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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP annual re-assessment report for COXEVAC (EMEA/V/C/000155/S/0007)

Common name: Q fever vaccine (inactivated)

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

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Background information on the annual reassessment

1.1. Submission of the application

A marketing authorisation under exceptional circumstances was granted on 30 September 2010 by the European Commission for COXEVAC.

On 14 July 2014 the marketing authorisation holder (MAH), Ceva Santé Animale, pursuant to Article 39(7) of Regulation 726/2004/EC submitted to the European Medicines Agency (the Agency) an application for the fourth annual re-assessment of COXEVAC and conversion of the marketing authorisation (MA) of the vaccine currently under exceptional circumstances to a normal status based on claim that the specific obligation is fulfilled.

This is the fourth annual re-assessment for COXEVAC (that is, re-assessment of the benefit-risk balance). The CVMP opinion on the previous annual re-assessment (third annual reassessment) was adopted on 14 January 2014.

1.1.1. Scope of the annual reassessment

This annual re-assessment relates to the following specific obligation:

- An efficacy confirmatory study in goats under laboratory or field conditions should be performed, establishing a duration of immunity, based on a reduction of abortions and/or a reduction in shedding (duration, intensity, frequency) in milk (which seems to be the main route of bacterial shedding), and/or faeces, and/or vaginal excretion. The corresponding claim would then be established in compliance with the parameters tested, and the results obtained (when satisfactory). This trial should be conceived in a way showing consistency with the vaccination scheme (time and number of injections, minimum age at vaccination). The maximum time allowed to prepare the report should be 1 year after the claimed duration of immunity.

1.2. Steps taken for the assessment of this annual reassessment

- The application for the COXEVAC annual re-assessment was submitted on 30 June 2014.
- The procedure started on 14 July 2014.
- A list of questions was adopted on 11 September 2014.
- Responses from the MAH to the list of questions were received by 7 October 2014.
- The CVMP adopted an opinion on 6 November 2014.
- On 12 January 2015, the European Commission adopted a Commission Decision for this application.

2. Scientific discussion

2.1. Assessment

The MAH submitted documentation to address firstly the specific obligation (concerning the goat claim) and also the recommendation remaining from procedure EMEA/V/C/000155/IB/001/G (stability data in 100 ml bottles).

2.1.1. Specific obligation

The company conducted 2 trials in goats to fulfil the specific obligation in compliance with the scientific advice which the CVMP adopted in June 2011.

The first study aimed to determine the duration of efficacy in goats, whilst the second study aimed to establish the efficacy of a single dose re-vaccination given one year after the initial vaccination.

Study 1 - to determine the duration of immunity of COXEVAC vaccine in goats

Method:

The objective of this study was to determine the duration of immunity in goats.

This first study was performed using 80 female goats negative for *C. burnetii* which were initially included in the trial. The goats came from a farm without abortion and with tank milk negative to *C. burnetii* by polymerase chain reaction (PCR) and with adult animals seronegative by screening by Q fever enzyme-linked immunosorbent assay (ELISA) test. They had not previously been vaccinated against *Coxiella burnetii* and were 3 months old at time of vaccination.

Half of the goats (40 animals) received one dose of COXEVAC, 2 times, 21 days apart (D0 being the day of first injection and D21 the second day of injection); 4 animals died because of coccidiosis before the 2nd injection. The other half of the goats (40 animals) served as controls.

Post-vaccination follow-ups consisted of blood sampling from D21 (day of second injection) to D384 for serology (ELISA) and vaginal swab sampling up to D384 for qualitative real-time PCR. Also any unusual events or diseases were recorded.

Goats were then synchronized (non-seasonal induced oestrus at D318) and mated at around 14 months of age (at D337). They were examined for pregnancy at D384, D393 and D407: only 21 goats were diagnosed as pregnant: 14 vaccinated animals and 7 control animals.

Pre-challenge follow-up consisted of blood sampling at D404 and D408 for serology (ELISA); faeces and vaginal swab sampling at D404 and D408 for PCR; and individual clinical examination at D407, D411 and D412 (including rectal temperature at D411 and D412 (before challenge)).

