8 December 2010
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EPAR for ZULVAC 8 Ovis

Type II variation (EMEA/V/C/147/II/001)

Scope of variation: Revision of sections 4.2 and 4.9 of the SPC in order to provide precise information on duration of immunity and revaccination schedule.

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1. Background information on the variation

In January 2010, the European Medicines Agency (the Agency) granted a marketing authorisation for ZULVAC 8 Ovis for the "active immunization of sheep from 1.5 months of age for the prevention of viraemia* caused by Bluetongue Virus, sereotype 8, following the application for an authorisation under exceptional circumstances".

*(Cycling value (Ct) ≥ 36 by a validated RT-PCR method, indicating no presence of viral genome).

As a post-approval commitment, the applicant agreed to provide as soon as feasible results of the ongoing duration of immunity (DoI) study.

In May 2010, the Marketing Authorisation Holder, Pfizer Limited, submitted to the Agency an application for a type II variation for ZULVAC 8 Ovis to revise the sections 4.2 and 4.9 of the SPC 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 7 – 9 December 2010, the CVMP issued an opinion recommending the revision of sections 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 21 January 2011 the Commission adopted a Commission Decision approving the recommended amendment of the marketing authorisation for ZULVAC 8 Ovis.

Scope of the variation

Previous	**Proposed by applicant**
SPC and corresponding package leaflet section **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 4.9** Amounts to be administered and administration route Revaccination: As the duration of 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.	**SPC and corresponding package leaflet section** **Section 4.2** Indications for use, specifying the target species The duration of immunity is at least 12 months after the primary vaccination course. **Section 4.9** Amounts to be administered and administration route Revaccination: Annual revaccination is recommended.

2. Scientific discussion

Duration of immunity study of ZULVAC 8 Ovis 2 shots vaccine in lambs

The objective of the study was to verify the efficacy of the monovalent ZULVAC 8 Ovis, given the 2-shots vaccination regimen, to prevent viraemia (no detection of viral genome by the validated qRT-PCR during 4 weeks after challenge) in sheep challenged 6 and 12 months after completion of the basic vaccination scheme (2 administrations, by subcutaneous route, of one 2ml dose of vaccine given 3 weeks apart). The non GLP compliance of this study was justified.

The study initially included healthy 9 to 10 weeks old crossbred lambs, without antibodies against BTV. Two batches of ZULVAC 8 Ovis vaccine were used, one with a titre of $10^{6.7}$ $TCID_{50}$ and another with $10^{6.5}$ $TCID_{50}$ of BTV8 per 2 ml dose. Those batches confirmed to have been produced according to the same method as proposed for commercial batches.

Experimental Design

Seronegative 9 to 10-weeks-old cross bred lambs were included in the study (the CVMP considered that the use of animals that were a couple of weeks older than the minimum recommended age should not have significantly affected the validity of the study for its intended purpose). At D0, in none of the lambs was viral genome detected by the validated qRT-PCR and they were randomly allocated into three treatment groups (using Microsoft Excel program), as follows:

Group 1: 33% of lambs were vaccinated (D0) and revaccinated (D+21), by subcutaneous route with a batch of ZULVAC 8 Ovis vaccine containing $10^{6.7}$ $TCID_{50}$ of BTV8 per 2 ml dose

Group 2: 34% of lambs were vaccinated (D0) and revaccinated (D+21), by subcutaneous route with a batch of ZULVAC 8 Ovis vaccine containing $10^{6.5}$ $TCID_{50}$ of BTV8 per 2 ml dose

Group 3: 33% of control lambs were left as unvaccinated controls

Challenge 6 months post revaccination

On day D+202 (i.e. 6 months after completion of the basic vaccination scheme), 30% of sheep from groups 1 and 2 respectively and 15% from group 3 were submitted to a virulent challenge with BTV-8.

Challenge 12 months post revaccination

On day D+402 (i.e. approximately 12 months after completion of the basic vaccination scheme) 36% of sheep from groups 1, 2 and 3, respectively, were submitted to a virulent challenge with BTV-8.

Challenge inoculum

For the challenge, a virus suspension containing the homologous BTV8 strain was administered subcutaneously to vaccinated and control animals 6 and 12 months after completion of the basic vaccination scheme, respectively. The use of a homologous challenge was justified by the lack of time to source and qualify a suitable heterologous strain at the time when this study was carried out. However, the relevance to the current circulating strains of the challenge strain has been substantiated by the Community reference laboratory in IAH-Pirbright, UK.

Definition of protection

Consistent absence of viral load detectable by qRT-PCR in all the vaccinated animals during the monitoring period of 4 weeks, defining viral load detectable by qRT-PCR as the one that provides as a result a Ct value lower than 36.0.

Clinical signs after challenge

Monitored clinical signs: rectal temperatures, nasal discharge and/or oedema, ocular discharge and/or ocular oedema (eyelid oedema, corneal oedema, uveitis), lameness, prostration.

