EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 August 2013
EMA/389517/2013
Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP Assessment Report for AFTOVAXPUR DOE (EMEA/V/C/002292/0000)

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Introduction

An application for the granting of a Community marketing authorisation of AFTOVAXPUR DOE has been submitted to the Agency on 28 September 2010 by MERIAL in accordance with Article 3(2) of Regulation (EC) No. 726/2004 as an immunological for the treatment of animal diseases that are subject to Community prophylactic measures. This scope includes foot-and-mouth disease (FMD) for which this product is intended.

The CVMP adopted an opinion and CVMP assessment report on 16 May 2013.

On 15 July 2013, the European Commission adopted a Commission Decision for this application.

AFTOVAXPUR DOE contains 1-3 purified, inactivated foot-and-mouth disease (FMD) virus strain antigens and is presented in packs/containers of 1 and 10 bottles containing 10, 25, 50, 100 or 150 doses. indication is for active immunisation of cattle and sheep from 2 months of age and pigs from 10 weeks of age against foot-and-mouth disease to reduce clinical signs.
The onset of immunity is 4 weeks after vaccination.

The proposed routes of administration are intramuscular and subcutaneous. The proposed target species are cattle, pigs andsheep.

The application for AFTOVAXPUR DOE has been submitted in accordance with the multi-strain dossier approach which was introduced in the revised Annex I to Directive 2001/82/EC. Seven strains of FMD virus are included in the dossier, namely foot-and-mouth disease virus O1 Manisa, O1 BFS, O Taiwan 3/97, A22 Iraq, A24 Cruzeiro, A Turkey 14/98 and Asia 1 Shamir. The vaccine may contain up to three types of inactivated, purified FMD virus antigens in a double oil emulsion adjuvant, chosen from the seven included in the dossier depending on epidemiological need.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that 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 Community or in a third country has been provided.

Manufacturing authorisations and inspection status

All sites involved in the manufacture of AFTOVAXPUR DOE are routinely inspected by EU regulatory authorities and have been inspected within the last three years. They are therefore considered to be in compliance with GMP. No additional inspections specific to this vaccine were considered necessary.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the manufacturing and batch release sites are considered in line with legal requirements.

Part 2 - Quality

Composition

The vaccine may contain between one and three of the following purified, inactivated foot-and-mouth disease virus strain antigens at concentrations equivalent to ≥ 6 PD_{50} per cattle dose:

O1 Manisa
O1 BFS
O Taiwan 3/97
A22 Iraq
A24 Cruzeiro
A Turkey 14/98
Asia 1 Shamir

The adjuvant is a double oil emulsion and mannide monooleate, polysorbate 80, trometamol, sodium chloride, potassium dihydrogen phosphate, potassium chloride, disodium phosphate anhydrous, potassium hydroxide and water for injections are included as excipients.

Container

The vaccine is filled into polypropylene bottles closed with butyl elastomer stoppers and subsequently sealed with an aluminium cap. The bottles and stoppers all meet pharmacopoeial standards. The use of Polyethylene terephthalate (PET) bottles was proposed and abandoned during assessment as the proposed containers were not intended for sales.

Development pharmaceutics

AFTOVAXPUR DOE has been developed in accordance with the multi-strain dossier concept introduced in the revised Annex I to Directive 2001/82/EC. The seven strains of FMD virus that may be incorporated into the finished product depending on epidemiological need have been selected based on advice from the World Reference Laboratory for foot-and-mouth disease, at the Institute of Animal Health in Pirbright, United Kingdom. The vaccine is adjuvanted with a double oil emulsion selected for its ability to stimulate immunity in all of the three intended target species.

The target quantities of each of the respective antigens per dose have been determined on the basis of a statistical analysis of serology and protection data from efficacy studies included in Part 4 of the dossier, using a common approach for all strains except pig-adapted strain O Taiwan 3/97.

The vaccine does not contain a preservative because published data have suggested that thiomersal is detrimental for the long-term stability of the product. The SPC accordingly states that the vaccine should be used immediately after broaching; the applicant has justified that this is practical for presentations as large as 150 doses per bottle. To reduce the risk of contamination while vaccinating a large number of animals the use of a multiple injection device is recommended.

Method of manufacture

The vaccine is manufactured by a fairly conventional procedure. The FMD virus strains are cultured in baby hamster kidney (BHK 21) suspension cell cultures, and inactivated by treatment with binary ethylenimine (BEI). The inactivated antigen is then purified by filtration. To formulate the finished product, the selected combination of one to three antigens are incorporated in a water-in-oil emulsion (W/O) which is subsequently emulsified in a secondary aqueous phase to give the double oil emulsion

(DOE; W/O/W), leading to external water phase and reduced viscosity. The process is adequately described.

Control of starting materials

Active substance

Detailed specifications have been provided for all starting materials used to manufacture the vaccine. The BHK 21 cell line and the various FMD virus master seeds are adequately tested to demonstrate freedom from extraneous viruses.

Excipients

The liquid paraffin used is a low viscosity oil that complies with European Pharmacopoeia (Ph. Eur.) monograph 0239 with the exception of its viscosity. All of the other excipients (mannide mono-oleate, polysorbate 80, trometamol, sodium chloride, potassium dihydrogen phosphate, potassium chloride, disodium phosphate anhydrous, potassium hydroxide and water for injections) comply with respective Ph. Eur. monographs.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

All of the starting materials of animal origin have been assessed and considered to be in compliance with the TSE Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathies agents via human and veterinary medicinal products (EMA/410/01 rev.3). The overall TSE risk associated with the inactivated vaccine is considered negligible.

Control tests during production

Control tests carried out during antigen production include virus titration, inactivation kinetics (a specific requirement for FMD antigens in Ph. Eur. monograph 0063), presence of thiosulphate (to confirm complete neutralisation of the inactivant), antigen content, residual live virus, identity of FMD serotype, bacterial and fungal sterility and pH. Validation of the in-process tests is satisfactory.

Control tests on the finished product

The description of the following methods used for the control of the finished product: appearance, pH, emulsion type, conductivity and bacterial and fungal sterility, and the related specifications were provided. In some cases (pH, viscosity and conductivity) rather wide limits were initially proposed and these were either justified or amended by the applicant during the assessment. Other than this, the specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product.

While the initially proposed potency test methodology might be useful to determine an efficacious formulation for a trial blend the proposal to use the same system for all final batch testing on serology could only serve to reduce the precision, and hence reliability, of the proposed methods. An alternative testing regime was therefore provided. Serological potency tests in cattle (or pigs in the case of O Taiwan 3/97) will be performed on the trial blend only. The proposed pass criteria are based on an analysis similar to that used to determine the quantities of each antigen required for formulation and have been adequately justified.

In order to confirm that production batches have been formulated to contain the same quantity of inactivated FMD virus as the respective trial blends the applicant proposes to introduce a quantitative test specific for FMD virus for both the trial blend and the production batches. A PCR test for identity of the virus strains included in the vaccine is also being introduced.

The applicant has proposed to waive the batch safety test on the basis of results of 17 batches of vaccine containing different combinations of FMD virus antigens. Further information on the batches referenced has been provided. Since the target animal batch safety test has now been deleted from the general Ph. Eur. monograph it should no longer be performed.

