15 February 2023
EMA/85639/2023
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for an extension to the marketing authorisation for Coxevac (EMEA/V/C/000155/X/0015)

Vaccine common name: Coxiella burnetii vaccine (inactivated)

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

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Introduction

The applicant CEVA Santé Animale submitted to the European Medicines Agency (the Agency) on 21 October 2021 an application for an extension to the marketing authorisation for Coxevac, through the centralised procedure, under Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I thereof.

Coxevac is a suspension for injection containing ≥ 72 QF Units/ml (Q Fever Unit: relative potency of phase I antigen measured by ELISA in comparison with a reference item) of inactivated *Coxiella burnetii*, strain Nine Mile. Coxevac is contained in LDPE bottles containing 40 or 100 ml of suspension and it is authorised for subcutaneous use in cattle and goats.

Coxevac was authorised for use in the Union on 30 September 2010.

This extension application is to add a new target species: sheep.

The rapporteur appointed is Christine Miras and the co-rapporteur is Cristina Muñoz Madero.

The dossier has been submitted in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions).

On 15 February 2023, the CVMP adopted an opinion and CVMP assessment report.

On 31 March 2023, the European Commission adopted a Commission Decision granting an extension to the marketing authorisation for Coxevac.

Marketing authorisation under exceptional circumstances

Not applicable.

Scientific advice

Not applicable.

MUMS/limited market status

MUMS status was granted as Coxevac is considered a minor use, including cattle and goats as target species. The applicant did not request MUMS/limited market status for sheep before submission of this extension. Therefore, no MUMS status can be considered for this application. The assessment has been carried out in this context.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated June 2017) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Union or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the active substance and final product as well quality control tests and batch release take place in CEVA-Phylaxia Co.Ltd., Hungary. The site has a manufacturing authorisation issued on

26/04/2021 by the Hungarian N. GMP certification, which confirms the date of the last inspection (12/03/2019) and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided.

Secondary packaging within the EU takes place at CEVA-Phylaxia Co.Ltd., Hungary. An additional site for secondary packaging is at CEVA Santé Animale, Libourne, France for which GMP compliance was confirmed by the competent national authority ANSES (22/06/2021).

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of the active substance(s) and of the finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 – Quality[1]

The extension application does not concern Part II of the dossier. No changes have been made to the quality part linked to this application.

Part 3 – Safety

Introduction and general requirements

Coxevac is an inactivated vaccine licensed for the active immunisation of cattle and goats to reduce infection and shedding of *Coxiella burnetii*, the causative agents of Q fever. The aim of this dossier is to add a new target species, sheep, as a claim to Coxevac's centralised license.

Safety studies presented in the extension dossier were conducted according to Directive 2001/82/EC as amended by 2004/28/EC and Ph. Eur. monograph 5.2.6. "Evaluation of safety of veterinary vaccines and immunosera". They were carried out in conformity with principles of GLP. These studies were already presented in the initial marketing authorisation dossier.

Safety documentation

Three laboratory safety studies were conducted to investigate the safety of the vaccine when administered as one dose, repeated dose and overdose. One field trial focusing on safety of the vaccination is also provided. The vaccine was administered by the subcutaneous (SC) route, as recommended. Laboratory studies were reported to be GLP compliant and carried out in lambs of the minimum age recommended for vaccination, using production batches containing target antigen quantity. Production batches were also used in the field trials.

Study title
Safety of administration of one dose of Coxevac vaccine in 3 months old lambs
Safety of administration of an overdose of Coxevac vaccine in 3 months old lambs

[1] Any headings not applicable for a particular product should be deleted (e.g. Environmental risk assessment for products not containing or consisting of genetically modified organisms)

Study title
Safety of the repeated administration of one dose of Coxevac vaccine in 3 months old lambs
Field safety of Coxevac in sheep in Hungary

Laboratory tests

Safety of the administration of one dose

Fourteen 3 months old seronegative lambs were vaccinated with one dose of Coxevac vaccine (2 ml / SC route) and 14 lambs, receiving placebo, were kept as controls. The lambs were daily observed for 14 days to detect possible signs of systemic reactions (abnormal behaviour, appetite, clinical signs, rectal temperature and body weight) and local reactions (injection site, thickness of the skin). Post-mortem macroscopic and microscopic examinations of the injection sites were performed on day 14.

The results showed that the administration of 1 dose of Coxevac vaccine is safe in 3 months old lambs. No systemic adverse reactions were observed. Local inflammatory reaction, diminishing with time, was observed in 2 vaccinated lambs.

In the study, the vaccine was administered in the left axillar region behind the elbow, whereas the administration site stated in the PI is the neck region. It has been agreed that local reactions observed in this study are representative of the administration in the neck, as per label use.

Information on the local adverse reactions (e.g. duration and size) are correctly stated in the relevant section of the Product Information.