Challenge of the pregnant goats was performed with *C. burnetii* strain CbC1 at D412, carried out at the time of 75 ± 7 days of pregnancy. The *C. burnetii* strain CbC1 was originally isolated from the placenta of an aborted goat seropositive for Q fever in France.

Post-challenge follow-up consisted of general health recording (rectal temperature from D413 to D415 and from D418 to D422; rectal temperature above 39.6 °C was regarded as fever); faeces and vaginal swab sampling at D426, D440, D454 and D468 for PCR; delivery/abortion on an ongoing basis (Dpk0 being the day of kidding or abortion for each goat). A parturition was considered as an abortion when foetus(es) died at kidding, when kids do not survive more than 24 hours and when goats give birth to weak kids. The parturition parameters (date of kidding, viable or dead kid, death of kid within 24 hours) were recorded. In case of twin kids, if one of them was not viable, the kidding was regarded as an abortion case.

Post-delivery/abortion follow-up: the post-challenge observation period lasted till the 35th day after kidding or abortion (DpK35), and the following parameters were noted:

- primary parameters:

  Abortion, as follows: Proportion of abortions; Proportion of *C. burnetii* infected placenta at parturition; Proportion of *C. burnetii* infected aborted foetuses and non-viable kids.

  C. burnetii excretion, as follows: shedding of *C. burnetii* in faeces; shedding of *C. burnetii* in milk; shedding of *C. burnetii* in vaginal mucus.

  Faeces, vaginal swab, placenta and milk samples were taken as follows: faeces at Dpk0 up to Dpk35; vaginal mucus at Dpk0 up to Dpk35; milk at Dpk0 up to Dpk35; cotyledon (3 per placenta) and stomach content of aborted foetuses/non-viable kids after the event, for differential diagnosis (to check for *Coxiella burnetii*, *Chlamydophila abortus* and *Toxoplasma gondii* by PCR).

- secondary parameters: daily individual clinical examination and rectal temperature.

Euthanasia and necropsy of the goats (at Dpk35) – end of the animal phase on D530. Kids originating from normal birth were neither necropsied nor sampled.

Statistical analyses:

Comparison of the percentage of aborting goats by Fisher's exact test between both groups.

Comparison of the ratio of aborted or non-viable kids by using the cluster-adjusted version of Pearson chi-square test. The adjustment was needed because the sample units were the goats, not the foetuses.

Comparison of the difference in percentages of goats that shed *C. burnetii* (positive qualitative PCR results) between the two groups, for each route of excretion and on each day, by one-sided Fisher's exact tests.

Comparison of the level of excretion (quantitative PCR) between the two groups, for each route of excretion and on each day, by the Wilcoxon rank-sum test.

Results:

- Serology:

The ELISA results obtained during phase I and phase II before challenge showed that only the vaccination triggered an immune response in the vaccinated animals. The control animals remained seronegative until challenge.

- Protection against abortion caused by *Coxiella burnetii*

The COXEVAC vaccine had a significant effect against abortion in the vaccinated goats. The proportion of observed abortions was 71.4% (five abortions versus two normal kidding) in the unvaccinated/control group whereas this proportion was 21.4% in the vaccinated group (three abortions versus 11 normal kidding). The difference was statistically significant between the two groups (one-sided Fisher exact test, p=0.0408).

The vaccine increased the ratio of viable kids after parturition. The rate of non-viable or aborted kids was significantly higher in the control group (71.4% - 10 aborted or non-viable kids versus 4 viable kids) comparing to the vaccinated group (11.1% - 3 aborted or non-viable kids versus 24 viable kids) (cluster-adjusted version of Pearson chi-square test, p=0.0017).

- Protection against shedding via placenta

The vaccine had a significant effect in the goats against shedding via the placenta. Both the ratio of shedder goats and the number of shed bacteria was significantly higher in the control group after challenge.

Ratio of positive placentas: The proportion of placenta contamination by *C. burnetii* was significantly higher in the control group (100%) than in the vaccinated group (14.3%), (one-sided Fisher's exact test, p=0.0003).

