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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for AFTOVAXPUR DOE Type II variation (EMEA/V/C/002292/II/0001)

Scope of the variation:

Addition of a new foot-and-mouth disease virus antigen strain: SAT2 Saudi Arabia to take into account recommendations of the World Reference Laboratory for FMD, (Pirbright, U.K.) for antigens to be included in vaccine or antigen banks.

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

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder, MERIAL (the applicant), submitted to the European Medicines Agency (the Agency) an application for a type II variation for AFTOVAXPUR DOE. The rapporteur was A.-M. Brady and the co-rapporteur was M. Tollis.

1.2. Scope of the variation

Addition of a new foot-and-mouth disease (FMD) virus vaccine strain, South African Territories 2 (SAT2) Saudi Arabia to take into account recommendations of the World Reference Laboratory for FMD, (Pirbright, UK) for antigens to be included in antigen banks.

The addition of a new strain results in a number of minor textual modifications, including the number of new possible strain combinations, an updated list of strains in the product information and various tables including the table of qualitative and quantitative composition.

The specific elements supporting the quality of this new antigen and its similarity with existing ones have been included in the documentation. Since the maximum amount and number of antigens is the same and the composition of the finished product remains unchanged, no new safety data were required.

Current	**Proposed**
SPC **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** **Active substances:** Maximum three of the following purified, inactivated foot-and-mouth disease virus strains: O1 Manisa ≥ 6 PD_{50}* O1 BFS ≥ 6 PD_{50}* O Taiwan 3/97 ≥ 6 PD_{50}* A22 Iraq ≥ 6 PD_{50}* A24 Cruzeiro ≥ 6 PD_{50}* A Turkey 14/98 ≥ 6 PD_{50}* Asia 1 Shamir ≥ 6 PD_{50}* **5. IMMUNOLOGICAL PROPERTIES** Vaccination of cattle with strains O1 Manisa, O1 BFS, A22 Iraq, A24 Cruzeiro, A Turkey 14/98 and Asia1 Shamir resulted in a reduction of clinical signs in animals exposed to infection.	**SPC** **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** **Active substances:** Maximum three of the following purified, inactivated foot-and-mouth disease virus strains: O1 Manisa ≥ 6 PD_{50}* O1 BFS ≥ 6 PD_{50}* O Taiwan 3/97 ≥ 6 PD_{50}* A22 Iraq ≥ 6 PD_{50}* A24 Cruzeiro ≥ 6 PD_{50}* A Turkey 14/98 ≥ 6 PD_{50}* Asia 1 Shamir ≥ 6 PD_{50}* SAT2 Saudi Arabia ≥ 6 PD_{50}* **5. IMMUNOLOGICAL PROPERTIES** Vaccination of cattle with strains O1 Manisa, O1 BFS, A22 Iraq, A24 Cruzeiro, A Turkey 14/98, ~~and~~ Asia1 Shamir and SAT2 Saudi Arabia resulted in a reduction of clinical signs in animals exposed to infection. *The package leaflet has been updated accordingly.*

2. Scientific discussion

2.1. Assessment

AFTOVAXPUR DOE consists of up to three types of inactivated, purified foot-and-mouth disease virus antigens, chosen from seven that are included in the dossier, in a double oil emulsion adjuvant. The only change to the composition of the vaccine in relation to the current variation is the addition of the SAT2 Saudi Arabia strain to the list of strains that may be included in the vaccine either alone or in combination with up to two of the other listed strains.

Concerning the pharmaceutical development of this strain, care was taken not to change the production process or the test design (allowing a manageable multi-strain dossier approach). In addition, the active substance payload and the serological pass level have been determined using the same method as for the existing strains. The payload determination was based on PD_{50} (the dose of vaccine that protects 50% of the animals challenged) experiment results in which the relation between µg of 146S antigen and protection in cattle was established.

To ensure a measure of consistency across strains and to compensate for any possible stability losses, a minimum payload was set at a higher quantity (≥ 6 PD_{50}).