Safety of one administration of an overdose

Ten 3 months old seronegative lambs were vaccinated with two doses of Coxevac vaccine (4 ml / SC route) and 10 lambs, receiving placebo, were kept as controls. The lambs were daily observed for 14 days to detect possible signs of systemic reactions (abnormal behaviour, appetite, clinical signs, rectal temperature and body weight) and local reactions (injection site, thickness of the skin). Post-mortem macroscopic and microscopic examinations of the injection sites were performed on day 14.

The results showed that the administration of 2 doses of Coxevac vaccine is safe in 3 months old lambs. No systemic adverse reactions were observed. Local inflammatory reactions, diminishing with time, were observed in 6 vaccinated lambs.

An overdose study is not mandatory for inactivated vaccines. The applicant, in the interest of animal welfare, should consider and follow the 3Rs principles in future veterinary medicinal products developments.

In this study and in the single dose safety study, diarrhoea was observed. In both cases, the applicant states that the cause is a change of diet which occurred before the study. During the course of the study, the diet was kept the same. This is considered acceptable and the diarrhoea observed properly justified.

Nasal discharge was also observed, for one day, in 2 out of 10 vaccinated animals. Based on the justification provided by the applicant, it was agreed that this is not likely to be linked to vaccination.

Safety of the repeated administration of one dose

Twelve 3 months old seronegative lambs were vaccinated with three doses of Coxevac vaccine 14 days

apart (2 ml / SC route / D0, D14, D28) and 12 lambs, receiving placebo, were kept as controls. The lambs were daily observed for 14 days after each vaccine injection to detect possible signs of systemic reactions (abnormal behaviour, appetite, clinical signs, rectal temperature and body weight) and local reactions (injection site, thickness of the skin).

The results showed that the repeated administration of 1 dose of Coxevac vaccine is safe in 3 months old lambs. No systemic adverse reactions were observed. Local inflammatory reactions, diminishing with time and with no increase or exacerbation after the repetition of the vaccinations, were observed in 4 vaccinated lambs.

Examination of reproductive performance

Use during pregnancy:

In the SPC section 4.9 "Amounts to be administered and administration route", it is recommended by the applicant that the primary course of vaccination with Coxevac shall be finished at least 3 weeks before artificial insemination or mating. Considering that none of the vaccine components is a suspected risk factor to reproduction and that PSUR and literature data support the safety of the vaccine if administered during pregnancy, no specific study was conducted which is considered acceptable. A relevant statement has been included in the SPC to indicate that safety of the VMP has not been established during pregnancy.

Use in lactation:

No data have been provided on the safety of the vaccination during lactation and this has been adequately reflected in the SPC.

Examination of immunological functions

No further studies were conducted to investigate the effects of the product on immunological functions. It is unlikely that this vaccine would have such an adverse effect due to the nature of the product (i.e. inactivated vaccine). This is considered acceptable.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with the CVMP guideline EMEA/CVMP/IWP/54533/2006 (and EMEA/CVMP/543/03-Rev.1).

The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of accidental self-injection. The active substance is an inactivated protein and is not infectious. The excipients including adjuvants are commonly used in other vaccines and do not pose a risk for the user.

As a result of the user safety assessment the advice to users/warnings for the user already present in the current SPC is considered appropriate: "In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician."

This is considered acceptable.

Study of residues

Thiomersal (less than 0.02% in the final product) and Phosphate Buffer saline, the excipients used in the product, are commonly present in other vaccines and do not raise any safety concern.

The withdrawal period is set at zero days. This is considered acceptable.

Interactions

Data investigating the interactions of the vaccine with other veterinary immunological products are not provided. Therefore, the applicant proposed to include a statement in Section 4.8 "Interaction with other medicinal products and other forms of interaction" of the SPC that 'No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.' This is considered acceptable.

Field studies

A large-scale study in lambs and adult sheep was performed in 2 sites located in Hungary. It includes 100 sheep older than 3 months vaccinated with two doses of Coxevac 3 weeks apart (D0 and D21) (50 sheep at one site and 50 at the other site) and 100 controls sheep (50 at one site and 50 at the other site).

The study was well designed and conducted and confirmed that the product is safe. Clinical investigations included recording of general reactions (with measure of rectal temperature in 20 vaccinated sheep and 20 control sheep) and daily monitoring of local reactions at the injection site for 14 days after each injection.

No general reactions were observed after Coxevac injections. Transient local reactions, that disappeared with time and with no effect on the general health or animal welfare, were recorded frequently in vaccinated animals.

The data show that the product is safe when used in sheep and the study is considered satisfactory. However, local reactions appear to be more frequent in site 2 with more frequent and severe reactions including suffusions, wheals or petechiae after the 2nd vaccination. No explanations for these reactions could be provided, however, a statement about the fact that reactions are expected to be more severe after the 2nd injection is included in the SPC. This is considered acceptable.