The applicant has presented data from three batches of vaccine to demonstrate batch-to-batch consistency. The consistency of these batches has been satisfactorily addressed.

Stability

Stability data have been presented for the bulk antigen. Storage of the FMD bulk antigens at -70 °C for at least 5 years is acceptable.

Stability data have been provided for three batches of the finished product. For each of the three vaccines tested, in addition to monitoring the mean titres at each time point, the applicant compared the titres to those observed in pigs following vaccination with a '6 PD_{50} vaccine of the same serotype' but did not indicate what these values were or how they were determined. Furthermore, with the exception of the A Turkey 14/98 strain the titres in pigs could not be related to titres proposed as the pass levels for potency tests and since the potency test method had not yet been adequately validated it was not possible to reliably assess these results. However, it is noted that the titres for all strains appear to have declined significantly during the storage period. It is also noted that the viscosity of the vaccines declined during storage, although it stayed within the proposed acceptable range throughout. In the absence of data at around 12-15 months storage, the 12 months shelf life proposed by the applicant could not be accepted.

Titres for O1 Manisa and A Turkey 14/98 strains remained more or less stable for up to 11 months and 9 months respectively but declined thereafter. Titres for the Asia 1 Shamir strain, however, fell significantly within 6 months. An additional stability study for an Asia 1 Shamir vaccine did not confirm stability of a vaccine containing Asia 1 Shamir antigen for longer than three months.

Taking into account all of the available stability data a shelf life of six months was deemed acceptable for vaccine batches that do not contain the Asia 1 Shamir antigen. A shelf life of only two months was appropriate for batches that contain the Asia 1 Shamir antigen; this was considered acceptable considering the expectation that FMD vaccines would only be used in the EU in response to an emergency, when it would be expected that batches of vaccine would be used immediately after release.

Overall conclusions on quality

Information regarding the qualitative and quantitative composition, the starting materials, production method, quality controls, and stability are provided in this part of the dossier. Three batches were provided in order to demonstrate batch-to-batch consistency.

The production methods as well as the in-process and final product quality control are appropriate to ensure the compliance with the specifications and a reproducible and consistent quality of the vaccine. The production process is described in sufficient detail to give confidence that the manufacture will yield a safe and effective vaccine of consistent quality and adequate stability suitable for the expected use of the vaccine in the EU.

Compliance of starting materials of animal origin used during production with the requirements of the Note for guidance on minimising risk of transmitting animal spongiform encephalopathy agents via human and veterinary products was shown (EMA/410/01 rev.3).

In-process controls during manufacture and control tests on the finished product are appropriate to ensure the compliance with the quality specifications mentioned. Acceptance limits are properly established.

Regarding the stability, the inactivated bulk antigen is demonstrated to be stable over the proposed shelf life of 5 years (at ≤-70 °C). Since there are no tests on production batches that confirm the quality of the antigens used (only the quantity of virus) the CVMP agreed on a recommendation that periodic tests for the quality of the stored 146S antigens should be carried out. This could probably be done by a suitable *in vitro* test.

A shelf life of six months at 2 °C - 8 °C is justified for the finished product presentation (bottle) for batches that do not contain the Asia 1 Shamir antigen. A shelf life of only two months for batches that contain the Asia 1 Shamir antigen was justified.

The CVMP considers the presented analytical dossier as fully adequate and sufficiently detailed to give confidence that the finished product is produced according to a consistent procedure of adequate standards and including adequate controls.

Part 3 – Safety

Safety documentation

The applicant has provided reports of studies in which an overdose and a repeated dose of vaccine was administered to each of the target species (cattle, sheep and pigs). Studies in pregnant animals of each species have also been carried out.

No field studies have been carried out and this is justified because the use of FMD virus vaccines in the EU is currently prohibited.

Laboratory tests

Safety of the administration of one dose and an overdose

The CVMP guideline on Data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), bluetongue (BT) and foot-and-mouth disease (FMD) (EMA/CVMP/IWP/105506/2007) and the CVMP Position paper on requirements for vaccines against foot-and-mouth disease (EMEA/CVMP/775/02) indicate that safety studies should be performed with the maximum number of FMD strains allowed and the maximum permitted amount of each antigen. Ph. Eur. monograph 0063 describes a general safety test for FMD virus in ruminants. The monograph indicates that the test should be conducted in not fewer than 10 animals of the minimum age to be recommended. Each animal should receive a double dose of the vaccine and be observed daily for 14 days.

Studies in cattle

Two studies were performed to demonstrate the safety of one dose in cattle.

The 1st study was GLP compliant and was performed with a double dose (4 ml) administered to 10 calves, 8-12 weeks of age. A vaccine batch, which contained 15 µg of O1 Manisa antigen, 7.5 µg of A

Turkey 14/98 antigen and 7.5 µg of Asia 1 Shamir antigen per 2 ml dose, was used in this study. It therefore contained a total antigen payload per dose that exceeded the maximum that might be formulated into a trivalent batch on the basis of estimated quantities for 6 PD_{50} for each strain.

During this study vaccinated calves showed a significant increase in body temperature (highest recorded was 40.1 °C) and all vaccinated calves developed local injection site reactions (range 18–72 cm^3). Sections 4.6 and 4.10 of the SPC reflect the frequency and intensity of reactions observed in this study.

In the 2nd study, a vaccine batch containing 2 µg of A Turkey 14/98 antigen or 4 µg of A22 Iraq antigen per dose was administered to 15 calves at 2-3 weeks of age. The study was not performed in line with the guidelines and can only be considered as supportive. Body temperatures remained within normal range and local injection site reactions were observed in all calves (largest 100 x 70 mm).

The reactions were considered consistent with what is generally observed with oil-adjuvanted vaccines.

In consideration that safety had not been adequately demonstrated in cattle as young as 2 weeks of age the minimum age was increased from 2 weeks to 2 months.

Studies in lambs

A GLP compliant study was performed using the vaccine batch as described above. A significant rise in body temperature was not observed in this study but it was noted that a number of the lambs were pyrexic before vaccination and presented with pre-existing pathology at necropsy. However, the validity of the study was justified.

To supplement these conclusions, an additional safety study in 2 month old lambs was provided. Primary vaccination with a standard dose did not lead to pyrexia or systemic clinical signs. Local reactions were consistent with what is generally observed with oil-adjuvanted vaccines (lesion diameter 33 ± 14 cm^2 (mean ± sd)). Although this study was not fully compliant with GLP and Ph. Eur. requirements, it confirmed the safety for 2 month old lambs of a batch formulated with a standard antigen content. The magnitude of the reactions observed are reflected in the SPC.

In consideration that safety had not been adequately demonstrated in sheep as young as 2 weeks of age the minimum age was increased from 2 weeks to 2 months, which is in line with the ages of the animals used in the safety studies.

Studies in pigs

A GLP compliant study was performed with the vaccine batch as described above. Primary vaccination did not lead to pyrexia or systemic clinical signs, however it was noted that body temperatures were high pre-vaccination; an acceptable explanation was provided. Local reactions were consistent with what is generally observed with oil-adjuvanted vaccines (lesion diameter 0.23 ± 0.46 cm^2 (mean ± sd)). The magnitude of the reactions observed are reflected in the SPC.

