EPAR for ZULVAC 8 Bovis

Type II variation (EMEA/V/C/145/II/002)
Scope of the variation: Revision of sections 4.2 and 4.9 of the SPC and matching sections of the package leaflet in order to provide precise information on duration of immunity and revaccination schedule.

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1. Background information on the variation

ZULVAC 8 Bovis was granted an EU marketing authorisation in January 2010 following the application for an authorisation under exceptional circumstances in accordance with Article 39(7) of Regulation (EC) No. 726/2004 and the guidance applicable to Bluetongue virus vaccines (EMEA/CVMP/IWP/220193/2008). As a post-approval commitment, the applicant agreed to provide as soon as feasible results of the ongoing duration of immunity study.

The marketing authorisation holder, Pfizer Limited, submitted to the European Medicines Agency (the Agency) on 6 December 2010 an application for a Type II variation for ZULVAC 8 Bovis to revise sections 4.2 and 4.9 of the SPC and matching sections of the package leaflet in order to provide precise information on duration of immunity and revaccination schedule.

The final report of this study is presented in section 2 "Scientific discussion".

During the meeting on 8-10 February 2011, the CVMP issued an opinion recommending the revision of section 4.2 of the SPC in order to provide precise information on duration of immunity. The proposed changes on section 4.9 and the revaccination schedule were not agreed. On 14 March 2011 the Commission adopted a Commission Decision approving the recommended amendment of the marketing authorisation for ZULVAC 8 Bovis.

Scope of the variation

Previous	Proposed
Section 4.2 Indications for use, specifying the target species The duration of immunity is not yet fully established, although interim results of ongoing studies demonstrate that the duration is at least 6 months after the primary vaccination course.	**Section 4.2 Indications for use, specifying the target species** The duration of immunity is at least 12months after the primary vaccination course.
Section 4.9 Amounts to be administered and administration route Revaccination: As the duration of the immunity is not yet fully established, any revaccination scheme should be agreed by the Competent Authority or by the responsible veterinarian, taking into account the local epidemiological situation.	**Section 4.9 Amounts to be administered and administration route** Revaccination: Annual revaccination is recommended.

Documentation submitted

In accordance with the requirements laid down in Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder submitted the following documentation:

- Administrative data (application form, English version of the product literature);

- The final report of the study of duration of Immunity of ZULVAC 8 Bovis vaccine in cattle;

- An efficacy expert report Type II variation for ZULVAC 8 Bovis to extend the claimed duration of immunity and change the recommendations for revaccination;

- One recent publication: Evaluation of humoral response and protective efficacy of three inactivated vaccines against Bluetongue virus vaccines one year after vaccination of sheep and cattle, 2010.

2. Scientific discussion

Duration of immunity study of ZULVAC 8 Bovis vaccine in calves

The objective of the study was to verify if the administration of ZULVAC 8 Bovis vaccine was able to prevent viraemia (no detection of viral genome by real time RT-PCR technique during 28 days post challenge) in cattle challenged 7 and 12 months post vaccination. The non GLP compliance of the concerned study was considered acceptable.

The study included 79 of 2.5 to 3 months old crossbreed Frisean calves, without antibodies against Bluetongue virus (BTV).

Three vaccine batches (manufacturing batch protocols were provided) were used containing different amount of vaccine antigen as shown below.

ZULVAC 8 Bovis composition per dose (2 ml)

	Batch 1	Batch 2	Batch 3
BTV inactivated serotype 8 Aluminium hydroxide 3% Saponin Saline solution Thiomersal	$10^{7.3}$ TCID$_{50}$ 4 mg Al^{3+} 0.4 mg q.s. 2.0 ml 0.2 mg	$10^{7.0}$ TCID$_{50}$ 4 mg Al^{3+} 0.4 mg q.s. 2.0 ml 0.2 mg	$10^{6.7}$ TCID$_{50}$ 4 mg Al^{3+} 0.4 mg q.s. 2.0 ml 0.2 mg

Experimental Design

The seronegative crossbreed Frisean calves were randomly allocated into three treatment groups according to Microsoft Excel program, as follows:

Group 1:   22 calves, vaccinated and revaccinated with ZULVAC 8 Bovis vaccine containing $10^{7.3}$ TCID$_{50}$ of BTV8 per 2 ml dose.