Quantity of excreted C. burnetii: In the control group, the mean level of excretion reached 9.3 $\log_{10}$ *Coxiella burnetii*/g at parturition (Dpk0), whereas in the vaccinated group the mean level of excretion was less than 50 *C. burnetii*/g. The excretion in placenta was significantly higher in the control group (Wilcoxon rank-sum test, p=0.0001).

- Protection against shedding via faeces

The vaccine had a significant effect in the goats against shedding via faeces. Both the ratio of shedder goats and the number of shed bacteria was significantly higher in the control group after challenge.

Ratio of shedder animals: After experimental infection, the percentage of goats excreting *C. burnetii* via faeces was higher in the control group than in the vaccinated group at each time point, except on D454. From D468 to Dpk35 the rate of animals excreting *C. burnetii* in faeces was significantly higher in the control group than in the vaccinated group (one sided Fisher's exact test, $p \leq 0.003$).

Quantity of excreted C. burnetii: In the control group, the mean level of excretion in faeces reached 6.5 $\log_{10}$ *C. burnetii*/g on D468 and 6.6 $\log_{10}$ *C. burnetii*/g at parturition (Dpk0) whereas in the vaccinated group the mean level of excretion in faeces never exceeded 400 *C. burnetii*/g (2.6 $\log_{10}$). The excretion in faeces was significantly higher in the control group on all days from D56 to Dpk35 than in the vaccinated group (Wilcoxon rank-sum test, $p<0.001$).

- Protection against shedding via vaginal mucus

The vaccine had a significant effect in the goats against shedding via vaginal mucus. Both the ratio of shedder goats and the number of shed bacteria were significantly higher in the control group after challenge.

Ratio of shedder animals: After experimental infection, the percentage of goats excreting *C. burnetii* in vaginal mucus was higher in the control group than in the vaccinated group at each time point, except on D426. From D468 to Dpk35 the rate of animals excreting *C. burnetii* via vaginal mucus was significantly higher in the control group than in the vaccinated group (one sided Fisher's exact test, $p \leq 0.002$).

Quantity of excreted C. burnetii: In the control group, the mean level of excretion in vaginal mucus reached 7.3 $\log_{10}$ *C. burnetii*/ml on D468 and 8.7 $\log_{10}$ *C. burnetii*/ml at parturition (Dpk0) whereas in the vaccinated group the mean level of excretion in vaginal mucus never exceeded 100 *C. burnetii*/ml. The excretion in vaginal mucus was significantly higher in the control group on all days from D468 to Dpk35 (Wilcoxon rank-sum test, $p<0.001$).

- Protection against shedding via milk

The vaccine had a significant effect in the goats against shedding via their milk. Both the ratio of shedder goats and the number of shed bacteria were significantly higher in the control group after parturition.

Ratio of shedder animals: From Dpk0 to Dpk35 the excretion of *C. burnetii* via milk was significantly higher in the control group than in the vaccinated group (one sided Fisher's exact test $p < 0.03$).

Quantity of excreted C. burnetii: In the control group the mean level of excretion in milk reached 5.5 $\log_{10}$ *C. burnetii*/ml on Dpk2, whereas in the vaccinated group the mean level of excretion in milk never exceeded 50 *C. burnetii*/ml. The excretion in milk was significantly higher in the control group on all days from Dpk0 to Dpk35 (Wilcoxon rank-sum test, $p<0.0002$).

Conclusion:

The protocol for this study was correctly scheduled and the results demonstrated that COXEVAC significantly reduced the rate of abortion, the shedding of bacteria via faeces, vaginal mucus, placenta and milk after a challenge of goats with *C. burnetii* 1 year after the initial vaccination.

The CVMP considered that the duration of immunity of COXEVAC vaccine had been sufficiently demonstrated to be at least one year after the initial vaccination.

Study 2 – efficacy assessment of the yearly single dose re-vaccination with COXEVAC vaccine in goats.

Method:

The objective of this study was to establish the efficacy of a single dose re-vaccination given one year after the initial vaccination.