Pharmacovigilance data covering a period from April 2016 till 2022 are also provided. Generally, these data confirm the absence of safety concerns both in the already approved target species (cattle and goats) and in sheep (off-label use). The adverse reactions reported in sheep – local reactions at the injection site or systemic unspecific signs as anorexia, fever or lethargy - were in line with the known adverse effects of the product as observed in experimental studies or in the already approved target species cattle and goats and are adequately reported in the SPC.

Considerations for the environmental risk assessment

Coxevac is an inactivated vaccine. The components are not toxic. The vaccine is intended for parenteral vaccination and unused product and waste materials should be destroyed.

Based on the data provided, the ERA can stop at Phase I. Coxevac is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Generally, the studies provided show that the vaccine is globally well-tolerated in sheep and its use is not raising safety concerns. Mild to moderate local swellings (sometimes with redness) at the injection site appear to be quite common. They are transient and disappear with time. They are characterised by slight inflammatory infiltration and are consistent with histological findings at the injection site of any successful and necessary immune reactions. Signs of toxic reaction, necrosis, fibrosis haemorrhages and

abscesses were not found. General reactions as hyperthermia were observed in field study but these were not affecting the general health. The safety profile in sheep is similar to the one in the already approved target species cattle and goats.

No data are available on the safety of the vaccine when used during pregnancy or lactation and this has been adequately reflected in the SPC.

Part 4 – Efficacy

Introduction and general requirements

Coxevac contains inactivated *Coxiella burnetii* – Nine Mile *Coxiella burnetii* phase I bacteria – selected to provide protection. It is currently authorised in cattle and goats to reduce infection and shedding of the bacteria.
With this application, the applicant wishes to extend the indications of the vaccine to sheep. Based on the applicant desired claim, a 2 ml dose of Coxevac is intended to be administered in sheep in 2 injections 3 weeks apart (at least 3 weeks before artificial insemination or mating). It is recommended that primary vaccination should be applied before each planned pregnancy. The vaccine is expected to reduce the colonisation of *Coxiella burnetii* on the organs of the host animal. Efficacy claims are reduction of the shedding via milk, vaginal discharge and faeces. No significant effect of the vaccination on pregnancy or health of offspring could be evidenced, therefore, this claim should be removed from the indication.
Efficacy was demonstrated in compliance with the European Directive 2001/82/EC (as amended by 2004/28/EC and Directive 2009/9/EC), and the European Pharmacopoeia (Ph. Eur.) chapter 5.2.7. "Evaluation of efficacy of veterinary vaccines and immunosera".

Challenge model:

The *Coxiella burnetii* Nine-Mile challenge strain was used. Homology between the vaccine strain and the challenge strain was noted. However, the justifications provided were considered acceptable and the challenge strain can be considered representative.

Efficacy parameters and tests:

The efficacy parameters investigated in the efficacy studies are presence of the bacteria in tissues and shedding in milk, faeces and vaginal secretions detected by qPCR. Adverse pregnancy outcomes after challenge were also monitored.

Efficacy documentation

Study title
Efficacy assessment of Coxevac in a pregnant ewe challenge model

Laboratory trials

Onset of immunity

One study was carried out to support efficacy of the vaccine in sheep.

In this study (report E34/18) 20 seronegative 3 years old ewes were vaccinated at D0 and D21 (1 dose

of 2 ml via SC route) and 20 unvaccinated 3 years old ewes were kept as controls. Two weeks after the 2nd vaccination, oestrus of these ewes were synchronised and 2 weeks later ewes were inseminated. Six pregnant vaccinated ewes and 6 pregnant unvaccinated controls were selected for challenge. The experimental challenge took place at D151 i.e. about 4 months after the second vaccine injection. Animals included in this study were 3 years old which is above the minimal age recommended in the SPC as 3 months. As the vaccine scheme describes to have completed the vaccination at least 3 weeks before artificial insemination or mating, and considering both the sexual maturity from 6 months and the gestation period of approximatively 5 months, this study and ewes included were considered relevant and supportive of a minimum age recommended for vaccination of 4 months.

Following the challenge, the animals were investigated for the pregnancy and lambing outcomes and shedding of *C. burnetii* in milk, faeces and vaginal secretions after lambing (daily 3 days then weekly for 3 weeks).

One vaccinated ewe was found infected with *Chlamydia abortus* and removed from the study. Prevention of the bacteria in milk was demonstrated in the vaccinated ewes (while all controls shed bacteria in milk) and significant reduction of the shedding was demonstrated in vaginal secretions and faeces.