A GLP certificate was not provided for the 2nd study. Pyrexia and local reactions were recorded post-vaccination. These piglets were from previously vaccinated sows and the validity of these data for evaluating safety is questionable. Shortly after vaccination, there was a transient rise in body temperatures (lesion diameter 40.2 ± 0.2 °C (mean ± sd)). Local injection site reactions were observed shortly after vaccination in three out of 30 piglets.

In consideration that safety had not been adequately demonstrated in pigs as young as 2 weeks of age the minimum age was increased from 2 weeks to 10 weeks, which is in line with the ages of the animals used in 1st study.

Additional studies

A study of the safety of vaccine containing 2 µg of 146S FMD strain O1 BFS antigen in 2 week old calves, lambs and piglets was provided. Pyrexia was not recorded, local injection site reactions were common and the vaccine was well tolerated. However, these data were only considered as supporting evidence.

In conclusion, the safety of the administration of one dose and an overdose has been adequately justified in cattle and sheep of 2 months of age and pigs of 10 weeks of age.

Safety of the repeated administration of one dose

Calves, lambs and pigs which received a double dose of the batch as described in the section above concerning safety of the administration of one dose, received an additional dose (2 ml) two weeks later at a different site in order to evaluate the safety of the administration of a repeated dose. The additional dose contained 15, 7.5 and 7.5 µg of 146S O1 Manisa, A Turkey 14/98 and Asia 1 Shamir antigen, respectively.

Studies in calves

In contrast to the first vaccination, the second administration did not result in a significant rise in body temperature. At necropsy the size of the local injection site reactions ranged from 13.5 to 84 cm^3 and the local reactions were highly comparable to those observed after the first administration.

Studies in lambs

In contrast to the first administration, the second vaccination resulted in a significant rise in body temperature. The resulting average body temperature was 40.4 ± 0.4 °C (mean ± sd). The second administration resulted in significant local reactions, with an estimated surface of 33 ± 19 cm^2 (mean ± sd). Significantly 6/10 cases were accompanied by skin ulceration. The gradual development after the first vaccination and the rapid development after the second vaccination suggest a specific immune response consistent with the development of a delayed-type hypersensitivity reaction. A warning has been added to the SPC.

Studies in pigs

There was a slight rise in the average body temperatures shortly after vaccination (mean ± sd, 39.8 ± 0.5 ºC) which was mainly caused by one pig (41.2 °C) and which returned to normal values the following day. In contrast to the first administration, palpable local reactions developed in 9 pigs. The estimated surface of the local reactions were small in most of the animals (range 0.25-6 cm^2) but reached 35 cm^2 in one animal. It was concluded that administration of a repeat dose resulted in rapid and more severe local granulomatous reactions than observed following the first administration; these were consistent with the development of delayed type hypersensitivity reactions. The possible occurrence of these reactions is reflected in the SPC.

Additional studies

The applicant highlighted that the safety studies conducted in pregnant animals of each target species also provide information on the safety of administration of a repeated dose.

In conclusion, the safety of the repeated administration of one dose has been adequately demonstrated.

Examination of reproductive performance

Safety studies have been performed in pregnant animals of each target species. Ph. Eur. monograph 0063 describes the safety studies to be performed; *"use not fewer than 10 pregnant animals at the beginning of each trimester for which the use is not contra-indicated. Administer to each animal a double dose of the vaccine and observe at least daily to parturition. The vaccine complies with the test if no animal shows abnormal local or systemic reactions or dies from causes attributable to the vaccine and if no adverse effect on the pregnancy and offspring are observed".*

Studies in cows

This study was GLP compliant. Three doses of a vaccine batch, containing 10 µg of O1 Manisa antigen, 4 µg of A Turkey 14/98 antigen and 4 µg of Asia 1 Shamir antigen, were administered to 15 pregnant heifers, a double dose of 4 ml in the first trimester and single doses of 2 ml in the second and third trimesters. No changes in general health were observed after any of the three vaccinations. One cow aborted 12 weeks after the second vaccination; a clear cause could not be established but it was concluded that the abortion was not vaccine related. The first vaccination did not result in a change in body temperature. A transient rise was seen following further vaccinations; 39.0 ± 0.5 °C after the second vaccination and 39.4 ± 0.9 °C after the third vaccination (mean ± sd). Local reactions were observed in all animals. The largest average diameters of the injection site reactions were 77 ± 17 mm, 89 ± 30 mm and 64 ± 10 mm (mean ± sd) after the 1st, 2nd and 3rd vaccination respectively.

At parturition, 13 live calves and one dead calf were born; the probable cause of death was due to intra partum problems (possible dystochia) with no relation to vaccination. One day after birth a calf was euthanized; it was concluded that this calf was suffering from acute enteritis unrelated to vaccination. Another calf developed depression and inappetence and was found dead 4 days after birth. The most probable cause was believed to be intra partum problems with no relation to vaccination.

Studies in ewes

This study was GLP compliant. Three doses of a vaccine batch containing 10 µg of O1 Manisa antigen, 4 µg of A Turkey 14/98 antigen and 4 µg of Asia 1 Shamir antigen per dose, were administered to 17 pregnant ewes, a double dose of 4 ml in the first trimester and single doses of 2 ml in the second and third trimesters. One ewe was euthanized 46 days after the 2nd vaccination due to vaginal prolapse. Vaccination resulted in pyrexia, 39.5 ± 0.3 °C, 40.4 ± 0.5 °C and 39.7 ± 0.6 °C after the 1st, 2nd and 3rd vaccination respectively (mean ±sd). Local reactions were observed in all animals. The largest average diameters of the injection site reactions were 71.8 ± 19.6 mm, 65.3 ± 18.3 mm and 47.8 ± 13.8 mm (mean ± sd) after the 1st, 2nd and 3rd vaccination respectively. Open abscesses were observed in six ewes after the 1st vaccination. Three ewes developed open abscesses after the 2nd vaccination and open abscesses were observed in 9 ewes after the 3rd vaccination.

Twenty eight lambs were born from 16 ewes. Three lambs were not accepted by the ewes and were euthanized. One lamb was lame from 9 days post-partum, the post-partum events were not considered to be a result of vaccination.

Studies in sows

This study was GLP compliant. Three doses of a vaccine batch, containing 10 µg of O1 Manisa antigen, 4 µg of A Turkey 14/98 antigen and 4 µg of Asia 1 Shamir antigen per dose, were administered to 15 pregnant primiparous sows, a double dose of 4 ml in the first trimester and single doses of 2 ml in the second and third trimesters. Two sows were removed from the study before the 2nd vaccination (about 8 weeks of pregnancy) as the ultrasound to check pregnancy was not clear. At necropsy, one sow was normal and the other carried 7 foetuses but had aplasia of one of the uterine horns. One of the seven

foetuses had a deformed skull and open abdomen. These findings were not considered to be related to the first vaccination.

None of the vaccinations resulted in a significant rise in body temperature of the sows. Local reactions were observed in all animals. The largest average diameters of the injection site reactions were 8 ± 8.6 mm, 17 ± 18.2 mm and 36 ± 32.3 mm (mean ± sd) after the 1st, 2nd and 3rd vaccination respectively.

A total of 175 piglets were born from 13 sows. Thirteen piglets were born dead, including 5 mummified foetuses from 4 different sows. One piglet was born with a claw malformation. The resulting number of 12.5 live piglets/sow corresponds to the expected number of piglets for this breed. The claw malformation was considered as in incidental finding.