Monitoring of animals and sampling

During the first 24 hours after vaccinations, the lambs were carefully observed for the detection of any systemic reactions, such as anaphylactic shock, anorexia, prostration, etc.

Blood samples were taken for the detection of ELISA or virus neutralising antibodies against BTV8 from the lambs: at D0 (before vaccination), D+21 (before administration of the 2nd dose of the vaccine), D+43, D+98, D+190 and D+202 (just sheep being challenged at 6 months post revaccination), D+248, D+288, D+359 and D+402 (just sheep being challenged at 12 months post revaccination).

In the challenge performed 6 months after revaccination (D+202), blood samples were taken from the sheep on days 0, 2, 4, 7, 10, 14, 17, 21, 24 and 28 post infection, for the evaluation of the presence of the BTV genome using the validated qRT-PCR.

In the challenge performed 12 months after revaccination (D+402), blood samples were taken from the sheep on days 0, 3, 5, 7, 10, 13, 17, 20, 24 and 27 post infection, for the evaluation of the presence of the BTV genome using the validated qRT-PCR.

In the challenge performed 6 months after revaccination (D+202), the appearance of clinical signs related with the BTV disease was monitored on days 0, 2, 4, 7, 10, 14, 17, 21, 24 and 28 post infection.

In the challenge performed 12 months after revaccination (D+402), the appearance of clinical signs related with the BTV disease was monitored on days 0, 3, 5, 7, 10, 13, 17, 20, 24 and 27 post infection.

With the exclusion of rectal temperatures, one point was attributed to each of any other clinical signs that lambs presented. A daily clinical sign score was given to each lamb at every recording day. The intensity of the clinical signs was also recorded**.**

Results

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

Evaluation of the serological response after vaccination

At D0, none of the lambs selected for the study presented ELISA antibodies against BTV. Blood samples obtained at D+21 were not tested.

Evolution (geometric means) of neutralising antibody titres against BTV-8 (Serum Neutralisation test) in groups 1, 2 and 3 lambs from vaccination until 6-months or 12-months challenge is shown in the table below.

GROUP	**Geometric Mean titres of neutralising antibodies against BTV-8**							
	D+43	D+98	D+190	D+202* challenge (6-months DoI)	D+248	D+288	D+359	D+402 * challenge (12-months DoI)
1	43	38	17	11	22	15	18	14
2	35	35	18	13	16	14	14	11
3	<2	<2	<2	<2	<2	<2	<2	<2

* Just tested blood samples of lambs selected to be challenged

Group 1 = ZULVAC 8 Ovis, $10^{6.7}TCID_{50}$/2ml)

Group 2 = ZULVAC 8 Ovis, ($10^{6.5}TCID_{50}$/2ml)

Group 3 = Control (<2= negative)

Evaluation of viraemia after 6-months challenge

The evolution of viraemia was graphically presented. In none of the sheep from groups 1 and 2, vaccinated and thereafter challenged with BTV serotype 8, viral genome was detected by the validated qRT-PCR during four weeks after challenge. Contrary, in all the non-vaccinated (group 3) and challenged sheep the viral genome was detected from D4 post infection (p.i.) (mean Ct value on the day of maximal viraemia, i.e. 7 p.i. = 24.67).

Evaluation of clinical signs after 6-months challenge

There were statistical significant differences regarding the rectal temperatures between the vaccinated and the control group on days 7 p.i. (p= 0.002) and 10 p.i. (p= 0.042), with controls showing higher values at time points corresponding with the days of maximal viraemia.

Clinical signs (6-months challenge)

There were no statistically significant differences (regarding the clinical signs score between the vaccinated (groups 1 and 2, Mean vacc) and the control group (group 3).

Evaluation of viraemia after 12-months challenge

In none of the sheep from groups 1 and 2 vaccinated and thereafter challenged with virulent BTV8, viral genome was detected by the validated qRT-PCR during 27 days after challenge. Contrary, in all the non-vaccinated (group 3) and challenged sheep the viral genome was detected (mean Ct value on the day of maximal viraemia, i.e. 7 p.i. = 29.42).

Evaluation of clinical signs after 12-months challenge

There were statistical significant differences (T-test) regarding the rectal temperatures between the vaccinated (groups 1 and 2) and the control group on days 5 (p= 0.027), 7. (p= 0.000) and 10 post challenge (p= 0.048), these time points corresponding with the days when maximal viraemia was recorded.

Clinical signs (12-months challenge)

Sporadically, very few animals presented nasal discharge. No statistically significant differences regarding the clinical signs score were found between the vaccinated (groups 1 and 2) and the control group (group 3).

Challenge at 6 and 12 months did not elicit overt clinical signs in any test group. Nevertheless, as the results for viraemia for the controls were unequivocal (in that all of these animals had detectable viraemia at most of the post-challenge assessment points), and the primary endpoint was protection against viraemia (which is consistent with the approved indication for ZULVAC 8 Ovis), the CVMP concluded that the results were consistent to support the claimed duration of immunity.

