Annex I
List of the names, pharmaceutical form, strengths of the veterinary medicinal product, animal species, route of administration, marketing authorisation holder in the Member States

Member State (EU/EEA)	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Belgium	Ceva Santé Animale S.A/N.V. Metrologielaan 6 1130 Brussel Belgium	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection

Member State (EU/EEA)	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Animal species	Route of administration
Bulgaria	Ceva Animal Health Bulgaria ul. Elemag 26, vh.b, Et.1, Apt .1 Sofia -1113 Bulgaria	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Croatia	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Cyprus	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection

Member State (EU/EEA)	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Animal species	Route of administration
Czech Republic	Ceva Animal Health Slovakia, s.r.o. Račianska 153 831 53 Bratislava Slovakia	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Estonia	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne FRANCE	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Finland	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection

Member State (EU/EEA)	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Animal species	Route of administration
Germany	Ceva Tiergesundheit GmbH Kanzlerstr. 4 40472 Düsseldorf Germany	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Greece	Ceva Hellas LLC 15, Agiou Nikolaou str. 17455 ALIMOS Greece	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Hungary	CEVA-Phylaxia Veterinary Biologicals Co. Ltd Szállás u. 5. 1107 Budapest Hungary	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection

Member State (EU/EEA)	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Animal species	Route of administration
Iceland	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Ireland	Ceva Santé Animale 10, av. de La Ballastière, 33500 Libourne France	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Italy	Ceva Salute Animale S.p.A. Viale Colleoni 15, 20864 Agrate Brianza (MB) Italy	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection

Member State (EU/EEA)	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Animal species	Route of administration
Latvia	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Lithuania	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
The Netherlands	Ceva Sante Animale B.V. Tiendweg 8 c, 2670 AB Naaldwijk The Netherlands	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection

Member State (EU/EEA)	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Animal species	Route of administration
Poland	Ceva Animal Health Polska Sp. z o.o. ul. Okrzei 1A, 03-715 Warszawa Poland	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Portugal	Ceva Saúde Animal Produtos Farmacéuticos e Imunológicos, Lda. Rua Doutor António Loureiro Borges 9/9A - 9°A, Miraflores, 1495 – 131 Algès Portugal	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Romania	Ceva Santé Animale Romania Str. Chindiei nr. 5 Sector 4 040185 Bucharest Romania	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection

Member State (EU/EEA)	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Animal species	Route of administration
Slovakia	Ceva Animal Health Slovakia, s.r.o. Račianska 153 831 53 Bratislava Slovakia	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Slovenia	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection
Sweden	Ceva Animal Health A.B. Annedalsvägen 9 227 64 Lund Sweden	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection

Member State (EU/EEA)	**Marketing authorisation holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Animal species**	**Route of administration**
United Kingdom	Ceva Animal Health Ltd Unit 3, Anglo Office Park, White Lion Road Amersham, Bucks HP7 9FB United Kingdom	Coglapix suspension for injection for pigs	*Actinobacillus pleuropneumoniae* serotype 1 (strain NT3) and *Actinobacillus pleuropneumoniae* serotype 2 (strains PO, U3, B4, SZ II) expressing ApxI toxoid min. 28.9 ELISA unit/ml* ApxII toxoid min. 16.7 ELISA unit/ml ApxIII toxoid min. 6.8 ELISA unit/ml * Elisa unit/ml calculated serological titre in sera of immunised rabbits	Suspension for injection	Pigs	Intramuscular injection

Annex II

Scientific conclusions and grounds for the granting of the marketing authorisation for Coglapix suspension for injection for pigs

Overall summary of the scientific evaluation of Coglapix suspension for injection for pigs (*see Annex I*)

1. Introduction

Coglapix suspension for injection for pigs (hereafter called 'Coglapix') is an inactivated bacterial vaccine against porcine actinobacillosis. The vaccine contains five, formaldehyde-inactivated strains of *Actinobacillus pleuropneumoniae*. The strains belong to the serotype 1 or serotype 2 groups. The vaccine is supplied in multidose containers as a suspension for injection containing an aluminium hydroxide-based adjuvant. The vaccine is intended for active immunisation of pigs against pleuropneumonia caused by *A. pleuropneumoniae* serotypes 1 and 2, in order to reduce the clinical signs and lung lesions associated with the disease. The vaccination schedule is 2 doses administered to animals from 7 weeks of age with an interval of 3 weeks between doses. Onset of immunity is 21 days following second vaccination. Duration of immunity is 16 weeks following second vaccination.