This second study was performed with 52 female goats negative for *C. burnetii* which were initially included in the trial. The goats came from a farm without abortion and with tank milk negative to *C. burnetii* by PCR and with adult animals seronegative by screening with Q fever ELISA test. They had never been vaccinated against *Coxiella burnetii* and were 3 months old at time of vaccination.

Pre-vaccination sampling comprised blood sampling for serology (ELISA) at D-35 and vaginal swab sampling for qualitative real-time PCR at D-34 (to confirm that the goats are negative for *C. burnetii*).

Half of the goats (26 animals) received the primary vaccination course of COXEVAC (that is, one dose subcutaneous (SC) of COXEVAC, 2 times, 21 days apart (D0 being the day of first injection and D21 the second day of injection). 2 animals died because of coccidiosis at D22. The other half of the goats (26 animals) served as controls.

Post-initial vaccination follow-ups consisted of blood sampling from D42 to D422 for serology (ELISA). Also any unusual events or diseases were recorded.

The goats in group 1 all received a booster injection (one dose SC of COXEVAC) on D429. The goats in group 2 (controls) remained unvaccinated.

All the goats were naturally mated at around 18 months of age (at D456) at the time of natural seasonal oestrus. They were examined for pregnancy between D496 and D527: 44 goats were diagnosed as pregnant (22 vaccinated animals and 22 control animals).

Pre-challenge follow-up consisted of blood sampling at D503 and D523 for serology (ELISA); vaginal swab sampling at D503 and D523, and faeces samples at D523 for PCR, plus individual clinical examination at D527/528 and D531 (including rectal temperature at D530 and D531 (before challenge)).

Challenge of the pregnant goats was performed with *C. burnetii* strain CbC1 at D531, carried out at the time of 75 ± 7 days of pregnancy, as in the previous study and using the same strain as in the previous study.

Post-challenge follow-up consisted of general health recording (rectal temperature from D532 to D541; rectal temperature above 39.6 °C was regarded as fever); faeces and vaginal swab sampling at D546, D559, D573 and D587 for PCR; delivery/abortion on an ongoing basis (Dpk0 being the day of kidding or abortion for each goat) using the same criteria for abortion as in the study above.

The parturition parameters (date of kidding, viable or dead kid, death of kid within 24 hours) were recorded. In case of twin kids, if one of them was not viable, the kidding was regarded as an abortion case.

Post-delivery/abortion follow-up: the post-challenge observation period lasted till the 35th day after kidding or abortion, and the following parameters (each exactly as in the study above) were noted:

Abortion, as follows: Proportion of abortions; Proportion of *C. burnetii* infected placenta at parturition; Proportion of *C. burnetii* infected aborted foetuses and non-viable kids.

C. burnetii excretion, as follows: shedding of *C. burnetii* in faeces; shedding of *C. burnetii* in milk; shedding of *C. burnetii* in vaginal mucus.

Faeces, vaginal swab, placenta and milk samples were taken as follows: faeces at Dpk0 up to Dpk35; vaginal mucus at Dpk0 up to Dpk35; milk at Dpk0 up to Dpk35; cotyledon (3 per placenta) and stomach content of aborted foetuses/non-viable kids after the event, for differential diagnosis (to check for *Coxiella burnetii*, *Chlamydophila abortus* and *Toxoplasma gondii* by PCR).

Euthanasia and necropsy of the goats (at Dpk35) – end of the animal phase on D530. Kids originating from normal birth were neither necropsied nor sampled.

Statistical analyses were performed exactly as per the previous study and described above.

Results:

- Serology

The ELISA results obtained during phase I and phase II before challenge show that only the vaccination triggered immune response in the vaccinated animals. The control animals remained seronegative until challenge.

- Protection against abortion caused by *Coxiella burnetii*

The COXEVAC vaccine had a significant effect in the goats against abortion after excluding through differential diagnosis some abortions due to *Toxoplasma gondii* and *Chlamydophila abortus*, or due to *C. abortus* and *C. burnetii* together. The proportion of observed abortions was 47.6% (10 abortions versus 11 normal kidding) in the control group whereas this proportion was 4.5% in the vaccinated group (one abortion versus 21 normal kidding). The difference was statistically significant between the two groups (one-sided Fisher exact test, p=0.0014).

