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Veterinary Medicines Division

Committee for Veterinary Medicinal Products

CVMP assessment report for a type II variation for Respiporc FLUpan H1N1 (EMEA/V/C/003993/II/0013)

Vaccine common name: Porcine influenza vaccine (inactivated)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, CEVA Santé Animale (the applicant), submitted to the European Medicines Agency (the Agency) on 30 April 2021 an application for a type II variation for Respiporc FLUpan H1N1.

1.2. Scope of the variation

Variation(s) requested		**Type**
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

To amend the product information to allow the use during pregnancy and lactation.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 3.

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

The applicant has submitted **two laboratory studies** in support of the safety for use in gilts and sows:

Study 1: *Evaluation of the safety of Respiporc FLUpan H1N1 in gilts after repeated administration of a single dose prior to insemination and during pregnancy*

Study 2: *Evaluation of the safety of Respiporc FLUpan H1N1 in gilts after repeated administration of a single dose during pregnancy and during lactation*

The studies were GLP compliant and followed the requirements in Ph. Eur. Monograph 0963 (01/2017), and Ph. Eur. 5.2.6 Evaluation of safety of veterinary vaccines and immunosera (section 1-4 on Examination of reproductive performance) and VICH GL 44. The study groups consisted of 10 to 12 gilts. The worst-case scenario using maximum potency batch and seronegative animals was followed in principle.

Together the two laboratory studies covered the period before insemination, each trimester during pregnancy and post-farrowing (during lactation). For study 1 the five vaccinations were given at 5 and 8 weeks before insemination and approximately 3 and 8 weeks after insemination as well as 3 weeks before expected farrowing date. In study 2 the four vaccinations were given approximately 6 and 3 weeks before the expected farrowing date and approximately 1 and 4 weeks after farrowing.

The gilts and sows were examined for injection site reactions according to the study protocol (on the day before each vaccination, once immediately before each vaccination, approximately 4 hours after each vaccination and once daily on days 1 to 4 after each vaccination) and a scoring system. No injection site reactions were observed.

Body temperatures were determined three times on the day before each vaccination, once immediately before each vaccination, approximately 4 hours after each vaccination and once daily on days 1 to 4 after each vaccination. The mean body temperature per group increased with a maximum of 0.16 °C and the highest increase for an individual gilt/sow was 0.9 °C.

For reproductive parameters, there were no differences between vaccinated and control gilts with regard to the proportion of live-born piglets, still-borne piglets and still-born mummified piglets.

Mean live weight of piglets did not differ between vaccinated and control groups (Study 1: test item: 1330 g, reference item: 1184 g; p=0.0639; Study 2: test item: 1305 g, reference item: 1361 g; p=0.5408).

In conclusion, no injection site reactions were observed after the vaccinations. Mean increases in body temperatures were limited and maximum increases in individual animals were up to 0.9 °C. Vaccination did not affect reproductive performance seen as proportion of live-borne piglets and proportion of still-borne piglets.

A GCP compliant **field study** was submitted.

Field study to test the safety and serology of Respiporc FLUpan H1N1 after basic and booster vaccination in gilts and sows at all stages of gestation and during lactation in Germany

The study was designed as a placebo controlled randomised, blinded study conducted on a single farm in Germany. 200 gilts / sows were included which belonged to four different stages their reproductive cycle: Stage 1 were pregnant gilts / sows in their first trimester, stage 2 were in their second trimester, stage 3 were in their third trimester of pregnancy, and animals from stage 4 were lactating sows.

On study days 0 and 21 the animals received the basic vaccination. On study day 147 (each stage at the same point in cycle as at first vaccination) all animals were booster vaccinated with a single dose of Respiporc FLUpan H1N1.

The gilts/sows were monitored for systemic reactions (day before each vaccination, on the day of each vaccination (prior to each vaccination and at 4 hours (h) post each vaccination) as well as 1, 2, 4, 7, 10 and 14 days after each vaccination), rectal temperature (the day before each vaccination, on the day of each vaccination (prior to each vaccination and 4 hours post each vaccination) as well as 1 and 2 days after each vaccination), and injection site reactions (prior to each vaccination and 4 hours post each vaccination, as well as 1, 2, 4, 7, 10 and 14 days after each vaccination).

Safety for reproduction was evaluated by the number of live born piglets, stillborn piglets, mummies as well as viable piglets (no deficiencies that make the piglet incapable of surviving). As the study included a booster vaccination during the following reproduction cycle, the study was conducted over 2 farrowings for stage groups 1 – 3.

For all stage groups the highest increases in rectal temperature were mostly observed at 4 hours post each vaccination and lasted for no longer than 1-2 days. The highest individual increase was 2.0 °C in the IVP group, and the mean increases were low (highest value 0.33 °C) and not significantly different between groups.

There were no local reactions at the injection site in either of the treatment groups during the three vaccination periods. There were no abnormal findings in either of the treatment groups during the three vaccination periods regarding the general condition parameters behaviour, respiration, skin and digestion.

There were no significant differences between the treatment groups with regard to reproductive performance. Data on live-borne and still-borne piglets were given as absolute litter sizes and as proportions.