The marketing authorisation holder (MAH), Ceva-Phylaxia Veterinary Biologicals Co. Ltd., submitted an application for mutual recognition of the marketing authorisation granted by Hungary in accordance with Article 32 of Directive 2001/82/EC. For the mutual recognition procedure (MRP), Hungary acted as a reference Member State and Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden and the United Kingdom were concerned Member States.

During the MRP the MAH reduced the initial indication from four clinical parameters (clinical signs, losses, lung lesions and infection associated with the disease) to only two i.e. reduction of clinical signs and lung lesions (both of which are included in the European Pharmacopoeia (Ph. Eur.) Monograph 04/2013:1360, Porcine Actinobacillosis Vaccines (inactivated)).

During the MRP Italy, as a concerned Member State, considered that Coglapix may present a potential serious risk to animal health. In particular, Italy considered that (i) the correlation between the reduction of lung lesions and the reduction of clinical signs has not been adequately demonstrated; (ii) the benefit of the vaccine under practical conditions of use (i.e. reduction of lung lesions and clinical signs resulting in reduced weight losses in vaccinated animals) has not been demonstrated and (iii) inconsistent results were obtained from duration of immunity studies. These issues remained unresolved and therefore a referral under Article 33(1) of Directive 2001/82/EC to the Coordination group for Mutual recognition and Decentralised procedures (veterinary) (CMD(v)) was started. Since the issues raised by Italy remained unresolved, the Member States concerned failed to reach agreement regarding the efficacy of Coglapix and consequently the matter was referred to the CVMP on 24 October 2014 under Article 33(4) of Directive 2001/82/EC.

The CVMP was asked to consider the available data supporting the efficacy of Coglapix and conclude whether the veterinary medicinal product may present a potential serious risk to the animal health.

2. Assessment of the data submitted

Efficacy data

The MAH submitted data from 12 laboratory studies and 3 field studies to support the efficacy claim. To demonstrate the immunogenicity of the vaccine, six laboratory efficacy studies were conducted to an acceptable standard and design to establish the onset and duration of immunity and meet the criteria of the Ph. Eur. Monograph 04/2013:1360. The MAH conducted 2 studies to evaluate the onset of immunity and 4 studies to evaluate the duration of immunity, using appropriate challenge strains for both *A. pleuropneumoniae* serotypes (1 and 2) included in the vaccine. In these studies vaccinated

animals showed lower incidence of the typical clinical signs (dyspnoea, coughing and vomiting) and lung lesions of porcine pleuropneumonia associated with infection by the microorganism when compared with controls.

Six additional laboratory studies were also provided, but these studies were carried out for the marketing authorisation of Coglapix in a country outside the EU and in some elements did not meet the criteria of Ph. Eur. Monograph 1360. The main difference was that the vaccine batch used in these studies had a higher antigen content than the minimum one proposed for the EU market.

Regarding the three field studies no significant differences in mortality rate and lung lesion scores were observed between vaccinated and control groups but the level of field challenge from *A. pleuropneumoniae* in the one significant field study was low.

The reduction of the indication to two clinical parameters required a further demonstration of significance for these two remaining efficacy parameters between vaccinates and controls. Although acknowledging the justifications provided by the MAH concerning the complexity of the topic and the technical difficulties encountered, a major question arose as to whether a parameter shown to be significant in one relevant study is sufficient to erase the non-significance of the same parameters in a "non-significant" study. The market sales over the past 15 years provided by the MAH were not considered sufficient to support the claims. Furthermore, the information gathered from Periodic Safety Update Reports was similarly considered to be only supportive and did not substantiate the claims. Based on these considerations, the MAH was requested to demonstrate that the significance shown for clinical signs in some laboratory efficacy studies is sufficient to overcome the non-significance of the same parameter in 'non-significant' laboratory efficacy studies.

The MAH presented the results of all the laboratory studies to support the efficacy claims. An overview of the statistical analyses to demonstrate significant differences between vaccinated and control animals in terms of reduction of clinical signs and lung lesions was also provided. Major issues concerning the complex nature of *A. pleuropneumaniae* infections, and compliance with the requirements of European Pharmacopoeia was also addressed. Special attention was given to the use of a combined analysis using a limited number of animals for sample size and the use of global clinical scores as measure of the primary efficacy parameter. The CVMP agreed that although the incidence of typical clinical signs and lung lesions were not significantly lower for vaccinates, when compared with controls, in all laboratory efficacy studies, the overall results of the efficacy of the vaccine were supportive for reduction of lung lesions and clinical signs. Therefore the relevant sections of the Summary of Product Characteristics and package leaflet should be amended in order to clearly reflect this conclusion.