The vaccine increased the ratio of viable kids after parturition. The rate of non-viable or aborted kids caused by *C. burnetii* was significantly higher in the control group (48.3%) (14 aborted or not viable kids versus 15 viable kids) comparing to the vaccinated group (6.1%) (two aborted or not viable kids versus 31 viable kids) (cluster-adjusted version of Pearson chi-square test, p=0.0016).

- Protection against shedding via placenta

The vaccine had a significant effect in the goats against shedding via the placenta. Both the ratio of shedder goats and the number of shed bacteria was significantly higher in the control group after challenge.

Ratio of positive placentas: The proportion of placenta contamination by *C. burnetii* was significantly higher in the control group (100%) than in the vaccinated group (23.8%), (one-sided Fisher's exact test, p=0.0000).

Quantity of excreted C. burnetii: In the control group the mean level of excretion reached 9.3 $\log_{10}$ *Coxiella burnetii*/g at parturition (Dpk0) whereas in the vaccinated group the mean level of excretion was less than 60 *C. burnetii*/g. The excretion in placenta was significantly higher in the control group (Wilcoxon rank-sum test, p=0.0000).

- Protection against shedding via faeces

The vaccine had a significant effect in the goats against shedding via faeces. Both the ratio of shedder goats and the number of shed bacteria was significantly higher in the control group after parturition.

Ratio of shedder animals: After abortion/kidding from Dpk0 to Dpk35 (Dpk = day post-kidding/abortion), the ratio of goats excreting *C. burnetii* in faeces was significantly higher in the control group compared to the vaccinated animals (one sided Fisher's exact test, p≤0.002).

Quantity of excreted C. burnetii: In the control group, the mean level of excretion in faeces reached 8.76 $\log_{10}$ *C. burnetii*/g at parturition (Dpk0); whereas in the vaccinated group, the mean level of excretion in faeces never exceeded 800 *C. burnetii*/g (2.9 $\log_{10}$/g). From the parturition (Dpk0) until the end of the observation period (Dpk35), the excretion via faeces was significantly higher in the control group than in the vaccinated animals (Wilcoxon rank-sum test, p<0.001).

- Protection against shedding via vaginal mucus

The vaccine had a significant effect in the goats against shedding via vaginal mucus. Both the ratio of shedder goats and the number of shed bacteria was significantly higher in the control group after parturition.

Ratio of shedder animals: After parturition (from Dpk0 to Dpk35), the ratio of goats excreting *C. burnetii* via vaginal mucus was significantly higher in the control group than in the vaccinated group (one sided Fisher's exact test, p≤0.001).

Quantity of excreted C. burnetii: In the control group, the mean level of excretion in vaginal mucus reached 8.91 $\log_{10}$ *C. burnetii*/ml at parturition (Dpk0); whereas in the vaccinated group, the mean level of excretion in vaginal mucus never exceeded 200 (≤2.3 $\log_{10}$) *C. burnetii*/ml. From Dpk0 until the end of the observation period (Dpk35), the excretion via vaginal mucus was significantly higher in the control group than in the vaccinated group (Wilcoxon rank-sum test, p<0.0001).

- Protection against shedding via milk

The vaccine had a significant effect in the goats against shedding via milk. Both the ratio of shedder goats and the number of shed bacteria significantly higher in the control group after parturition.

Ratio of shedder animals: After experimental infection, from the parturition (Dpk0) to Dpk35, the ratio of goats excreting *C. burnetii* in milk was significantly higher in the control group than in the vaccinated group at each time point (one sided Fisher's exact test, p<0.001).