Two weeks after birth 9.8 piglets/sow were still alive, i.e. a loss of 22%. Gross pathology revealed that the loss of piglets was mostly due to trauma, myofibrillar hyoplasia (splay leg) or weakness. Although the loss of piglets in the first two weeks after birth is higher than to be expected in this sow production line (12.2% until weaning), there was no clinical or pathological evidence that the repeated vaccinations of the sows induced teratogenic or other undesirable effects.

General comments on examination of reproductive performance

It was noted that the batch did not meet the initially proposed final product specifications for potency for FMD strain O1 Manisa and A Turkey 14/98 but the applicant has justified that the quantity of antigen per dose for this batch was suitable to demonstrate safety of the vaccine.

The monograph indicates that separate groups of animals should receive a double dose of vaccine at the beginning of each trimester. Therefore these studies in pregnant animals were not performed strictly according to Ph. Eur. monograph for FMD strains O Taiwan 3/97 and A22 Iraq. However, taking into account the trend towards increasing reaction size following repeat vaccination in the repeated-dose safety tests, the study conducted can be considered as a more extreme test of safety during pregnancy and indeed a worst case.

In the interests of animal welfare and taking into account the likely use of this vaccine to deal with an emergency situation it is not reasonable to repeat this study and it is accepted that the vaccine can be used for pregnant animals.

Although the SPC states that the vaccine can be used during lactation, no studies were provided to support this claim. A statement that no safety data are available to demonstrate the impact of vaccination on lactation has been included in the SPC.

Examination of immunological functions

AFTOVAXPUR DOE is a conventional inactivated vaccine containing classical compounds with no known adverse effect on immunological function.

Special requirements for live vaccines

Not applicable.

Study of residues

In view of the nature of the active substance and considering that the excipients including the adjuvant are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No

37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009, a zero day withdrawal period is appropriate.

Interactions

No specific studies have been conducted and a statement to this effect is included in the SPC.

Field studies

The use of FMD vaccines is prohibited in the European Union and the applicant's justification for lack of field studies is accepted. Appropriate information was gathered from laboratory studies and where insufficient information was available appropriate warnings have been included in the SPC.

User safety

An appropriate user safety assessment was provided. With regard to the user safety, the likelihood, the consequences and the level of risk of human exposure is expected to be low. Except for accidental injection, injuries from needles and damaged primary packages, there is no risk for the user. The vaccine contains a mineral oil adjuvant and an appropriate safety warning concerning the risks of accidental injection is included in the SPC.

Environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment.

A phase I environmental risk assessment was provided outlining that the potential exposure of the environment to the product and the level of risk associated with it is considered negligible. The conclusion of this first phase is that there is no potential exposure of the environment to the product and therefore no phase II assessment is necessary.

AFTOVAXPUR DOE is not expected to pose a risk to the environment when used as recommended. An appropriate warning is included in section 6.6 of the SPC regarding the disposal of any unused product.

Environmental risk assessment for products containing or consisting of genetically modified organisms

Not applicable.

Overall conclusion on safety

The applicant has evaluated the safety of the administration of one dose of AFTOVAXPUR DOE under laboratory conditions in calves, lambs and pigs. Most of the studies were performed with a double dose of vaccine (4 ml) containing 15, 7.5 and 7.5 µg of 146S antigen per dose of strains O1 Manisa, A Turkey and Asia 1 Shamir respectively (i.e. a total of 30 µg of FMD antigen per 2 ml dose). These studies were performed in calves from approximately 9 weeks of age, and in pigs and lambs from 8 weeks of age.

Vaccination of calves resulted in pyrexia and local swelling at the injection site, no behavioural changes were observed.

Vaccination of lambs resulted in local swelling at the injection site, no behavioural changes or pyrexia were observed.

Vaccination of pigs resulted in local swelling, no behavioural changes were observed and no pyrexia was recorded.

The applicant has also provided data from safety studies in 3-week old calves and piglets. These studies were not performed in line with the CVMP Position paper on requirements for vaccines against foot-and-mouth disease (EMEA/CVMP/775/02) and Ph. Eur. monograph 0063 and can only be considered as supportive. The proposal to indicate AFTOVAXPUR DOE for calves, sheep and pigs from 2 weeks of age is not supported as safety has not been demonstrated in animals of the youngest age.

Additional safety data have been presented during the studies performed to examine reproductive performance. The applicant has also provided a publication as supporting evidence which demonstrates the safety of a vaccine containing 2 µg of O1 BFS 146S antigen in calves, lambs and piglets at 2 weeks of age. Safety has not been adequately demonstrated in 2 week old animals and on basis of the data provided the minimum age recommended in the SPC should be 2 months. The inclusion of information in the SPC that there was limited data to support the safety of the vaccine if used for cattle and pigs from 3 weeks of age in an emergency situation was however accepted.

The animals in the studies described above that received a double dose of vaccine to evaluate the safety of the administration of one dose, were also used to evaluate the safety of the administration of a repeated dose. The single dose of 2 ml was administered at a separate site, two weeks after receiving the double dose. In cattle, the local reactions were comparable to those observed after the first administration and no significant pyrexia or behavioural changes were recorded. In lambs, the second vaccination resulted in significant pyrexia and open abscesses at the injection sites. No behavioural changes were observed and it was considered that these extreme reactions were consistent with the development of a delayed-type hypersensitivity reaction. An appropriate warning is included in the SPC. A hypersensitivity reaction was also documented in pigs. Besides the more severe local reactions observed in pigs receiving a second dose compared to a primary dose, no pyrexia or behavioural changes were recorded. Additional safety data on administration of a repeated dose were also presented during the studies performed to examine reproductive performance.

Safety studies were performed in pregnant animals of each target species vaccinated during each trimester of pregnancy. The studies were in general performed in compliance with the safety studies to be performed in pregnant animals, as described under section 2-4-1-2 of Ph. Eur. monograph 0063. It was noted that the batch used to evaluate safety in pregnant animals did not meet the final product specifications for potency for FMD strain O1 Manisa and A Turkey 14/98, however the quantity of antigen per dose for this batch was confirmed sufficient to demonstrate safety of the vaccine. In addition, the monograph indicates that each group of animals should receive a double dose of vaccine at the beginning of each trimester. Therefore these studies in pregnant animals were not performed according to Ph. Eur. monograph for FMD strains O Taiwan 3/97 and A22 Iraq. However, taking into account the trend towards increasing reaction size following repeat vaccination in the repeated-dose safety tests the study conducted can be considered as a more extreme test of safety during pregnancy and indeed representing a worst case scenario. In the interests of animal welfare and taking into account the likely use of this vaccine to deal with an emergency situation it is not reasonable to ask to repeat this study and it is accepted that the vaccine can be used for pregnant animals.

A warning has been included in the SPC that no safety data are available to demonstrate the impact of vaccination on lactation.

AFTOVAXPUR DOE is a conventional inactivated vaccine containing classical compounds with no known adverse effect on immunological function.

Concerning consumer safety, there are no components that require an MRL and no specific risks for the consumer have been identified. A zero days withdrawal period as stated in section 4.11 of the SPC is considered appropriate.