 Group 2:   21 calves, vaccinated and revaccinated with ZULVAC 8 Bovis vaccine containing $10^{7.0}$ TCID$_{50}$ of BTV8 per 2 ml dose.

Group 3:   21 calves, vaccinated and revaccinated with ZULVAC 8 Bovis vaccine containing $10^{6.7}$ TCID$_{50}$ of BTV8 per 2 ml dose.

Group 4:   15 control calves, non vaccinated.

In groups 1, 2 and 3, calves were vaccinated and revaccinated 3 weeks later, with 2 ml of the vaccine by intramuscular route (i.m.). Calves in group 4 were left as unvaccinated controls.

Challenge 7 months post revaccination

On day D+212, calves from group 3 were eliminated from the study, since from the results of the Immunogenicity study ZULVAC 8 Bovis vaccine containing $10^{6.7}$ TCID$_{50}$ of BTV8 per 2 ml dose was considered to be subpotent for calves.

On day D+231, calves from groups 1, 2 and 4 were challenged with BTV-8.

Each calf was inoculated by the intravenous route with 2 ml containing $2 \times 10^{6.2}$ TCID$_{50}$ of BTV8 strain BE 2006/02.

Challenge 12 months post revaccination

On day D+304, calves from group 2 were eliminated from the study, since from the results of the challenge performed 7 months after revaccination ZULVAC 8 Bovis vaccine containing $10^{7.0}$TCID$_{50}$ of BTV8 per 2 ml dose was considered to be subpotent.

On day D+387, calves from groups 1 and 4 were challenged with BTV-8.

Each calf was inoculated by the intravenous route with 2 ml containing $2 \times 10^{6.1}$ TCID$_{50}$ of BTV strain BE 2006/02.

Observation of the animals (parameters and duration)

After vaccination and revaccination, the calves were monitored for the appearance of any systemic reaction associated with the vaccine administration (e.g. anaphylactic shock, anorexia).

Blood samples were taken from the calves: At D<0 (before vaccination), D+31 (before revaccination), D+43, D+107, D+188, D+213, D+232 (only calves challenged 7 months post revaccination), D+252, D+269, D+286, D+350 and D+388.

In the challenge performed 7 months after revaccination (D+231), blood samples were taken from the animals on days 0, 2, 5, 7, 9, 12, 15, 19, 23 and 27 post infection, for the evaluation of the presence of the BTV genome by the real time RT-PCR technique.

In the challenge performed 12 months after revaccination (D+387), blood samples were taken from the animals on days 0, 3, 5, 7, 11, 14, 18, 21, 25 and 28 post infection, for the evaluation of the presence of the BTV genome by the real time RT-PCR technique.

In the challenge performed 7 months after revaccination (D+231), the appearance of clinical signs related with the BTV disease was monitored on days 0, 2, 5, 7, 9, 12, 15, 19, 23 and 27 post infection.

In the challenge performed 12 months after revaccination (D+387), the appearance of clinical signs related with the BTV disease was monitored on days 0, 3, 5, 7, 11, 14, 18, 21, 25 and 28 post infection.

Results

Observation of systemic reactions after vaccination

None of the calves manifested any systemic reactions (anaphylactic shocks, anorexia, prostration) after 1st and 2nd vaccination.

Evaluation of the serological response after vaccination

At D<0, none of the calves selected for the study presented antibodies against any of the BTV serotypes (ELISA). Also, at D<0, in none of the calves viral genome was detected by real time RT-PCR.

Evaluation of viraemia after 7 months challenge

In none of the calves from group 1 (vaccinated with ZULVAC 8 Bovis vaccine formulated at $10^{7.3}$ TCID$_{50}$/ml), viral genome was detected by real time RT-PCR during 27 days after challenge.

In calves from group 2 (vaccinated with ZULVAC 8 Bovis vaccine formulated at $10^{7.0}$TCID$_{50}$/ml), viral genome was detected by real time RT-PCR in 28.6% of vaccinated calves from day D+2 post infection. The mean Ct value on the day of maximal viraemia, 9 post-infection was of 34.33.

In the non-vaccinated (group 4) and challenged calves the viral genome was detected from day D+2 post-infection. The mean Ct value on the day of maximal viraemia, 9 post infection was of 28.13.

Evaluation of clinical signs after 7 months challenge

Rectal temperatures

There were no statistical significant differences regarding the rectal temperatures between the vaccinated (groups 1 and 2) and the control group after challenge.

