Annex I

List of the names, pharmaceutical form, strength of the Veterinary medicinal products, animal species, routes of administration, withdrawal period, marketing authorisation holders in the Member states

Member State / EEA	Marketing Authorisation Holder	Product name	Strength	Pharmaceutical form	Animal species	Indications	Withdrawal period
Austria	Intervet GmbH Siemensstrasse 107 1210 Wien Austria	Porcilis PRRS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
Belgium	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	PORCILIS PRRS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
France	INTERVET RUE OLIVIER DE SERRES ANGERS TECHNOPOLE 49071 BEAUCOUZE France	PORCILIS PRRS IM	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
Germany	Intervet Deutschland GmbH Postfach 1130 85701 Unterschleißheim Germany	Porcilis PRRS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
Greece	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	PORCILIS PRRS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days

Ireland	Intervet Ireland Limited Magna Drive Magna Business Park Citywest Road Dublin 24 Ireland	Porcilis PRRS IM	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
Ireland	Intervet Ireland Limited Magna Drive Magna Business Park Citywest Road Dublin 24 Ireland	Porcilis PRRS IDAL	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
Italy	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Porsilis PRRS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
Luxembourg	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	PORCILIS PRRS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
Portugal	Intervet Portugal – Saúde Animal, Lda Rua Agualva dos Açores, n.º 16, 2735 – 557 Agualva-Cacém Portugal	PORCILIS PRSS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days

Spain	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	PORCILIS PRSS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
The Netherlands	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Porcilis PRRS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days
United Kingdom	Intervet UK Ltd. Walton Manor, Walton Milton Keynes, Bucks MK7 7AJ United Kingdom	Porcilis PRRS	live attenuated PRRS virus strain DV: $10^{4.0}$ - $10^{6.3}$ $TCID_{50}$ per dose	Lyophilisate and solvent for suspension for injection	Pigs	For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus	Zero days

Annex II

Scientific conclusions and grounds for the granting of the variation of the marketing authorisations

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF PORCILIS PRRS (SEE ANNEX I)

1. Introduction

Porcilis PRRS is an immunological veterinary medicinal product containing the Porcine Reproductive and Respiratory Syndrome (PRRS) virus. The live vaccine is composed of a lyophilised fraction, which includes the antigen, and a solvent for suspension for injection. The solvent includes dl-α-tocopherol acetate as adjuvant. It is indicated for use in breeding and finishing pigs from 2 weeks of age. For finishing pigs a single dose is given, which may be administered intradermally or intramuscularly.

The marketing authorisation holder Intervet International BV submitted a Type II variation application subject to the Mutual Recognition Procedure to the Marketing Authorisations of the veterinary medicinal product Porcilis PRRS in the framework of Article 6 of Commission Regulation (EC) No 1084/2003.

The variation of concern consists of allowing the mixing of two vaccines, Porcilis PRRS and Porcilis M Hyo, before administration. The lyophilised fraction of Porcilis PRRS (containing the live virus antigen) would be reconstituted in the inactivated vaccine Porcilis M Hyo. The proposed vaccination scheme for finishing pigs with the mixed product is: first administration of Porcilis M Hyo from one week of age followed by the administration of Porcilis PRRS mixed with Porcilis M Hyo from 4 weeks of age.

Following the absence of agreement between the Reference Member State (the United Kingdom) and one of the Concerned Member States (Spain) at day 90 of the CMDv procedure, the matter was referred to the CVMP on 2 October 2009. The National Competent Authority of Spain was concerned that some aspects regarding the quality and the efficacy after mixing the two products (Porcilis PRRS and Porcilis M Hyo) were not adequately justified.

2. Discussion

2.1 In-use shelf-life proposed after mixing the two products (Porcilis PRRS and Porcilis M Hyo)

The marketing authorisation holder has provided data of the PRRS virus titration after mixing Porcilis PRRS with Porcilis M Hyo at 0, 1, 2 and 3 hours. The results indicated that there was a limited drop in the PRRS virus titre after mixing with Porcilis M Hyo (average drop after the claimed 1 hour in-use shelf life of 0.05 log). This would support an in-use shelf life of one hour, except for the lack of information necessary to properly evaluate the results: the batch release protocols of the batches used and the protocols with the conditions of the assay were not provided. In order to ascertain that there is no significant decrease in the titre right after mixing (i.e., at t=0), it was considered important to know the titre at release (or after reconstitution in the diluent fraction of Porcilis PRRS). In addition, it was not known whether the studies were performed with batches of vaccines approaching the end of their shelf life.