Quantity of excreted C. burnetii: In the control group, the mean level of excretion in milk reached 4.84 $\log_{10}$ *C. burnetii*/ml one day after parturition (Dpk1); whereas in the vaccinated group, the mean level of excretion in milk never exceeded 40 (1.6 $\log_{10}$) *C. burnetii*/ml. From Dpk0 (i.e. after abortion/kidding) to Dpk35, the excretion via milk was significantly higher in the control group than in the vaccinated group (Wilcoxon rank-sum test, $p<0.0001$).

Conclusion

The protocol for this study was correctly scheduled and the results demonstrated that a single dose booster revaccination of goats with COXEVAC vaccine 3 weeks before the pregnancy significantly reduced the rate of abortion, the shedding of bacteria via faeces, vaginal mucus, placenta and milk after a laboratory challenge with *C. burnetii*.

2.1.2. Recommendation

The following recommendation arose from procedure EMEA/V/C/000155/IB/001/G (quality) to extend the shelf life of the product to 24 months: "However, the results of another additional batch (100 ml plastic bottle) need to be provided post-authorisation within an acceptable time frame. A timetable should be provided for agreement by the Agency."

The MAH committed to place a second batch of the product in 100 ml plastic bottles in a stability study in early 2013, and to test the product up to 27 months. Data from this confirmatory stability testing were provided for up to 9 months testing, however as this stability study is still ongoing (and not due to finish before late 2015) the CVMP concluded that the recommendation is still pending and therefore no changes were necessary.

2.2. Variations

The following variations or changes have been granted since the initial granting of this marketing authorisation:

- An extension of the shelf life of the finished product to 24 months, approved in May 2011 (procedure EMEA/V/C/000155/IB/001/G).
- Updating of the sections 4.5 and 4.7 of the SPC linked to the decrease in milk production in goats, approved in October 2012 (as a result of the 2nd annual reassessment, procedure EMEA/V/C/000155/S/003).
- Waiving of the Target Animal Batch Safety Test, approved in March 2013. (This was a notification following changes implemented in the Ph. Eur. monograph.)
- An extension of the shelf life of the active ingredient to 12 months, approved in July 2014 (procedure EMEA/V/C/000155/II/006).

2.3. Summary and conclusions

In this annual re-assessment, data were provided to address the (only) specific obligation, which concerned the duration of immunity in goats (detailed in section 1.1.1 of this report).

Two trials were presented to confirm the duration of immunity in goats. Both of the trials had been designed in an appropriate manner and the CVMP concluded that the results demonstrated that, when administered to goats as recommended in the SPC:

- The vaccine reduced the rate of abortion, the shedding of bacteria via faeces, vaginal mucus, placenta and milk in goats 1 year after the initial vaccination.
- A single booster injection 3 weeks before the pregnancy significantly reduced the rate of abortion, the shedding of bacteria via faeces, vaginal mucus, placenta and milk after a challenge with *C. burnetii*.

The CVMP therefore concluded that the only specific obligation had been satisfactorily fulfilled.

The CVMP noted that the MAH is still required to finalise the stability recommendation arising from procedure EMEA/V/C/000155/IB/001/G and not linked to this annual reassessment as the stability study has not yet been completed, and therefore that one recommendation is still pending.

As a result of the satisfactory resolution of the only specific obligation the CVMP considered that a conversion of the marketing authorisation provided under exceptional circumstances to normal status should be recommended.

The CVMP also concluded that the information included in the pharmacovigilance data submitted for this vaccine to date was acceptable, and that based on these data, no update of the SPC and other product information is deemed necessary due to safety concerns. The CVMP considered that the periodic safety update report (PSUR) cycle did not need to be restarted as goats were authorised as a target species when the vaccine was initially authorised in 2010. Furthermore adverse effects reported on goats had already been considered by the CVMP, which lead to the previous SPC amendment in 2012 about reduced milk production in goats. The current SPC changes (reduction of shedding and the vaccination scheme) were also considered not to have any impact on the pharmacovigilance requirements for this product.

3. Benefit-risk assessment

3.1. Benefit assessment

Direct therapeutic benefit

The vaccine COXEVAC is an inactivated phase-I *Coxiella burnetii*, strain Nine Mile, bacterial vaccine for cattle and goats. The vaccine induces active immunity against Q fever in cattle and goats.