Following completion of the PD_{50} experiment, a statistical analysis was performed to assess the relationship between protection and serological titre in order to establish at least a 6 PD_{50} pass level. The serological results obtained for SAT2 Saudi Arabia were assessed and the pass level for the new strain was determined as with the initial 7 cattle strains. Further discussion of the challenge study and determination of serological pass level for the SAT2 Saudi Arabia strain are presented below.

The manufacturing process as previously described was followed without any modifications for manufacture of the new active substance as a result of the similarity in behaviour between the different FMD virus strains.

In 2003 a sample of an isolate of the FMD virus strain SAT2 Saudi Arabia was received from the Pirbright Institute, Pirbright, United Kingdom which is the World Reference Laboratory for foot-and-mouth disease (WRL Pirbright).Virus material was adapted to growth on BHK21 cells grown in suspension. The SAT2 Saudi Arabia master seed virus (MSV) was produced on BHK cells.

Each control test was carried out on a sample from the homogeneous batch of MSV.

All the control tests were carried out in compliance with the European Pharmacopoeia (Ph. Eur.) and The rules governing medicinal products in the European Union Vol. 7B Guidelines on veterinary medicinal products, immunologicals, quality (General requirements for the production and control of inactivated mammalian bacterial and viral vaccines for veterinary use, 7BIm2a and Table of extraneous agents to be tested for in relation to the general and species specific guidelines on production and control of mammalian veterinary vaccines, 7BIm10a).

Control tests carried out on the working seed virus (WSV) were appropriate and satisfactory.

The applicant carried out a risk assessment for SAT2 Saudi Arabia FMD virus in accordance with the requirements of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicinal products (EMA/410/01 rev.3) and the CVMP Position paper on the assessment of the risk of transmission of animal spongiform encephalopathy agents by master seed materials used in the production of veterinary vaccines (EMEA/CVMP/019/01).

On the basis of the information provided it can be concluded that the risk of transmitting TSE through the administration of the SAT2 Saudi Arabia FMD virus strain has been adequately addressed and is considered low.

Specific validation studies were carried out to demonstrate the pertinence of the following tests for the new strain:

- Validation of residual live virus test method and
- Validation of virus quantification.

The methods were therefore satisfactorily validated for strain SAT2 Saudi Arabia.

The applicant provided production parameters of three consecutive batches of SAT2 Saudi Arabia antigen. In addition, a summary of the production of batches of vaccine was provided.

Control test results during the production of three consecutive batches were also provided.

On the basis of the information given the consistency of production of the SAT2 Saudi Arabia antigen was satisfactorily demonstrated.

There were no modifications to the test regime with the exception of the PCR test for identification of the SAT2 strain.

For strain SAT2 Saudi Arabia the identity was confirmed in a PCR test using strain-specific primers. Validation of the VN test for each of the respective strains was provided and the determination of the serological pass level were also described and provided for each strain.

On the basis of the provided results storage of the SAT2 Saudi Arabia active substance for up to five years and as agreed for the other approved strains, the stability of the bulk antigen, can be accepted. As the measurement of the 146S antigen content by physico-chemical means did not give assurance that the immunological quality of the antigen is maintained during storage, the applicant has agreed to carry out serological potency tests after 2–3 years and 5 years storage to confirm the quality of the stored antigens.

The applicant provided the results of a stability study for a single batch of vaccine containing SAT2 Saudi Arabia plus some additional data from challenge studies carried out with another batch. This falls short of the normally expected three batches to demonstrate stability. However, the data suggest that this strain is at least as stable as most of the other strains approved for inclusion in the vaccine and therefore the approved shelf life of 6 months (for all strains except Asia1 Shamir) can be maintained for the SAT2 Saudi Arabia strain. The applicant has given a commitment to initiate a real-time stability study for two additional batches containing the SAT2 Saudi Arabia strain (to have a set of three batches eventually).

In line with 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), the efficacy for cattle of a batch of vaccine containing a defined content of 146S antigen from strain SAT2 Saudi Arabia per 2 ml dose was investigated in a single challenge study. This study was carried out in general in line with that described in Ph. Eur. monograph 0063 but with the addition of an extra batch of animals vaccinated with 1/64 dose of vaccine. As in previous studies carried out on other strains already included in the authorisation, challenge was carried out four weeks after vaccination.