Concerning user safety, the risk posed by the product is considered low when used as recommended. For the user there is a low risk of (self-) injection or injuries from needles and damaged primary packages. The vaccine does contain mineral oil and an appropriate user safety warning is included on the SPC.

No specific studied have been conducted to investigate the interactions with other veterinary medicinal products and the lack of field safety data are justified due to the prohibition of use in the European Union.

The product is not expected to pose a risk to the environment when used as recommended. An appropriate advice is included in section 6.6 of the SPC regarding the disposal of any unused product and the avoidance of any risk from remains of the vaccine after use.

Part 4 – Efficacy

Introduction and general requirements

Foot-and-mouth disease virus (FMD virus; family *Picornaviridae*; genus *Aphthovirus*) causes an acute disease of cloven-hoofed animals characterised by fever, lameness, and vesicular lesions. These debilitating effects, rather than high mortality rates, are responsible for severe productivity losses. The virus can spread extremely rapidly, has the potential to cause enormous economic losses and is the single most important constraint to international trade in livestock and animal products. Spread of the virus can be controlled by early detection of new cases, slaughtering animals on affected farms, vaccination of susceptible hosts and by implementing movement restrictions.

There are seven serotypes of FMD virus, namely O, A, C, SAT1, SAT2, SAT3, and Asia 1 that infect cloven-hoofed animals. Infection with any one serotype does not confer protective immunity against another.

AFTOVAXPUR DOE was developed to be a "multi-strain" vaccine. The applicant has incorporated seven FMD virus high priority strains belonging to three different FMD serotypes (O, A and Asia 1) as recommended by the World Reference Laboratory for foot-and-mouth disease, at the Pirbright Institute in Pirbright, United Kingdom.

FMD serotype O	**FMD serotype A**	**FMD serotype Asia 1**
O1 Manisa	A22 Iraq	Asia 1 Shamir
O1 BFS	A24 Cruzeiro	
O Taiwan	A Turkey 14/98	

AFTOVAXPUR DOE vaccine can be formulated containing one to three of these antigens. The maximum number of three strains is based on the safety studies (part 3), as is the maximum payload of 30 µg of 146S FMD antigens.

It is not practical to test all aspects relevant to the efficacy for all strains and all possible combinations included in the multi-strain dossier, as acknowledged in CVMP guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), bluetongue (BT) and foot-and-mouth disease (FMD) (EMA/CVMP/IWP/105506/2007) and the CVMP Position paper on requirements for vaccines against foot-and-mouth disease (EMEA/CVMP/775/02). For crucial tests,

such as the test for immunogenicity (Ph. Eur. monograph 0063), monovalent AFTOVAXPUR DOE vaccines have been formulated for each of the strains included in the dossier. For other efficacy studies, AFTOVAXPUR DOE vaccines with representative antigens were used, based on the similar nature of FMD antigens, on the practical and animal welfare problems and in line with the aforementioned guidelines.

All efficacy studies were performed with monovalent vaccines. Guideline EMA/CVMP/IWP/105506/2007 provides guidance on efficacy studies. Under section 6.3, the guideline indicates that it will be admitted that efficacy of any multi-strain vaccine containing a combination of these antigens (within the maximum number of antigens previously established) will be at least as efficacious as shown for each of the mono-strain vaccine.

Laboratory trials

Efficacy assessed by challenge experiments

For all strains, one test in pigs and several tests in cattle were conducted for immunogenicity in line with the requirements described in Ph. Eur. monograph 0063. In cattle, five studies were carried out using O1 Manisa, one using O1 BFS, three using A22 Iraq, one using A24 Cruzeiro, three using A Turkey 14/98 and three using Asia 1 Shamir. A single study in pigs was carried out using O Taiwan 3/97.

The study design for all the tests in cattle was basically the same. In each individual trial, three groups of 5 cattle aged 6-8 months were vaccinated subcutaneously with full dose, 1/4 dose and 1/16 dose by volume restriction. Two cattle served as unvaccinated controls. Four weeks after vaccination all animals were challenged by intra-lingual inoculation of homologous FMD virus. Eight days after challenge, all animals were slaughtered and animals showing lesions at sites other than the tongue were scored as unprotected. The value of one PD_{50} was calculated. A theoretical extra group was included in the analysis in line with Position paper EMEA/CVMP/775/02. In this theoretical group, all animals receiving the next lower dose volume in the sequence (1/64) were assumed to be unprotected. The method used to calculate PD_{50} was justified.

The immunogenicity study for O Taiwan 3/97 was performed in pigs. The OIE Terrestrial Manual describes a test using three groups of five pigs, similar to the potency test described for cattle. However, in this study five groups of three pigs, aged 3 months, were used. This study design which differed significantly from the generic design was justified because of the increased risk of transmission of large quantities of virus between infected and vaccinated animals within pens.

Statistical regression analyses was performed in order to determine the value of one PD_{50} using a logistic regression model for all strains except O Taiwan 3/97. In the case of O Taiwan 3/97, which is a pig adapted strain, the results of only one study were used to extrapolate the quantity of antigen required for a 6 PD_{50} vaccine.

A justification was provided for the virus neutralising antibody titres detected pre-vaccination in the cattle used to demonstrate the immunogenicity of AFTOVAXPUR DOE containing Asia 1 Shamir antigen. With the exception of one study, virus neutralising antibody titres reported for the studies ranged from <0.3 to 1.13.

In addition to cattle, the vaccine is also indicated for sheep and pigs. A robust justification based on published papers and other submitted data support the extrapolation of efficacy data generated in cattle to these other species.

Virus transmission and onset of immunity

The applicant originally proposed to indicate AFTOVAXPUR DOE for active immunisation of cattle, sheep and pigs at least 2 weeks of age to reduce clinical signs, viraemia and virus transmission and to reduce mortality following FMD infection. The claimed onset of immunity was 2 weeks.

A series of experiments were conducted to investigate the effect of a single vaccination of AFTOVAXPUR DOE on virus transmission and to support the efficacy claims. These investigations were performed in all target species: cattle (both calves and adult dairy cows), sheep and pigs. In all experiments, animals were exposed to virulent FMD virus two weeks after vaccination and compared to a non-vaccinated control group. The studies were designed to mimic natural infection.

The results of these studies have been published in a number of peer-reviewed papers by Orsel et al. Studies were only conducted using AFTOVAXPUR DOE vaccine containing antigen from FMD strain O1 Manisa.

Design for calves

Twenty-six calves were divided over 6 groups of 4 animals each and 2 control animals. The trial was conducted twice using the same design.

Design for dairy cows

Twenty-two dairy cows were divided over 2 groups of 10 animals each and 2 control animals. The trial was conducted twice using the same design.

Design for lambs

Fifty-two lambs were divided over 13 groups, one group of 4 animals served as controls.

For calves, dairy cows and lambs; half of the groups were vaccinated with AFTOVAXPUR DOE containing antigen from FMD strain O1 Manisa. The control group of 2 or 4 animals was vaccinated simultaneously and served as a vaccine control group (not inoculated or otherwise exposed to FMDV). Two weeks post vaccination, half of the animals of each group were removed to a separate unit to be infected with field strain O/NET 2001. Twenty-four hours after infection, the animals were re-united with their group members.

