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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for AFTOVAXPUR DOE (EMEA/V/C/002292/II/0009)

Common name: Foot-and-mouth disease vaccine (inactivated) (multi-strain: 1-3 strains out of a set of 8)

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

Rapporteur: Noemi Garcia del Blanco

Co-rapporteur: Paolo Pasquali

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5545
Send a question via our website www.ema.europa.eu/contact

Table of contents

Introduction 3
Submission of the variation application 3
Scope of the variation 3
Changes to the dossier held by the European Medicines Agency 3
Scientific advice 3
MUMS/limited market status 3

Scientific Overview 3
Onset of immunity 4

Benefit-risk assessment of the proposed change 5
Benefit assessment 5
Direct therapeutic benefit 5
Additional benefits 6
Risk assessment 6
Quality: 6
Safety: 6
Risk management or mitigation measures 6
Evaluation of the benefit-risk balance 6

Conclusion 7

Introduction

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) on 7 March 2018 an application for a type II variation for AFTOVAXPUR DOE.

Scope of the variation

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The variation is to change the onset of immunity for cattle and sheep. The variation also introduces changes to the Summary of Product Characteristics (and other product information).

Changes to the dossier held by the European Medicines Agency

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

Part 1 and Part 4

Scientific advice

On 26 January 2015, the company MERIAL requested scientific advice for a new indication for the veterinary medicinal product AFTOVAXPUR DOE, which is a purified, inactivated viral vaccine against foot-and-mouth disease (FMD) in cattle, sheep and pigs. The applicant received scientific advice from the CVMP on 10 September 2015 (EMA/V/SA/211/15/I). The scientific advice pertained to the efficacy part of the dossier and the applicant sought scientific advice on two different aspects related to this product. Directly relevant to this variation, the applicant sought guidance on the technical requirements for demonstration of the onset of immunity, and more specifically, on a proposed study which was aimed at demonstrating an earlier onset of immunity following vaccination. This is seen as desirable in order to rapidly inhibit disease spread within and between herds during an outbreak situation. This proposed study is one of the three studies submitted in this variation application, in which the applicant principally followed the scientific advice in its execution.

MUMS/limited market status

Not applicable.

Scientific Overview

Following scientific advice on the technical requirements for demonstration of the onset of immunity (EMA/V/SA/211/15/I), which included a proposed study aimed at demonstrating an earlier onset of immunity following vaccination, the applicant has submitted the reports from three *in vivo* studies to support a change in the onset of immunity for AFTOVAXPUR DOE from four weeks post vaccination

to 7 days post vaccination for the ruminant target species, cattle and sheep. The studies, two of which were confirmed to be carried out in Good Laboratory Practice (GLP) facilities, involved challenge with FMD virus serotype O.

Efficacy was demonstrated in compliance with European Directive 2009/9/EC, European Pharmacopoeia (Ph. Eur.) monograph 0062, Ph. Eur. monograph 0063, position paper for FMD vaccines (EMA/CVMP/775/02-FINAL) and guideline for multi-strain dossiers (EMA/CVMP/IWP/105506/2007).

The first study is considered to be pivotal to support the proposed claim and was overall in line with CVMP scientific advice.

Onset of immunity

The first study was in line with the study proposal tabled for scientific advice, and therefore considered as pivotal, involving the use of a trivalent vaccine formulated at a minimum payload for each of the three strains O1 Manisa, A22 and SAT 2 included. O1 Manisa was considered one of the least immunogenic of the approved vaccine strains and as such a suitable candidate to demonstrate onset of immunity by challenge. The use of a vaccine encompassing two other different serotypes reduced the need for using experimental animals and, as cross-reaction or synergy between serological responses to the other serotypes in the vaccine was discounted, it supported the early onset of immunity by serological means.

Thirty cattle, approximately 6-9 months of age, were allocated to three groups of 10. On D-14 (14 days before virus challenge), all cattle in group G1 were subcutaneously vaccinated with 2 ml of the trivalent vaccine. On D-7 (7 days before virus challenge), the same vaccine was administered to all cattle in group G2. The ten remaining cattle in group G3 were unvaccinated controls.

Vaccinated animals were challenged with O1 Manisa, either at 7 or 14 days post vaccination by the intranasal route, and assessment of the efficacy of the vaccine encompassed a number of parameters and clinical outcomes, which allowed a global clinical score to be considered and not just an evaluation based on generalisation of disease to the feet, as is accepted for routine challenge potency testing for FMD vaccines. Clinical monitoring after challenge included rectal temperatures, general clinical signs with particular attention to non-specific clinical aspects like appetite, oral and nasal mucosa and posture. Examination and recording for the presence of specific FMD lesions on the tongue, nose, mouth, lips and each claw of the feet included scoring under sedation. Sampling for virological analyses, by plaque assay and titration, included mouth swabs and blood. Blood was also taken for serological analyses. Local reactions at site of the injection were also recorded, though safety of the vaccine was not an objective of this study.