Correlation between the reduction of lung lesions and the reduction of clinical signs

Although a positive correlation between the reduction of lung lesions and the reduction of clinical signs as a consequence of the vaccination is predictable, it was not possible to evaluate the magnitude of such a correlation. The MAH was requested to confirm, in writing, that the statistical analysis was performed using the results of relevant studies and to provide assurance the data-analysis method used was adequate and submit, if possible, a meta-analysis of all the results obtained from the different studies.

The MAH confirmed that the statistical analyses aiming to establish the correlation between reduction of lung lesions and reduction of clinical signs were performed using the results of all relevant studies (i.e., 12 challenge studies, 6 for each serotype). The MAH clarified that inferential statistics was used for the data analysis and addressed the relevance of the method used. Furthermore, it was confirmed that standardisation of variables was applied. Details of statistics were provided for each serotype in order to support the magnitude of the positive relationship between the two concerned measures. As

the correlation coefficient was highly significant in each case, the MAH concluded that it is very unlikely that the observed relationship between clinical and lung lesion scores is only due to chance. Specifically, the p-value is below 0.0001 which means that the probability of a false positive correlation is under 0.01%. The MAH confirmed that a meta-analysis of all the results obtained from the different studies has been provided.

When assessing the results of efficacy studies an additional point for concern was raised in relation to the consistency of the vaccine batches used for these trials. The variability of the results observed in the efficacy studies was suggested to be correlated with the quality of the vaccine batches administered in the trials, with sub-potent batches formulated with insufficient antigen content. Furthermore, the formulation of the finished product, either in terms of antigen content or of additional components, was questioned.

The MAH confirmed that the batches were produced according to a consistent manufacturing process under EU Good Manufacturing Practice (GMP) standards and of adequate quality for use in the efficacy trials. To complement the answer, the batch release protocols for two batches were provided revealing consistent germ-count-based target formulation. These batches had been tested according to the requirements when the product was first authorised in Hungary. However, the MAH confirmed that a re-test was carried out according to the finished product specifications agreed during the MRP and the vaccine batches were found to conform to them. The MAH confirmed that future commercial batches for the EU market will be produced based on fixed formulation targets and will be controlled in line with the finished product specifications agreed during the MRP. The MAH also provided clarification in relation to some discrepant data emerging from a comparative analysis of the batch protocols of the two vaccines.

In conclusion, the CVMP agreed that the MAH has provided satisfactory evidence that Coglapix is manufactured and tested to an acceptable quality standard regarding the batch potency test and consequently the appearance of clinical signs are correlated with the presence of lung lesions.

Efficacy of the vaccine under practical conditions of use

From the available laboratory efficacy studies, there was little evidence, if any, concerning the measurement of the impact of the vaccination on weight gain. Non-significant results have been obtained in 3 out of 5 studies carried out for both serotypes 1 and 2. Field trials have not corroborated the results obtained under laboratory conditions and there were concerns regarding the benefit of the vaccine under practical conditions of use.

The MAH was therefore requested to further support the conclusion that the efficacy of the vaccine under practical conditions of use has been adequately demonstrated. In particular, the MAH was requested to provide evidence that the reduction of lung lesions and clinical signs would result in reduced weight losses in vaccinated animals as compared to controls. Furthermore, the MAH was requested to comment on whether the significance (for both serotypes 1 and 2) of the results (concerning the impact on weight gain) shown in two laboratory studies is sufficient to erase the non-significance of the results in three ‘non-significant’ laboratory studies.

The MAH explained that the positive effect on clinical signs and lung lesions would lead to at least partial protection of the losses in weight gain due to *A. pleuropneumaniae* infections. However, the MAH clarified that the efficacy in the field has only been partially demonstrated and that lack of relevant information could be reflected in the Summary of Product Characteristics.

A sentence is included in section 5 Immunological properties of the Summary of Product Characteristics to reflect the lack of data from field trials. ‘Efficacy was demonstrated under laboratory but not under field conditions’. It is also considered that the indication is acceptable taking account of the intended use of the vaccine and the existing data from the laboratory studies.

Duration of immunity

Based on the assessment of the overall efficacy of Coglapix vaccine, duration of immunity was established for both serotypes (1 and 2) up to 16 weeks after vaccination according to the results of relevant challenge studies carried out at 16 and 24 weeks.