Design for piglets

Four groups of 4 non-vaccinated pigs were inoculated with O/NET 2001 and served as "seeder pigs". Twenty four hours after infection, a group of 4 seeder pigs was housed with 5 contact pigs (either vaccinated or non-vaccinated). As soon as FMD was confirmed in one of the contact pigs, the seeder pigs were removed and the whole group of contact pigs was relocated to another pen and housed with 5 new contact pigs. This procedure was replicated 4 times; twice with vaccinated contacts and twice with non-vaccinated contacts.

Results for calves

Ten of twelve non-vaccinated calves developed clinical signs of FMD post challenge, FMD virus was detected in the plasma of ten calves, all produced virus neutralising antibodies and ten produced antibodies to non-structural proteins. Seven of twelve in-contact non-vaccinated calves also developed clinical signs of FMD, virus was detected in the plasma of ten, eight produced virus neutralising antibodies and five produced antibodies to non-structural proteins. In contrast, only one of the vaccinated calves developed clinical signs of FMD post challenge, although FMD virus was detected in the plasma of nine calves, all produced virus neutralising antibodies and six produced antibodies to non-structural proteins. None of twelve in-contact vaccinated calves developed clinical signs of FMD or

had detectable FMD virus in plasma samples, eleven produced virus neutralising antibodies and one produced antibodies to non-structural proteins.

Results for dairy cows

All of ten non-vaccinated and challenged cows and ten non-vaccinated in-contact cows developed clinical signs of FMD post challenge, FMD virus was detected in their plasma, produced virus neutralising antibodies and produced antibodies to non-structural proteins. In contrast, none of the ten vaccinated and challenged cows or ten vaccinated in-contact cows developed clinical signs of FMD post challenge, had FMD virus detected in their plasma or produced virus neutralising antibodies. Six of the vaccinated and challenged cows and none of the vaccinated in-contact cows produced antibodies to non-structural proteins.

Results for lambs

Nine of twelve non-vaccinated lambs developed clinical signs of FMD post challenge, FMD virus was detected in the plasma of eleven lambs, all produced virus neutralising antibodies and produced antibodies to non-structural proteins. Three of twelve in-contact non-vaccinated lambs also developed clinical signs of FMD, virus was detected in the plasma of five, four produced virus neutralising antibodies and three produced antibodies to non-structural proteins. In contrast, none of the vaccinated lambs developed clinical signs of FMD post challenge, although FMD virus was detected in the plasma of five lambs, all produced virus neutralising antibodies and seven produced antibodies to non-structural proteins. None of twelve in-contact vaccinated lambs developed clinical signs of FMD although one had detectable FMD virus in plasma samples, all produced virus neutralising antibodies and none produced antibodies to non-structural proteins.

Results for pigs

Transmission occurred to all of contact-exposed pigs in the non-vaccinated groups and to nine of ten contact-exposed pigs in the vaccinated groups.

The effect of vaccination on virus transmission was calculated in all experiments using a stochastic susceptible-infectious-recovered model. The number of susceptible, infectious and recovered animals was calculated at the beginning and at the end of the experiment. The reproduction ratio was estimated for the vaccinated groups (Rv) and the non-vaccinated groups (Rnv) based on the observed final size of the infection chain by means of maximum likelihood estimation. Orsel et al. tested whether Rnv was significantly above 1 which means that a major outbreak will most likely occur. To quantify the effect of vaccination on virus transmission Rv was tested if it was significantly below 1, so only minor outbreaks will occur and the epidemic will fade out. Orsel et al. also compared the control strategy with and without vaccination, by testing the one-sided hypothesis H0 = Rnv (H1:Rv<Rnv), i.e. are groups with and without vaccination the same against the one-sided alternative.

For calves the Rnv was significantly above 1, Rv was significantly below one and the R-values of both groups were significantly different ($p = 0.003$). For dairy cows the Rnv was significantly above 1, Rv was not significantly below one, however the R-values of both groups were significantly different ($p = 0.013$). This was not the case for lambs or pigs (i.e. Rv not significantly below one, R-values of both groups not significantly different).

With regards to pigs, the rate of transmission was significantly reduced in the vaccinated group but the estimated reproduction ratio in both groups was still above 1. Vaccination is therefore only moderately effective in reducing or preventing within-pen virus transmission. Orsel et al., 2007 concluded that a single vaccination was not sufficient to stop pig to pig virus transmission.

Due to a high number of deficiencies concerning the above data the claims for reduction of transmission and a 2 weeks onset of immunity were withdrawn by the applicant. The acceptable onset of immunity is 4 weeks which is in line with the time of challenge in the challenge studies used to determine PD_{50}.

No data have been provided to support a claim for reduced mortality following FMDV infection and this indication is therefore not justified.

In addition, a summary of a paper published by Roermund et al. (2010) was provided to demonstrate the absence of between-pen transmission of foot-and-mouth disease virus in vaccinated pigs.

The studies, which used three groups of 24 ten-week-old piglets, were designed to mimic FMD in pig stables in the field. To start an infectious chain, seeder pigs were obtained by infecting non-vaccinated pigs in the bulb of the feet with FMDV strain O/NET/2001. Twenty-four hours later, seeder pigs were housed together with pigs vaccinated 2-weeks earlier with an O1 Manisa vaccine or non-vaccinated contact pigs (C1). As soon as a sample of oro-pharyngeal fluid of one of the C1 pigs tested positive for FMDV genome by RT-PCR, seeder pigs were euthanized and the C1 contact pigs relocated and housed, under varying stable lay-outs, with fresh contact pigs (C2) which were either vaccinated or non-vaccinated. The animals were monitored daily for clinical signs. The infectious status was determined by virus isolation from oro-pharyngeal fluid collected daily. Other tests (VNT, antibodies against Non-Structural Proteins [NSPs], RT-PCR) were used for confirmation. The rate of virus transmission was expressed as the reproduction rate R which was calculated according to methods described previously. Compared to non-vaccinated pigs, virus excretion was reduced in vaccinated pigs. The study demonstrated that vaccination reduced between-pen transmission in pigs for FMD O1 Manisa.

In conclusion, the data presented support an indication for use for AFTOVAXPUR DOE for active immunisation of cattle, sheep and pigs at least 2 months of age to reduce clinical signs. The indication for use to reduce mortality following FMD infection is rejected due to lack of data to support this indication. The justified onset of immunity is 4 weeks.

Duration of immunity

Study data have been presented to support the claimed 6 months duration of immunity (DOI). Position paper EMEA/CVMP/775/02 indicates that manufacturers must demonstrate DOI by either challenge or the use of a validated test, such as serology, at the end of the claimed period of protection, in compliance with CVMP Note for Guidance on Duration of protection achieved by veterinary vaccines (CVMP/IWP/682/99). Position paper EMEA/CVMP/775/02 indicates that manufacturers should demonstrate the effectiveness of the recommended booster regime in line with the guidelines, usually by measuring the magnitude and kinetics of the serological response observed.

Three study reports were provided which assess the DOI in cattle, sheep and pigs respectively using a series of monovalent vaccines representing the different serotypes. The studies were each performed using 8 groups of 5 animals free from FMD antibodies at the time of vaccination as determined by virus neutralising antibody titres (3 groups for O1 Manisa, 3 groups for A Turkey 14/98, 2 groups for Asia 1 Shamir). Blood was collected from each animal prior to vaccination and then weekly for six weeks following vaccination, again at 8 weeks and subsequently every 4 weeks until the 24 week time point. The mean virus neutralising antibody titres of each group of 5 animals were calculated for each time point and analysed using an ANOVA for Repeated Measurements and using post-hoc multiple comparison tests.