Concerning Porcilis M Hyo the marketing authorisation holder has submitted data of adjuvant content (dl-α-tocopherol acetate), pH and sterility of the mixture after reconstitution of 2 batches of Porcilis PRRS in 2 batches of Porcilis M Hyo after storage for 3 hours at room temperature. In addition, it was considered that potency of the Porcilis M Hyo component

after mixing should have been analysed in order to the exclude a quality interference right after mixing (at t=0) and after the proposed in-use shelf life.

Batch release protocols for the in-use stability studies of Porcilis PRRS and Porcilis M Hyo were provided. The marketing authorisation holder provided data for PRRS virus titres of two batches of Porcilis PRRS reconstituted with each of ten batches of Porcilis M Hyo after 0, 1, 2 and 3 hours of storage at room temperature.

As regards why the stability studies were not performed with batches approaching the end of their shelf-life, the marketing authorisation holder has commented that there is no impact on the existing minimum titre proven to be efficacious:

1) The claimed in-use shelf life for the "mixed" product is one hour;
2) The apparent drop over 1 hour from the titre at release (6.4/6.2 $TCID_{50}$) is 0.12/-0.02 (mean 0.05) which is within assay variability;
3) The minimum efficacious titre is 4.0 $TCID_{50}$
4) this means that in the worst case scenario of a batch at the end of shelf being mixed there will be no statistically significant drop below the minimum titre over the claimed in-use shelf life of 1 hour.

As regards justifying why no potency test of the Porcilis M Hyo component has been carried out on the mixed vaccines both immediately after mixing and after the proposed in-use shelf life, the marketing authorisation holder has justified not performing a potency test for the Porcilis M Hyo component on the mixed vaccines that by provision of safety and efficacy studies using the mixed product the marketing authorisation holder has shown that there are no interactions within the mixture affecting the potency of the mixed product. The guideline on data requirements to support in-use stability claims for veterinary vaccines[1], states that "*For inactivated vaccines, if the proposed in-use shelf-life is within one working day (maximum 10 hours) it is acceptable to omit the potency testing from the in-use shelf-life stability study*."

2.2 Justification of the current claim for Porcilis PRRS concerning a significant improvement of rearing results (reduced morbidity due to PRRS infection, and a better daily growth and feed conversion) until the end of the fattening period when mixed with Porcilis M Hyo.

The claims of Porcilis PRRS, indications section of SPC (section 4.2) are:

"*For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia caused by infection with European strains of PRRS virus.*

Specific claims

For finishing pigs, the effect of the virus on the respiratory system is most relevant. A significant improvement of rearing results (reduced morbidity due to PRRS infection, an a better daily growth and feed conversion) until the end of the fattening period was observed in vaccinated pigs during field trials, particularly in piglets vaccinated at 6 weeks of age.

For breeding pigs…"

[1] CVMP Guideline on data requirements to support in-use stability claims for veterinary vaccines (EMEA/CVMP/IWP/250147/2008-CONSULTATION) - http://www.ema.europa.eu/pdfs/vet/iwp/25014708en.pdf

The marketing authorisation holder considers that the reduction of clinical signs is the direct effect of reduction of viraemia. Reduction of viraemia was shown in two laboratory efficacy studies and this was considered sufficient by the marketing authorisation holder for the assessment of the clinical efficacy.

However, it was considered that all the claims to appear in the SPC should be demonstrated. In addition to the above mentioned laboratory studies, the marketing authorisation holder has provided efficacy data for the mixed products of two field studies. In both of them, there was no gain in the average daily weight of the vaccinated animals, even when there were indications that PRRS infection had occurred. Therefore, the specific claim for finishing pigs of "*a significant improvement of rearing results (reduced morbidity due to PRRS infection and a better daily growth and feed conversion) until the end of the fattening period*" has not been demonstrated and the efficacy of the mixed product has not been proved.

The marketing authorisation holder has justified the absence of data demonstrating all efficacy claims for the mixed product. The marketing authorisation holder has justified by reference to the available data that the current efficacy claims for Porcilis PRRS are still supported when the two products are mixed. The marketing authorisation holder has demonstrated that the degree of protection conveyed by the individual products has not been altered by mixing the products by several laboratory challenge studies and field studies. These can be regarded as demonstrating equivalence of immune response and it would not be expected that if the immune response is not altered at one point in time that the duration of that response will be any different.