The benefit of the product is the prophylactic immunisation of cattle and goats against infections with *Coxiella burnetii*. The product is indicated for the active immunisation of cattle to lower the risk for non-infected animals vaccinated when non-pregnant to become shedders (5 times lower probability in comparison with animals receiving only placebo), and to reduce the shedding of *Coxiella burnetii* in these animals via milk and vaginal mucus. It is also indicated for the active immunisation of goats to reduce abortion caused by *Coxiella burnetii* and to reduce shedding of the organism via milk, vaginal mucus, faeces and placenta.

Two new studies demonstrated that the duration of immunity in goats is one year after the primary vaccination (2 doses given 3 weeks apart) and that an annual single dose revaccination 3 weeks before pregnancy provides continued protection.

Additional benefits

As concluded in the CVMP assessment of the initial marketing authorisation application, COXEVAC is a standard inactivated vaccine and as such fits in with accepted vaccination practices in the field.

In addition to the direct benefit to vaccinated animals, there is a benefit to the health of herds, both locally and regionally.

Duration of immunity of 280 days after completion of the first vaccination course has been demonstrated for cattle. Studies submitted for the purpose of this assessment have moreover demonstrated duration of immunity of one year after completion of the primary vaccination course.

3.2. Risk assessment

The CVMP agreed that that risk assessment remains unchanged from that in the assessment report for the initial marketing authorisation, in which the main potential risks identified were:

Quality:

The vaccine does not contain any adjuvant and the antigen is purified (specifically to removes egg yolk derived impurities); these measures reduce the risk of adverse reactions in the target animals. A satisfactory control of inactivation is applied twice during the production and the risk of the finished product containing any extraneous agents is negligible. Sterility tests are carried out at different stages of manufacturing and also on the finished product, providing additional assurance on the purity profile of the vaccine.

For the target animals:

The product is generally well tolerated in both of the target species, even if some mild to moderate local swellings (sometimes with redness) are common at the injection site in both target species, sometimes quite extended and lasting a few weeks. In both species however these local reactions gradually reduce and disappear without the need for any treatment.

Hyperthermia (sometimes above 40.5 °C) appears to be the only general reaction, and was only identified in goats.

Although the milk yield in goats was negatively impacted, the use of COXEVAC during lactation has been shown to be safe, for both cattle and goats. The SPC was updated in 2012 to inform users about the decrease in milk production in goats. The current SPC warning is deemed sufficient to allow users to make a suitable benefit-risk assessment on a case-by-case basis before using this vaccine, and to be in a position to potentially minimize this side effect.

Vaccination of already infected and/or pregnant cows has not demonstrated any benefits, however, COXEVAC was previously shown to be safe when used in these animals. Likewise, although no efficacy data are available following the vaccination of male animals, in safety laboratory trials vaccination of male animals with COXEVAC has also been demonstrated to be safe. It is therefore safe to vaccinate all the animals in a herd at the same time.

As the results of the 2 new studies in goats have not identified any changes to the target animal safety profile of the vaccine, the wording included in the SPC for these risks are still considered adequate.

Pharmacovigilance data have confirmed the safety of the product in accordance with the SPC.

For the user:

The conclusion remains that user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC (and other product information). No user safety concerns are related to this vaccine as the composition does not contain any substances that could involve any particular risk for the person handling this product. The SPC wording included for this risk is still adequate.

For the environment:

The product is not expected to pose any risk to the environment when used as recommended.

The vaccine is inactivated by a validated inactivation method and therefore is no risk of spread of live virus. The adjuvants appear to be pharmacologically inert substances.

If all measures described in the SPC (and other product information) are taken, the environmental risk is virtually zero. The SPC wording included for this risk is still adequate.

For the consumer:

Residue studies are not required for this product. The withdrawal period is set at zero days. COXEVAC has no vaccine components which require a maximum residue limit (MRL); therefore there are no concerns for the consumer.