It is acceptable that no sentinel control animals were included (as required by CVMP/IWP/682/99) as the studies were conducted in conventional facilities.

The DOI studies have been conducted with reduced volumes or with vaccines formulated to contain reduced antigen loads, based on statistical analysis of immunogenicity studies performed in cattle according to Ph. Eur. monograph 0063. The duration of immunity has been established on the basis of the evolution of antibody titres during 24 weeks after vaccination. A good correlation between antibody titre and protection from challenge four weeks after vaccination was established. Antibody titres in all three of the indicated species following vaccination were similar and followed similar development with time. Antibody titres of a representative strain of each of the serotypes (O1 Manisa, A Turkey 14/98 and Asia 1 Shamir) were shown to persist for at least 24 weeks after vaccination at titres similar or higher than at 4 weeks after vaccination (the time when the challenge studies were carried out) in cattle, sheep and pigs vaccinated using the minimum specified quantities of each of the respective strains. An indication of 6 months DOI is therefore acceptable.

In conclusion, 6 months duration of immunity is acceptable. The effectiveness of the recommended revaccination regime has not been demonstrated. However, since the primary course consists of only a single injection the recommendation to repeat this after 6 months is acceptable.

Effect of maternally derived antibodies

The applicant used piglets as a model to demonstrate the effect of vaccination in the presence of maternally derived antibodies (MDA). Forty piglets from vaccinated sows were vaccinated intramuscularly in the neck with a monovalent AFTOVAXPUR DOE vaccine containing at least 6 PD_{50} of A Turkey 14/98 antigen at respectively 2, 4, 6, and 8 weeks of age. One group of piglets with MDAs was not vaccinated. Ten additional piglets without MDAs were vaccinated with the same vaccine at 2 weeks of age.

In all vaccinated groups, the decline in antibody titres stopped and started to rise again following vaccination. The response at 8 weeks was similar to piglets without MDA. It is noteworthy that investigators have reported that calves with MDA vaccinated against FMD not only fail to respond, but vaccination depresses the serum titre of specific FMD virus antibody. However, in contrast to the published reports, the applicant has demonstrated that vaccination with AFTOVAXPUR DOE in the presence of MDAs does not suppress the titre of MDAs and a statement to this effect is included in the SPC.

The minimum age of 2 months is at a time when MDA titres have declined to non-significant levels and therefore no reference has been included in the SPC for an effect of MDAs on efficacy.

Non Structural Proteins (NSP) and marker vaccine

Vaccines containing highly purified FMD virus particles do not contain NSP and allow differentiation between vaccinated or infected animals by the presence or absence of antibodies against NSP.

Removal of NSP during the production process

Data were presented to demonstrate that NSP are largely removed during the production process. It is noteworthy that 3ABC protein is still detectable after filtration as determined by the FMDV IPC-3ABC test kit but data suggests that these are not sufficient to induce the production of anti-NSP antibodies in vaccinated animals.

Antibodies against NSP in sera after repeated administration of AFTOVAXPUR DOE

Sera from repeatedly vaccinated animals and vaccinated-challenged cattle were tested for the presence of antibodies against NSP. The results were described in the publication Chénard et al. (2008).

Serum samples collected from 10 calves, 10 lambs and 10 piglets following administration of a double dose and, two weeks later, a repeat dose of high payload trivalent AFTOVAXPUR DOE vaccine (A Turkey 14/98, Asia 1 Shamir and O1 Manisa) were tested for presence of antibodies to NSP. All serum samples collected two weeks following the administration of a double dose as well as those collected two weeks after the single dose booster were negative for antibodies against NSP.

In a series of vaccine potency experiments, serum samples were collected from 70 vaccinated cattle prior to and following exposure to infectious, homologous FMD virus. The animals had been vaccinated with monovalent vaccines containing various different FMD antigens (A Turkey 14/98, A Iran 2/87, Asia 1 Shamir, A22 Iraq, A24 Cruzeiro, O1 BFS, O1 Manisa). When testing the cattle sera taken 4 weeks after vaccination, one animal tested positive for the presence of antibodies against NSP; this was considered a false positive. Batch details of the vaccines used during these studies were not provided.

Although these studies did not exactly follow the vaccination regime suggested in the CVMP Position paper on requirements for vaccines against foot-and-mouth disease (EMEA/CVMP/775/02) a satisfactory justification was presented of the vaccination regimes used to demonstrate that antibodies to NSPs are not induced by the vaccine.

Testing serum from cattle, sheep and pigs vaccinated on three separate occasions

These studies were described above under section Examination of reproductive performance.

Repeated vaccination did not induce the production of antibodies against NSP in cattle, sheep, and pigs.

The CVMP Position paper on requirements for vaccines against foot-and-mouth disease EMEA/CVMP/775/02 provides quality requirements in support of information related to NSP. Tests should be conducted with vaccines containing the maximum permitted amount and number of antigens. The position paper recommends a test in 10 animals vaccinated with two doses of this vaccine on day 0, day 14-28 and day 42. The immunogenicity of O Taiwan 3/97 and A22 Iraq strains at the fixed quantity of antigen (7 and 5 µg of 146S respectively) have not been demonstrated therefore these studies may not be applicable. In addition, the applicant indicates in the dossier that the maximum payload is 30 µg of 146S FMD antigens. The applicant has also only administered a double dose on day 0 (20, 8 and 8 µg of 146S) and single doses for the 2nd and 3rd administration.

The regime used by the applicant is therefore not entirely compliant with the recommended immunisation testing program in the position paper EMEA/CVMP/775/02, although deviations are acceptable in the interest of animal welfare. Cows were vaccinated at 6-10, 13-17 and 26-30 weeks of pregnancy. Ewes were vaccinated at 5, 7-10 and 14-17 weeks of pregnancy. Sows were vaccinated at 5, 8 and 12 weeks of pregnancy. A description of the circumstances in which the lack of antibodies to NSP was demonstrated is included in section 5 of the SPC.

Field trials

Vaccination against FMD is currently prohibited in the EU so it was not possible to perform field trials with AFTOVAXPUR DOE in the EU.

Overall conclusion on efficacy

For all strains, one or more tests for immunogenicity have been conducted.

The method used to calculate the value of one PD_{50} for all strains except O Taiwan 3/97 use a global logistic regression model. A table of the quantities of 146S antigen for each FMD strain to reach a 6 PD_{50} per 2 ml dose has been provided.

A series of experiments were conducted to investigate the effect of a single vaccination of AFTOVAXPUR DOE intended to support the proposed indications for active immunisation of cattle, sheep and pigs at least 2 weeks of age to reduce clinical signs, viraemia and virus transmission and to reduce mortality following FMD infection. The proposed onset of immunity is 2 weeks.

The investigations were performed using only the O1 Manisa strain in all target species: cattle (both calves and adult dairy cows), sheep and pigs. In all experiments, animals were exposed to virulent FMD virus two weeks after vaccination. A number of deficiencies were however noted in this section. A reduced virus transmission was demonstrated in calves and dairy cows but not in lambs and pigs. No data have been provided which support the indication for reduced mortality, which is therefore rejected. The acceptable minimum age for vaccination is 2 months.