2.3 Potential impact on the efficacy parameter of duration of immunity due to an interference caused by mixing of the two products.

Data on two laboratory efficacy studies were provided showing that reduction of PRRS viraemia of pigs vaccinated with the mixed product is similar to the reduction of PRRS viraemia of pigs vaccinated with Porcilis PRRS alone. The serological response to PRRS vaccination was also found similar in both groups of pigs.

The marketing authorisation holder considered that, based on the Guideline on requirements for concurrent administration of immunological veterinary medicinal products[1], the efficacy data of the individual products, including duration of immunity, can be applied for the concurrent use of them if absence of immunological interference is demonstrated. Since the protective immunity against viraemia is not altered by the mixed administration, the marketing authorisation holder considered that all the other efficacy parameters will also not be altered, and therefore, no more data are required in support of the duration of immunity for the mixed administration.

The marketing authorisation holder has justified that the current duration of immunity for Porcilis PRRS is still supported when the two products are mixed. The marketing authorisation holder has demonstrated that the degree of protection conveyed by the individual products has not been altered by mixing the products by several laboratory challenge studies and field studies. These can be regarded as demonstrating equivalence of immune response and it would not be expected that if the immune response is not altered at one point in time that the duration of that response will be any different. The marketing authorisation holder has demonstrated that there is no immunological interference when the

[1] CVMP Guideline on requirements for concurrent administration of immunological veterinary medicinal products (EMEA/CVMP/550/02-FINAL) - http://www.ema.europa.eu/pdfs/vet/iwp/055002en.pdf

vaccines were mixed resulting in maintenance of the same level of efficacy by investigating one efficacy parameter, reduction in viraemia (reduction of 70-75% after simultaneous use and reduction of 72-75% after use of Porcilis PRRS alone). It should be borne in mind that PRRS is a multifactorial disease and therefore all clinical signs may not always be seen in laboratory studies (animals kept free from other agents) as in field studies. There is no reason to believe that other efficacy parameters would be influenced any differently in the field. The CVMP therefore considers that the efficacy of the mixed vaccine regarding the PRRS component has been sufficiently supported.

However the argumentation provided by the marketing authorisation holder to date raised some concerns that by mixing the products some of the efficacy claims for the monovalent products would not be achieved. The marketing authorisation holder was requested to provide additional data and justification that the efficacy claims and duration of immunity of Porcilis PRRS are not altered when the vaccine is administered mixed with Porcilis M Hyo. It should be noted that the general claim to reduce viraemia has only been demonstrated in laboratory studies. The specific claims for finishing pigs to improve the rearing results have not been demonstrated. Duration of immunity of Porcilis PRRS has also not been demonstrated for simultaneous administration. Nevertheless, absence of immunological interference has not been inferred but has been clearly demonstrated by providing laboratory challenge data which showed that there is no significant difference in protection between animals vaccinated with the mixed products and those vaccinated with single products.

3. Benefit / Risk assessment

There are both practical reasons as well as clinical advantages to administering these 2 products together which leads to an overall improvement in animal welfare. The in-use stability of the mixed vaccines has been adequately demonstrated over an in-use period of an hour which is sufficient to vaccinate the number of animals representative of a realistic scenario. The safety of the regimen for the both individual and mixed vaccines has been supported. The efficacy studies using appropriate challenges for Porcilis PRRS and Porcilis M Hyo have shown that there is no affect of simultaneous administration on the efficacy parameters of reduced viraemia and a reduction in lung lesions. Given that a lack of interference has been demonstrated at a specific time point the duration of immunity remains the same as originally proven. It should be noted that local and systemic reactions were unremarkable (mild and seen in a small proportion of animals) and consistent with those seen when vaccines were used alone. Thus, the overall the benefit/risk balance is considered to be positive.

GROUNDS FOR THE GRANTING OF THE VARIATION OF THE MARKETING AUTHORISATIONS

Whereas

- the CVMP considered that stability of the mixed product up to 1 hour after mixing as claimed on the Summary of Product Characteristics was supported by the data provided,
- the CVMP considered that the efficacy of the mixed vaccine regarding the PRRS component was sufficiently supported by the data provided,

the CVMP has recommended the granting of the variation of the Marketing Authorisations for Porcilis PRRS and associated names (see Annex I). The amendments of the relevant sections of the Summary of Product Characteristics and package leaflet are set out in Annex III.