In the study, no abortions attributed to *C. burnetii* challenge were observed. Considering that "Normal pregnancy" was defined as all lambs born healthy and survived to the end of the trial period, a tendency for higher number of abnormal pregnancies in the unvaccinated group (5/6) compared to the vaccinated group (1/5) was observed but no significant difference was observed (p=0.067). From the vaccinated group 10/11 lambs survived compared to 8/12 from the control group (p=0.18). The absence of statistical significance could be linked to the low number of animals included in the study and this does not allow to definitely conclude on any efficacy of the vaccination on pregnancy. Reanalysis of the data to evidence any significant effect is not acceptable.

No quantification of the bacteria in the samples has been performed; as a significant reduction in shedding (number of positive samples) is evidenced, this point is not questioned.

In the summary of the report in the dossier, the applicant underlines the known importance of protective antibodies in *Coxiella* and also states that available bibliographic data in mice suggest that serology response correlates with vaccine induced protection and could be used to define onset of immunity. The applicant concludes on these bases that the onset of immunity can be set at 14 days after the 2nd vaccination when the peak of vaccine-induced specific antibodies is seen and that this is used to justify a statement present in section 5 of the SPC. At the time of the challenge, the antibody levels, which were at significant levels after vaccination, have gone below the positivity threshold. Therefore, in the context of the study, the applicant's rationale to define the onset of immunity based on antibodies cannot be followed.

Based on this single efficacy study, the onset of immunity cannot be established. Considering the indication of this vaccine and the characteristics of *Coxiella burnettii* infection, the definition of an early onset of immunity is not considered critical (and as important as for other type of vaccines) due to the late clinical impact of an infection (mainly in the third trimester and after birth for what it concerns excretion). Considering the complexity of the disease, the difficulties to get usable statistically relevant results and also from a 3Rs perspective, the absence of additional data (a further challenge study) and an onset of immunity stated as "not established" in the SPC, is considered acceptable. This was already accepted for cattle and goats during the initial evaluation of the product.

Maternally derived antibodies (MDA)

The decline of the maternal antibodies was investigated in 1-week old sero-positive lambs. The lambs having high level of maternal antibodies at 1 week of age became sero-negative by the 13th week of age. At the age of 3 months, the chosen youngest age for vaccination, there were no more detectable maternal antibodies present in sheep.

Duration of immunity

The duration of immunity of 4 months can be considered acceptable based on the timing of challenge in the efficacy study described in the onset of immunity section above.

Field trials

No field study has been conducted. It is agreed that such study would hardly provide any additional information on the efficacy of the vaccine when considering efficacy claims limited to reduced excretion of the bacteria. The reasoning behind this omission is in line with the Guideline EMA/CVMP/IWP/260956/2021.

Overall conclusion on efficacy

With the additional challenge study provided, the applicant demonstrated the benefit of the vaccination in sheep to reduce shedding of the bacteria via the milk, vaginal discharge and faeces after an experimental infection with *Coxiella burnettii* 4 months after vaccination.

Part 5 – Benefit-risk assessment

Introduction

With this extension, the applicant wishes to extend the indication of the vaccine Coxevac to sheep.

The product has been classified as MUMS/limited market for cattle and goats but no classification has been requested and accepted for sheep. The assessment has been carried out in this context.

Benefit assessment

Direct therapeutic benefit

A new challenge study has been provided to demonstrate the benefit of the vaccination in sheep to reduce shedding via milk, vaginal mucus and faeces after challenge performed during pregnancy about 4 months after 2nd vaccine injection. No significant effect on pregnancy, parturition and offspring health could be evidenced probably linked to the low number of animals included in the study.

Additional benefits

As no vaccine is currently authorised, Coxevac provides a new prophylaxis possibility for sheep.

Although no data are provided in the dossier on this point, this reduction in excretion of this zoonotic agent could be of benefit to reduce Q-fever in humans. The SPC specifies that the biological significance of the levels of reduction shown in shedding in sheep is not known.

Risk assessment

Safety data are provided that confirms that the vaccine is globally well tolerated in sheep. Mild to moderate local reactions appear to be common and hyperthermia may be observed as general reaction. These reactions remained in acceptable limits, are already known in other target species (goats, cattle). They do not have any negative impact on the physiological status of animals. Some data are available on the off-label use of this vaccine during the last years.

Evaluation of the benefit-risk balance

The formulation and manufacture of Coxevac are well described and the specifications set will ensure that a product of consistent quality will be produced.

Coxevac is well tolerated by the target animals and presents a low risk for users and the environment. Appropriate warnings have been included in the SPC. A sufficient withdrawal period has been set.

Cattle:

For the active immunisation of cattle to lower the risk for non-infected animals vaccinated when non pregnant to become shedder (5 times lower probability in comparison with animals receiving a placebo), and to reduce shedding of *Coxiella burnetii* in these animals via milk and vaginal mucus.

Goats:

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.

Sheep:

For the active immunisation of sheep to reduce shedding of the organism via milk, vaginal mucus and faeces.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for Coxevac is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.