3. Benefit-risk assessment

Benefit assessment

Coglapix is intended for active immunisation of pigs against pleuropneumonia caused by *A. pleuropneumoniae* serotypes 1 and 2. Vaccination of pigs reduces the clinical signs and lung lesions associated with the disease, thus reducing the need for antimicrobial treatment and increasing the range of available prophylactic treatment possibilities against pneumonia caused by *A. pleuropneumoniae* serotypes 1 and 2. Healthier vaccinated pigs are expected to give better growth rates, although this was not demonstrated under field conditions.

Risk assessment

Quality and safety were not assessed in this referral procedure, as no concern was notified by the reference Member State.

This referral was raised due to concerns regarding the overall efficacy of the vaccine. Following vaccination of pigs with Coglapix reduction of clinical signs and lung lesions associated with the disease has been demonstrated in laboratory efficacy studies, although some concerns on the statistical significance of the results still remain. Therefore, the relevant sections of the Summary of Product Characteristics and package leaflet should be amended in order to reflect this (see Annex III).

Evaluation of the benefit-risk balance

The concern related to the overall efficacy of the vaccine have been assessed and it is concluded that Coglapix is expected to be efficacious in immunisation of pigs as an aid to control pleuropneumonia caused by *A. pleuropneumoniae* serotypes 1 and 2, by reducing the clinical signs and lung lesions associated with the disease.

Conclusion on the benefit-risk balance

Based on the data presented in relation to the concerns notified for this referral procedure, the benefit-risk balance is considered to be favourable. The CVMP concluded that the concerns expressed by Italy should not prevent the granting of marketing authorisations for Coglapix and recommended amendments in the relevant sections of the Summary of Product Characteristics and package leaflet (see Annex III).

Grounds for the granting of the marketing authorisations for Coglapix suspension for injection for pigs

Having considered all data submitted the CVMP concluded that:

- This referral was raised due to concerns regarding the overall efficacy of the vaccine. Coglapix is intended for active immunisation of pigs as an aid to control pleuropneumonia caused by *A. pleuropneumoniae* serotypes 1 and 2, and reduction of clinical signs and lung lesions associated with the disease has been demonstrated in laboratory studies.

Therefore the CVMP recommended the granting of the marketing authorisations for the veterinary medicinal products referred to in Annex I with amendments to the Summary of Product Characteristics

and package leaflet of the reference Member State. The amended sections of the Summary of Product Characteristics and package leaflet of the reference Member State are set out in Annex III.

Annex III

Amendments in the relevant sections of the Summary of Product Characteristics and package leaflet

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination Group procedure with the following amendments:

Add the following text in the relevant sections of the product information:

Summary of Product Characteristics

4.2 Indications for use, specifying the target species

For the active immunisation of pigs as an aid to control pleuropneumonia caused by *Actinobacillus pleuropneumoniae* serotypes 1 and 2, by reducing the clinical signs and lung lesions associated with the disease.
Onset of immunity: 21 days following second vaccination
Duration of immunity: 16 weeks following second vaccination

5. IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Actinobacillus/Haemophilus vaccine.

ATCvet code: QI09AB07

The vaccine contains inactivated *Actinobacillus pleuropneumoniae* bacteria. The total quantity is 20 x 10^9 inactivated germs per dose.

Strain NT3 belongs to the serotype 1, expressing ApxI whereas strains SzII, PO, U3 and B4 belong to the serotype 2, expressing ApxIII. All the strains express also ApxII.

Vaccinated pigs develop active immunity against disease caused by serotype 1 or 2 of *Actinobacillus pleuropneumoniae*. Efficacy was demonstrated under laboratory but not under field conditions.

…….

Package leaflet:

4. INDICATION(s)

For the active immunisation of pigs as an aid to control pleuropneumonia caused by *Actinobacillus pleuropneumoniae* serotypes 1 and 2, by reducing the clinical signs and lung lesions associated with the disease.
Onset of immunity: 21 days following second vaccination
Duration of immunity: 16 weeks following second vaccination

15. OTHER INFORMATION

Pharmacotherapeutic group: Actinobacillus/Haemophilus vaccine.

ATCvet code: QI09AB07

The vaccine contains inactivated *Actinobacillus pleuropneumoniae* bacteria. The total quantity is 20 x 10^9 inactivated germs per dose.

Strain NT3 belongs to the serotype 1, expressing ApxI whereas strains SzII, PO, U3 and B4 belong to the serotype 2, expressing ApxIII. All the strains express also ApxII.

Vaccinated pigs develop active immunity against disease caused by serotype 1 or 2 of *Actinobacillus pleuropneumoniae*. Efficacy was demonstrated under laboratory but not under field conditions.

…….