In line with the position paper EMEA/CVMP/775/02 and in view of the similar nature of FMD antigens, a series of studies were conducted to assess the duration of immunity in cattle, sheep and pigs using a series of monovalent vaccines representing the 3 serotypes. The duration of immunity studies were conducted with reduced volumes of vaccine or with reduced antigen formulations, based on the methods used to calculate the amount of 146S antigen for one PD_{50}. Antibody titres of a representative strain of each of the serotypes (O1 Manisa, A Turkey 14/98 and Asia 1 Shamir) have been shown to persist for approximately 6 months after vaccination at titres similar or higher than at 4 weeks after vaccination (the time when the challenge studies were carried out) in cattle, sheep and pigs vaccinated using the minimum specified quantities of each of the respective strains. The SPC therefore recommends revaccination every 6 months, based on the duration of immunity studies.

With the acceptance of the so-called "vaccinate to live" policy in the European Union (Council Directive 2003/85/EC), offspring may be born from FMD-vaccinated animals. In the case of a persisting FMD outbreak, Maternally Derived Antibodies (MDA) might interfere with an efficacious immune response to vaccination. Using piglets as a model, the effect of MDA on vaccination with AFTOVAXPUR DOE was investigated. The effect of MDA was only demonstrated for pigs and for FMD virus serotype A only. However, the acceptable minimum age recommended for vaccination is 2 months and information has been submitted to demonstrate that MDA titres will have declined to insignificant levels by this time and no claim with respect to MDAs is now included in section 4.2 of the SPC.

Studies were provided to support that AFTOVAXPUR DOE does not contain sufficient NSP to induce an antibody response in vaccinates following repeated administration.

The lack of field trials with AFTOVAXPUR DOE because vaccination against FMD is currently banned in the EU was considered acceptable.

Part 5 – Benefit risk assessment

Introduction

Foot-and-mouth disease virus (FMD virus; family *Picornaviridae*; genus *Aphthovirus*) causes an acute disease of cloven-hoofed animals characterised by fever, lameness, and vesicular lesions. These debilitating effects, rather than high mortality rates, are responsible for severe productivity losses. The virus can spread extremely rapidly, has the potential to cause enormous economic losses and is the single most important constraint to international trade in livestock and animal products. Spread of the virus can be controlled by early detection of new cases, slaughtering animals on affected farms, vaccination of susceptible hosts and by implementing movement restrictions.

There are seven serotypes of FMD virus, namely O, A, C, SAT1, SAT2, SAT3, and Asia 1 that infect cloven-hoofed animals. Infection with any one serotype does not confer protective immunity against another.

AFTOVAXPUR DOE consists of a maximum of three inactivated, purified FMD virus strain antigens (multi-strain) of the following seven strains: O1 Manisa, O1 BFS, O Taiwan 3/97, A22 Iraq, A24 Cruzeiro, A Turkey 14/98 and Asia 1 Shamir. This is an immunological veterinary medicinal product that is administered via the intramuscular or subcutaneous route to induce active immunity against foot-and-mouth disease in the target species.

Benefit assessment

Direct therapeutic benefit

Stimulation of active immunity of cattle, sheep and pigs against foot-and-mouth disease virus strains related to those contained in the vaccine.

In trials the following has been demonstrated:

Vaccination of cattle with strains O1 Manisa, O1 BFS, A22 Iraq, A24 Cruzeiro, A Turkey 14/98 and Asia 1 Shamir resulted in a reduction of clinical signs in animals exposed to infection.

Vaccination of sheep with strain O1 Manisa resulted in a reduction of clinical signs in animals exposed to infection.

Vaccination of pigs with strain Asia 1 Shamir resulted in a reduction of clinical signs and virus shedding in animals exposed to infection. Vaccination of pigs with strains O Taiwan 3/97 and A22 Iraq resulted in a reduction of clinical signs in animals exposed to infection.

Additional benefits

AFTOVAXPUR DOE containing O1 Manisa antigen reduced virus transmission in calves and cows. This was not the case for lambs or pigs and no data have been provided for the other strains.

Reduced between-pen transmission was demonstrated for monovalent AFTOVAXPUR DOE containing FMD O1 Manisa in pigs. No data have been presented to support this claim in cattle or sheep or for other serotypes or strains.

Inactivated foot-and-mouth disease antigens are purified and do not contain sufficient amounts of non-structural proteins (NSP) to induce an antibody response following administration of a trivalent vaccine containing an amount of antigen corresponding with at least 15 PD_{50} per strain per dose of 2 ml.

No antibodies to NSP were detected using the PrioCHECK FMDV NS test kit:

- in cattle following administration of a double dose followed by a single dose 7 weeks later and a third vaccination with a single dose 13 weeks after the second dose,
- in sheep following administration of a double dose followed by a single dose 5 weeks later and a third vaccination with a single dose 7 weeks after the second dose,
- in pigs following administration of a double dose followed by a single dose 3 weeks later and a third vaccination with a single dose 7 weeks after the second dose.

Risk assessment

The safety of AFTOVAXPUR DOE was assessed in cattle, sheep and pigs with batches of trivalent vaccines containing antigen from all three relevant serotypes. A repeat dose was well tolerated in cattle, however delayed-type hypersensitivity reactions and ulcerations were frequently associated with a repeat dose in 10 week old lambs. In addition, administration of a repeat dose in 10 week old pigs frequently resulted in more severe local reactions as a consequence of hypersensitivity reactions. The vaccine was indicated from 2 weeks of age; the risk of these reactions may not be acceptable in this age category and the minimum recommended age has subsequently been increased to 2 months.

The vaccine has been shown to be safe for use during pregnancy. No data have been provided to support the claim that the vaccine is safe during lactation.

Due to the nature of the vaccine components, a zero days withdrawal period is considered appropriate. The vaccine poses no risk to the environment when used as recommended.

AFTOVAXPUR DOE contains mineral oil as an adjuvant. The SPC contains appropriate warnings and directions for both the injured person and the treating physician.

Risk management or mitigation measures

Appropriate warnings have been included in the SPC to inform on the potential risks to the target animals and the user and the environment and to provide advice for reducing these risks.

Evaluation of the benefit risk balance

The product has been shown to have a positive benefit-risk balance overall.

AFTOVAXPUR DOE is a vaccine intended for use to combat an outbreak of foot-and-mouth disease. At present the only alternative control measure available for this disease is slaughter of infected herds. The application is based on a multi-strain dossier which enables selection of appropriate strains of virus depending on the epidemiological situation, up to a maximum of three strains in any one batch of vaccine. The vaccine has been shown to reduce clinical signs in cattle, sheep and pigs for each of the strains that might be included.

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

The vaccine is in general well tolerated by the target animals. The adverse reactions that have been identified following use of the vaccine are typical for this type of vaccine and can be tolerated for a disease with such a major welfare and economic impact.

The vaccine presents a low risk for users and the environment when used as recommended. Appropriate warnings have been included in the SPC and product literature.

A zero day withdrawal period is considered adequate.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that, the quality, safety and efficacy of AFTOVAXPUR DOE are considered to be in accordance with the requirements of Directive 2001/82/EC.