Annex III

Amendments to the summary of product characteristics and package leaflet

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS

4.8 Interaction with other medicinal products and other forms of interaction

Safety and efficacy data for intramuscular injection are available in finishing pigs from 4 weeks of age onwards, which demonstrate that this vaccine can be mixed with Porcilis M Hyo.
The product literature of Porcilis M Hyo should also be consulted before administration of the mixed product.
No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product except the product mentioned above. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be decided on a case by case basis.
No information is available on the safety and efficacy of the use of Porcilis PRRS mixed with Porcilis M Hyo in breeding animals or during pregnancy.

4.9 Amounts to be administered and administration route

Reconstitute the vaccine with the corresponding adjuvating diluent (use only Diluvac Forte).

Number of doses per vial	Volume (ml) of diluent needed for	
	intramuscular injection	intradermal application
10	20	2
25	50	5
50	100	10
100	200	20

Dosage:
Intramuscular injection: 2 ml in the neck.
Intradermal application: 0.2 ml on top or to the left or right side of the neck, or along the muscles of the back, using an intradermal device.
A small, transient, intradermal lump observed after the intradermal application is indicative of the appropriate vaccination technique.

Vaccination scheme:
A single dose is given to pigs from 2 weeks of age onwards.

Finishing pigs: a single vaccination is sufficient for protection until slaughter.
Breeding pigs: For gilts a (re)vaccination 2-4 weeks before mating is recommended. To maintain a high and homologous level of immunity, revaccination at regular intervals is recommended, either before each next gestation or at random at 4 month intervals. Pregnant sows should only be vaccinated after previous exposure to European PRRS virus.

It is advised to vaccinate all target pigs within a herd from the earliest recommended age onwards. Maternally derived antibodies may interfere with the response to vaccination.
Newly introduced PRRS virus-naïve animals (e.g. replacement gilts from PRRS virus-negative herds) should be vaccinated prior to pregnancy.

The vaccine may be reconstituted shortly before vaccination for simultaneous use with Porcilis M Hyo in finishing pigs from 4 weeks of age and the following instructions should be used:

Porcilis PRRS		Porcilis M Hyo
10 doses	+	20 ml
25 doses	+	50 ml
50 doses	+	100 ml

100 doses + 200 ml
A single dose (2 ml) of Porcilis PRRS mixed with Porcilis M Hyo is given intramuscularly in the neck.
Use sterile syringes and needles or clean intradermal equipment.

6.2 Incompatibilities

Do not mix with any other veterinary medicinal product, except the diluent supplied with the product or with Porcilis M Hyo.

6.3 Shelf life

Freeze-dried vaccine:
12 months (after storage by the manufacturer at ≤-20°C during maximum 12 months)
Diluent: in glass vials 4 years, in PET vials 24 months
After reconstitution: 3 hours at room temperature.
After mixing with Porcilis M Hyo: 1 hour at room temperature

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE PACKAGE LEAFLET

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

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The vaccine may be reconstituted shortly before vaccination for simultaneous use with Porcilis M Hyo in finishing pigs from 4 weeks of age and the following instructions should be used:

Porcilis PRRS		Porcilis M Hyo
10 doses	+	20 ml
25 doses	+	50 ml
50 doses	+	100 ml
100 doses	+	200 ml

A single dose (2 ml) of Porcilis PRRS mixed with Porcilis M Hyo is given intramuscularly in the neck.

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9. ADVICE ON CORRECT ADMINISTRATION

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Safety and efficacy data for intramuscular injection are available in finishing pigs from 4 weeks of age onwards, which demonstrate that this vaccine can be mixed with Porcilis M Hyo.

The product literature of Porcilis M Hyo should also be consulted before administration of the mixed product.

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product except the product mentioned above. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be decided on a case by case basis.

No information is available on the safety and efficacy of the use of Porcilis PRRS mixed with Porcilis M Hyo in breeding animals or during pregnancy.

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11. SPECIAL STORAGE PRECAUTIONS

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After mixing with Porcilis M Hyo: 1 hour (at room temperature)