst acknowledging the limitations of the pharmacovigilance data and the lack of appropriate control animals in some of laboratory studies, having evaluated the data available, the CVMP concluded the above-mentioned findings provide evidence to suggest a potential association between the occurrence of bovine neonatal pancytopenia and Pregsure BVD. Although the definitive aetiology of bovine neonatal pancytopenia is at present unknown, it appears to be a multi-factorial disorder and the possibility that it may be immune-mediated is consistent with available epidemiological data and is becoming a focus of research efforts to identify the causal factor(s) for calves developing bovine neonatal pancytopenia.

The data evaluated suggest that Pregsure BVD may be one of the contributing factors for bovine neonatal pancytopenia although investigations are currently ongoing to determine all the factors associated with the disorder and the underlying cause.

3. Benefit-risk evaluation

Administration of Pregsure BVD to female cattle allows prevention of BVDV type 1 transplacental infection and the birth of BVDV type 1 persistently infected calves and laboratory scale investigations have also demonstrated that vaccination can reduce fertility losses due to BVDV type 1 infection in the early stage of gestation. The product has also a claim of partial cross protection against BVDV type 2.

Whilst the economic and animal health and welfare benefits of vaccination against BVDV type 1 are acknowledged, there are valid alternative BVD vaccines available on the EU market with similar claims to that of Pregsure BVD.

From the data evaluated to date, there is evidence to suggest a potential association between vaccination of dams using Pregsure BVD and the occurrence of bovine neonatal pancytopenia in calves. The overall incidence for bovine neonatal pancytopenia events reported following use of the product was estimated to be over 0.016% across the EU, based on a single dose, between 2004 and 2009. In this particular case, for a prophylactic measure such as vaccination this figure was considered unacceptable for a potentially fatal disorder.

The aetiology of bovine neonatal pancytopenia is unknown at present and the potential association with Pregsure BVD is the focus of ongoing research. The marketing authorisation holder has taken precautionary measures to stop sales of the product in EU.

The potential risk of bovine neonatal pancytopenia following use of the product was not considered to be acceptable in comparison to the benefits provided by the product.

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

- adverse events of bovine neonatal pancytopenia reported after the use of Pregsure BVD appear to indicate an association with the product. These observations are further supported by data from epidemiological and laboratory studies;
- the aetiology of bovine neonatal pancytopenia is unknown and the risk factors associated with the disorder have yet to be determined;
- no specific measures could be recommended to ensure that the product is not associated with an unacceptable risk of bovine neonatal pancytopenia under the authorised conditions of use;
- the CVMP concluded that the benefit-risk balance for Pregsure BVD 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. In addition, the CVMP considered that temporary measures are needed and therefore recommends that all batches of the product be recalled at wholesale level.

Conditions for lifting the suspension

For the suspension to be lifted the marketing authorisation holders should provide the national competent authorities with scientific evidence to demonstrate that the administration of the vaccine to dams, according to the recommendations of the summary of product characteristics, does not lead to an increased risk of bovine neonatal pancytopenia or propose management measures to mitigate this risk and to demonstrate a favourable benefit-risk balance for the product.