The outcomes of this efficacy study demonstrated a significant reduction in the severity of clinical signs, viraemia and viral excretion at both 7 and 14 days post vaccination, as well as the early onset of serological responses against O1 Manisa, A22 and SAT 2 strains. The applicant has overall followed the advice provided; however there were issues relating to the virological assessment of samples collected and the consideration of potential cross-reactivity of the specific antibody responses observed. All these were resolved and it can be concluded that this study does support an onset of immunity for the AFTOVAXPUR DOE vaccine of 7 days post vaccination in cattle and sheep.

The second study was originally included in the previous onset of immunity variation application (EMEA/V/C/002292/II/0002) which, following assessment, was considered not adequate to support an early onset of immunity and consequently led to the applicant seeking scientific advice.

The key objective was to test the onset of immunity of a FMD type O1 BFS inactivated vaccine by

evaluating protection by direct contact challenge 7 days post vaccination, thus using a different challenge route to that of the first study. However, this study was also seen as a transmission experiment by the applicant, where an infected FMD donor animal was put together with a previously vaccinated (in this case 7 days earlier) and a non-vaccinated recipient animal to monitor virus transmission in a vaccinated herd. This study can only, at best, be considered as supportive data for this application.

The third study was aimed at assessing the onset of immunity of AFTOVAXPUR DOE vaccine in cattle, by evaluating the protection against an intranasal FMD O1 Manisa challenge route at 7 days following vaccination with a monovalent inactivated O1 Manisa FMD vaccine formulated at a standard fixed dose of antigen.

The challenge approach was in line with scientific advice, and a uniform exposure of animals to the challenge organism occurred and relevant signs of disease or infection developed in the unvaccinated controls. Since it was agreed at scientific advice that just focusing on generalisation of disease, as in 50% protective dose (PD_{50}) studies, may not be the most appropriate approach for demonstration of efficacy, this study also encompassed assessment of a number of parameters following challenge to a Global Clinical Score for each animal. Global Clinical Scores, including rectal temperature, general clinical signs and FMD lesions scores, were found to be significantly reduced in the vaccinated animals compared to the unvaccinated controls. Virological testing also showed significant reduction of both viraemia and virus in mouth swabs in the vaccinated animals. Early onset of the important serological response was also observed.

It can be concluded that the study provides further support for an onset of immunity for the AFTOVAXPUR DOE vaccine at 7 days post vaccination.

In conclusion, the provided studies supported the onset of immunity at 7 days after vaccination in cattle and sheep.

Benefit-risk assessment of the proposed change

AFTOVAXPUR DOE is an inactivated adjuvanted vaccine against FMD virus strains O1 Manisa, O1 BFS, O Taiwan 3/97, A22 Iraq, A24 Cruzeiro, A Turkey 14/98, Asia 1 Shamir and SAT2 Saudi Arabia, centrally registered as a multi-strain dossier. There is a maximum of 3 strains in each vaccine.

This product is intended for use in cattle, sheep and pigs to reduce clinical signs caused by FMD virus.

The proposed variation is to amend the onset of immunity to 7 days post vaccination for sheep and cattle. The benefit-risk assessment below will focus only on that. The onset of immunity remains 4 weeks in pigs.

Benefit assessment

Direct therapeutic benefit

The proposed benefit of this variation to AFTOVAXPUR DOE is an earlier onset of immunity, 7 days post vaccination in cattle and sheep. AFTOVAXPUR DOE, by conferring an earlier onset of immunity following vaccination, provides a more rapid means of inhibiting disease spread within and between herds during an outbreak situation.

Additional benefits

Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Risks for the target animal:

Risk for the target animals remains unaffected by this variation.

Administration of AFTOVAXPUR DOE (inactivated multi-strain: 1-3 strains out of a set of 8) in accordance with SPC recommendations is generally well tolerated. Whilst the new studies presented were not safety studies, the adverse events observed were no worse than those described in the current SPC.

Risk for the user:

Risk for the user remains unaffected by this variation.

Risk for the environment:

AFTOVAXPUR DOE is not expected to pose a risk for the environment when used according to the SPC recommendations.

Risk for the consumer:

Risk for the consumer remains unaffected by this variation.

Special risks:

No specific risks of the vaccine have been identified.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product. The proposed change should not impact on the target animal safety, user safety, environmental safety and consumer safety of the product as authorised.

Evaluation of the benefit-risk balance

Information on the development, manufacture and control of the active substance and the finished product has been presented and leads to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for AFTOVAXPUR DOE can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No 1234/2008), as follows:

- to change the onset of immunity to 7 days post vaccination for cattle and sheep.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the Annexes to the Community marketing authorisation: I and IIIB.