Risk assessment of this annual reassessment:

The data provided with this fourth annual reassessment are from two confirmatory efficacy studies performed in goats, the results of which have now established the therapeutic profile and the duration of immunity in that species.

The CVMP considered that that risk assessment remains unchanged from that in the assessment report for the initial marketing authorisation.

Specific potential risks, according to product type and application:

In the assessment report for the initial marketing authorisation no specific potential risks were identified.

As a result of this annual reassessment no further specific risks have been identified from the use of the product.

The last (6th) PSUR report, covering the period between 1 April 2013 and 31 March 2014 was provided in May 2014, and endorsed by the CVMP in June 2014.

Risk management or mitigation measures

On consideration of this annual reassessment, the CVMP agreed that that risk assessment remains unchanged from that in the assessment report for the initial marketing authorisation.

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, user, environment and consumer and to provide advice on how to prevent or reduce these risks.

3.3. Evaluation of the benefit-risk balance

The CVMP considered that that risk assessment remains unchanged from that in the assessment report for the initial marketing authorisation. In the initial evaluation of the benefit-risk balance it was noted that the formulation and manufacture of COXEVAC had been well described and both the specifications and shelf-life of the product in the marketed pack had been supported, although some confirmatory data from one stability batch remained outstanding (as a recommendation).

The initial assessment report also stated that the product had been shown to be efficacious for the proposed indication of the active immunisation of cattle to lower the risk for non-infected animals vaccinated when non-pregnant to become shedder, and to reduce shedding of *Coxiella burnetii* in these

animals via milk and vaginal mucus. Although the product had demonstrated some efficacy for the proposed indication of the active immunisation of goats to reduce abortion caused by *Coxiella burnetii* and to reduce shedding of the organism via milk, vaginal mucus, faeces and placenta, both the therapeutic indication and the duration of immunity remained to be conclusively confirmed and an additional study was requested. This resulted in a specific obligation and authorisation of the product under exceptional circumstances.

This annual reassessment has now provided data for the specific obligation from 2 efficacy studies in goats and this has enabled the CVMP to conclude that the indications and duration of immunity have both now been proven for the goat indication.

The pharmacovigilance data provided since initial authorisation have not showed any evidence of safety concerns or lack of efficacy, therefore supporting the consistency of production and also the stability profile of this vaccine.

COXEVAC remains well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate warnings have been included in the SPC and other product information. A sufficient withdrawal period has been set. No change to the impact on the environment is envisaged.

The information provided in the dossier and in responses to the specific obligations for COXEVAC was adequate to confirm that the benefit-risk balance for the product still remains positive.

Conclusion on benefit-risk balance

Based on the original and complementary data presented the CVMP concluded that the overall benefit-risk balance for COXEVAC and is further positively strengthened.

4. Overall conclusions of the evaluation and recommendations

On the basis of the documentation submitted for evidence of compliance with the specific obligations and for re-assessment of the benefit-risk balance of this veterinary medicinal product, the CVMP considered that this application, accompanied by the submitted documentation, demonstrated that the benefit-risk profile remains favourable for the product COXEVAC.

The only specific obligation for this vaccine has now been adequately resolved which therefore reduces the risks and confirms the positive benefit-risk balance of this product.

In view of the fact that the only specific obligation has been fulfilled, there are no remaining grounds to maintain the marketing authorisation for this product under exceptional circumstances and as a result the CVMP recommends the conversion of the marketing authorisation to a normal status.

The CVMP considered it was not necessary to restart the PSUR cycle for COXEVAC following the conversion of the marketing authorisation to a normal status.

One recommendation (relating to variation EMEA/V/C/000155/IB/001/G) concerning the provision of some confirmatory stability data remains to be fully addressed in the future after the stability study concerned has finished.

4.1. Changes to the community marketing authorisation

Changes are required in the following annexes of the Community marketing authorisation:

- Annex A (corrections)
- Annexes I, II and III (completion of advice regarding duration of immunity in goats and the revaccination schedule for goats, correction of the physical description of the product in line with the description in the finished product specification, harmonisation of the date format used, changes in line with the current QRD template and some editorial corrections and improvements).