Other clinical signs

After challenge, 2 calves presented mild clinical signs not clearly associated with the infection.

One calf presented a severe infection affecting the left hip joint and also abdominal wall of the same side, probably due to and old undetected injury and the animal was euthanasied. The necropsy confirmed the infection, the calf presented an abcess left hip joint that was producing necrosis of the leg and intercostal muscles.

Evaluation of viraemia after 12 months challenge

In group 1 (vaccinated with ZULVAC 8 Bovis vaccine formulated at $10^{7.3}$ $TCID_{50}$/ml), viral genome was detected by real time RT-PCR in 1 calf just on day D+5 post infection (Ct value= 33.88). In the rest of the calves no viral genome was detected during 28 days after challenge.

In the non-vaccinated (group 4) and challenged calves the viral genome was detected. The mean Ct value on the day of maximal viraemia, 11 post infection was of 28.70.

Evaluation of clinical signs after 12 months challenge

Rectal temperatures

There were no statistical significant differences regarding the rectal temperatures between the vaccinated and the control group after challenge.

Other clinical signs

After challenge, none of the calves presented clinical signs associated with the infection.

On the day of challenge (D0), 5 calves were detected to present nasal discharge. On day D+7 post infection two calves and on day D+9 post infection one calf presented nasal discharge.

Conclusions

In this study it has been verified that the administration of ZULVAC 8 Bovis vaccine at a concentration of $10^{7.3}$ $TCID_{50}$/2ml:

- Did not provoke any anaphylactic reactions in the calves;

- Induced (first duration of immunity study) an active immunity in vaccinated calves of at least 7 months, since in none of the vaccinated and challenged calves, viral genome was detected;

- Induced (second duration of immunity study) an active immunisation in vaccinated calves of 12 months, since viral genome was just detected in one vaccinated calf for one day (D+5 after challenge). This animal was considered non viraemic as viraemia is not persistent (it is unusual to find one animal viraemic for only one day). Moreover, in vaccinated calves, the detected viral genome can come from remnants of phagocytosis (no infectious virus) or from the action of the acquired immuno-response that has been able to eliminate any viral genome from the blood (virus neutralising antibodies or virus inactivated by cells involved in cell immediate immuno-response).

It can be concluded that the duration of immunity of ZULVAC 8 Bovis is at least one year.

An efficacy expert report (Type II variation to extend the claimed duration of immunity and change the recommendations for revaccination) was included within this variation documentation. The background and rationale of the proposed variation and of the efficacy data relevant to the proposed variation were provided, including detailed summaries and critical analyses of the study design and of the results obtained.

A duration of immunity (by serology) of 12 months has also been demonstrated by Wäckerlin et al. (Evaluation of humoral response and protective efficacy of three inactivated vaccines against bluetongue virus serotype 8 one year after vaccination of sheep and cattle. Wäckerlin et al. (2010). Vaccine 28: 4348–4355).

Overall conclusions

The results obtained from this study (Wäckerlin et al.) demonstrate that the vaccination of ZULVAC 8 Bovis according to the recommended scheme, 1 year after the completion of the primary vaccination course, prevented viraemia in the vaccinated animals. A duration of immunity of 12 months can therefore be established. Section 4.2 of the SPC should be amended accordingly. As far as the revaccination scheme is concerned, the data provided were not adequate to support the proposed revaccination scheme and therefore did not justify the proposed changes to section 4.9 of the SPC.

3. Benefit-risk assessment

The duration of immunity could be established with the new data provided and outstanding clarifications referring to this point can be included in the SPC.

The benefit-risk balance compared to the assessment performed during the initial authorisation phase of ZULVAC 8 Bovis vaccine remains positive.

No change to the impact on the environment is envisaged.

4. Overall conclusion

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, was approvable as far as the 12 month duration of immunity induced by the two dose vaccination regimen is concerned. The newly proposed text in relevant part of section 4.2 of SPC (the duration of immunity is at least 12 months after the primary vaccination course) was therefore acceptable. The effect of re-vaccination was not demonstrated therefore, the efficacy of the revaccination scheme still remains undetermined. The following statement in section 4.9 of the SPC should therefore remain unchanged and any revaccination scheme should be agreed by the Competent Authority or by the responsible veterinarian, taking into account the local epidemiological situation.