Before the first vaccination 83% (IVP) to 87% (CP) animals had serum-neutralizing antibodies against Influenza A virus/Jena/VI5258/2009(H1N1)pdm09. Seven days after the 2nd placebo vaccination the ratio of seropositive animals had increased to 97% among the control animals, indicating circulation of field influenza A virus of the H1N1pdm 09 subtype among the animals.

Active field infection(s) with strains of pan H1 subtype had been indicated to be widespread by serological investigations of the animals prior to the start of the field study. Circulation of pan H1N1 influenza A virus among the animals before vaccination (and potentially after vaccination) with Respiporc FLUpan H1N1 would imply that a major part of the animals was not immunologically naïve to the pan H1N1 antigens of the vaccine. This again would likely play a significant role for the determined 'boosting' of the specific serum antibody titers detected in the field study.

In conclusion, the field study supports that the vaccine is well tolerated in a seropositive herd in the investigated periods of gestation in pregnant gilts and sows with no apparent negative effects on reproductive parameters.

Overall, adequate data on vaccination of seronegative gilts have been presented in the laboratory studies, and supportive safety data have been provided in a field study in seropositive animals.

The wording in section 4.7. has been updated accordingly to state:

"Can be used during pregnancy up to three weeks before expected farrowing and during lactation."

The following wording **in bold** has been added to section 4.9 of the SPC:

Piglets:

2 injections of one dose (1 ml) from the age of 56 days, with an interval of 3 weeks between injections.

The efficacy of revaccination**s** has not been investigated and therefore no revaccination schedule is proposed.

Maternally-derived antibodies in piglets interfere with the RESPIPORC FLUpan H1N1 mediated immunity. Generally, maternally-derived antibodies induced by vaccination last for approximately 5–8 weeks after birth.

In cases of exposure of the sows to antigens (from either field infections and/or vaccination) the antibodies transmitted to the piglets can interfere with active immunisation at 12 weeks of age. In such cases the piglets should be vaccinated after the age of 12 weeks.

Gilts and sows:

Primary vaccination: 2 injections of one dose (1 ml) with an interval of 3 weeks between injections and up to 3 weeks before expected farrowing or during lactation.

The efficacy of single dose revaccination has not been investigated and therefore no single dose revaccination schedule is proposed for further pregnancies.

Potential clinical significance of antigenic differences between recent field strains and the pan H1 component of the vaccine (antigenic drift) was not addressed in the studies submitted with this variation application. This issue was not pursued as the present variation only concerns safety issues.

3. Benefit-risk assessment of the proposed change

Respiporc FLUpan H1N1 is a suspension for injection for pigs authorised for the treatment of active immunisation of pigs from the age of 8 weeks onwards against pandemic H1N1 porcine influenza virus to reduce viral lung load and viral excretion. The vaccine contains inactivated influenza A virus/human, strain A/Jena/VI5258/2009(H1N1)pdm09, as active substance.

The proposed variation is to amend the product information to allow the use in gilts and sows during pregnancy and lactation.

The current product information for the vaccine states in section 4.7 that "The safety of the veterinary medicinal product has not been established during pregnancy and lactation". It is proposed that this statement is replaced by **"The vaccine can be used during pregnancy up to three weeks before expected farrowing and during lactation"**.

In addition, for section 4.9 of the SPC the text has been modified **in bold** to include recommendation for use of the vaccine in gilts and sows:

Piglets:

2 injections of one dose (1 ml) from the age of 56 days, with an interval of 3 weeks between injections.

The efficacy of revaccination**s** has not been investigated and therefore no revaccination schedule is proposed.

Maternally-derived antibodies in piglets interfere with the RESPIPORC FLUpan H1N1 mediated immunity. Generally, maternally-derived antibodies induced by vaccination last for approximately 5–8 weeks after birth.

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Gilts and sows:

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3.1. Benefit assessment

Direct therapeutic benefit

The main benefit is that the provided safety data concerning gilts and sows supports the conclusion that the vaccine is considered safe for use in this category of pigs as indicated in the SPC. The variation will allow vaccination during pregnancy and lactation and will therefore expand the range of pigs which can be vaccinated.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Respiporc FLUpan H1N1 was generally well tolerated in the majority of animals with acceptable range of only a minimal temperature increase, apparently no negative effect on reproduction and absence of local and systemic reactions.

Concerns were raised with regard to the range of temperature increases after vaccination (including maximum body temperatures measured), missing data for litter sizes, and health status information from the field study site. Those issues have been satisfactorily addressed.

3.3. Risk management or mitigation measures

In general, appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal and to provide advice on how to prevent or reduce these risks. Questions raised in order to verify that the information on the temperature increase and frequency in the SPC were addressed, have been resolved by the data presented in this variation.

User safety:

User safety will not be affected by this variation.

Environmental safety:

Environmental safety is not affected by this variation.

Consumer safety:

Consumer safety is not affected by this variation.

3.4. Evaluation of the benefit-risk balance

Based on the data presented on the safety when used in gilt and sows the overall benefit-risk is deemed positive.

4. Conclusion

Based on the original and complementary data presented on safety the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Respiporc FLUpan H1N1 is approvable.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB

Please refer to the separate product information showing the tracked changes.

As a consequence of this variation, section 4.7 and 4.9 of the SPC is updated. The corresponding section of the Package Leaflet is updated accordingly.