The results of this study were used to calculate the PD_{50} of the batch, linked to the 146S antigen content, and the serological titre associated with the pass level for the serological potency test, using the model developed during assessment of the original marketing authorisation application.

The approach is similar to that used to demonstrate efficacy and establish serological pass levels for the other strains already authorised for this vaccine. The determination of the serological pass level for the SAT2 Saudi Arabia strain was described.

The principle of extrapolation of the efficacy data in cattle to the other target species was accepted during assessment of the original application. It was therefore accepted that the SAT2 Saudi Arabia strain had not been specifically tested for efficacy in sheep and pigs.

The general and local reactions at the injection site following vaccination were broadly in line with the description in the SPC.

In this context it is also relevant to consider the serological data presented in the original application dossier). This demonstrated that cattle vaccinated with AFTOVAXPUR DOE produced high antibody titres by two weeks after vaccination and that these titres remained at similar levels for several weeks thereafter.

Antibody titres after four weeks were therefore of the same order as titres after three weeks. As shown above, the applicant demonstrated that protection from disease is correlated to antibody titre so it can therefore be concluded that the protection elicited three weeks after vaccination would have been similar to that demonstrated at four weeks. Therefore AFTOVAXPUR DOE, which is manufactured with sufficient antigen for 6 PD_{50} per dose would have adequately met the minimum 3 PD_{50} standard of the Ph. Eur. if tested three weeks post-vaccination.

2.2. Summary and conclusions

Information on the source of the SAT2 Saudi Arabia strain, establishment and testing of the master virus seed stock has been provided. Satisfactory clarification concerning the range of extraneous agents tested and the methods used to test for freedom from mycoplasmas was provided.

The manufacturing process used for the new strain is the same as that approved for the other strains and there are no changes to other starting materials. The inactivation process has been satisfactorily validated for the new strain. The virus titration assay and sensitivity of the inactivation control test have also been shown to be satisfactory for the new strain. The methods used to confirm antigen identity and correct formulation of production batches were validated using primers specific for SAT2 Saudi Arabia.

Limited stability data provided indicated that the currently approved antigen storage time and vaccine shelf life can be maintained for the new strain but the applicant is reminded that vaccine stability should be confirmed on three production batches of vaccine when these are produced.

A single challenge efficacy trial was carried out and this was used to calculate the PD_{50}, and hence the amount of FMD antigen required for a 6 PD_{50} vaccine, and to establish a suitable antibody pass level for SAT2 Saudi Arabia in the serological potency test.

3. Benefit-risk assessment

3.1. Benefit assessment

This variation to add the SAT2 Saudi Arabia strain to the list of strains that may be used to manufacture the vaccine means that vaccines that contain this strain can be produced quickly in the event of an outbreak of FMD in Europe caused by a SAT2 serotype of the virus; this can be considered an additional benefit.

3.2. Risk assessment

The maximum number of FMD virus strains and the total quantity of FMD virus antigen that may be included in any one batch of vaccine is not changed by this variation. Data have been presented to show that the approved inactivation process is satisfactory to inactivate the SAT2 Saudi Arabia strain.

The master seed has been shown to be free from extraneous contaminants and quality control tests have been satisfactorily validated. The quality of batches of vaccine containing the new strain should be no different from those already approved. The risks presented by the use of this vaccine are therefore unchanged by this variation.

3.3. Evaluation of the benefit-risk balance

As a result of this variation the only impact on the benefit-risk balance is that the range of serotypes of FMD virus antigens that can be included has been expanded to include the SAT2 serotype, which is considered a benefit.

No negative impacts on the benefit-risk balance have been identified.

No change to the impact on the environment is envisaged.

The benefit-risk balance of the product therefore remains positive.

4. Overall conclusions of the evaluation and recommendations

The CVMP considered that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

4.1. Changes to the community marketing authorisation

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

Annexes A, I and IIIB.