The CVMP noted that the 6-month challenge appeared to be more intense after the 12-month challenge, in that in the former case the viral genome was detected in all control sheep at all time points from 4 days post-challenge, whereas there were some negative readings in the latter. Moreover, the CVMP noted that peak Ct values were marginally lower after the 6-month challenge, indicating higher titres of viraemia. The CVMP considered that this small difference might be the result of the development of a degree of age resistance in the older sheep (i.e. by 12 months of age). Irrespective of this factor, however, the viraemia observed after the 12-month challenge was unequivocal, with viral genome being detected in all control sheep and at all time points from 5 days post-challenge in some of these sheep, and with some of the sheep being viraemic at the final assessment for each animal.

Conclusion

From the safety point of view, the administration of ZULVAC 8 Ovis 2-shots vaccine to 2.5 month old lambs did not provoke any anaphylactic reactions.

As far as duration of immunity is concerned, it was verified that the administration of ZULVAC 8 Ovis 2-shots vaccine (containing minimum of $10^{6.5}$ $TCID_{50}$ per dose of 2 ml) is able to prevent viraemia in the vaccinated sheep challenged 6 months and 12 months after revaccination. All non-vaccinated controls were viraemic.

The administration of ZULVAC 8 Ovis 2-shots vaccine reduced hyperthermia in the vaccinated sheep on days of maximal viraemia.

It was not possible to evaluate the prevention of other symptoms associated to the infection since just mild and non specific clinical signs were registered after the challenge.

The duration of immunity of ZULVAC 8 Ovis 2-shots is at least 1 year.

Anamnestic response study

The results (up to approximately 3.5-4 months after the booster vaccination) were also provided, as obtained from an anamnestic study aiming to evaluate the immune response after the administration of a single booster dose of the vaccine (i.e., 12 months after completion of the basic vaccination scheme). A subset of vaccinated animals selected from group 2 of the above study were not challenged, and received a single dose booster at approximately 13 months after completion of the

basic vaccination scheme. Some sheep of group 3 (controls) were still kept as untreated control animals.

Anamnestic response study with ZULVAC 8 Ovis in lambs

Objective of the study

The objective of this study was to verify if lambs which were vaccinated twice (i.e. on D0 and D+21) according to the established vaccination schedule with a batch of ZULVAC 8 Ovis (containing : $10^{6.5}$ $TCID_{50}$ of BTV8 per 2 ml dose) were satisfactorily primed in terms of development of an immunologic memory response following a 2ml/dose booster vaccination carried out by subcutaneous route, approximately one year after completion of the basic vaccination scheme (i.e., on D+408, corresponding to D0 in the new study), using another vaccine batch confirmed to have been produced according to the same method as proposed for commercial batches and also containing $10^{6.5}$ $TCID_{50}$ of BTV8 per 2 ml dose.

The study included animals divided into two groups (group 1, vaccinated sheep and group 2, control, untreated sheep). Bleeding was carried out on D0 (D+408), D+19 (D+427), D+45 (D+463), D+72 (D+490), D+112 (D+520).

Results

The usual method for demonstrating efficacy of revaccination is to compare the serological profile after revaccination with that after initial vaccination – if the two profiles are equivalent then it is concluded that the immunological response to revaccination is equivalent to that after initial vaccination.

All vaccinated lambs had residual titres at time of revaccination and all developed high titres by 19 days after vaccination, giving clear evidence of an anamnestic response and the presence of 'immunological memory'. Although titres did decline somewhat over subsequent weeks, relatively high titres were still present at the end of the test period (112 days after revaccination). The antibody titre profile after revaccination was approximately equivalent to that observed after the primary vaccination course in the study described earlier regarding duration of immunity (DoI) of ZULVAC 8 Ovis after 2 shots of vaccine in lambs. Although there were differences between controls and vaccinates they were not of great significance.

Conclusion

A booster vaccination with ZULVAC 8 Ovis given 1 year after the completion of the primary course vaccination induced an amannestic response in primed lambs resulting in the production of a large amount of neutralising antibodies. These antibodies persisted at least for 3 months after booster vaccination.

Although a consistent immune response was evoked after booster vaccination, the comparative evaluation of the serologic profiles, alone, was not considered sufficient to demonstrate the relevance of the annual revaccination with one dose of the vaccine under application.

The results of two additional studies were further provided in order to confirm the 12 month duration of immunity and to support the relevance of the revaccination scheme. Specifically, a 12 month DoI study and the anamnestic response (by challenge) to one dose booster vaccination study were carried out using the combined vaccine ZULVAC 1+8 Ovis and was acceptable to extrapolate conclusions. Overall, the results presented using ZULVAC 8 Ovis vaccine, and those obtained from the response to booster challenge study, demonstrated that full protection (in terms of prevention of viraemia as demonstrated using the validated qRT-PCR) is achieved 12 months after completion of the primary vaccination scheme. Moreover, the data supplied from the ZULVAC 1+8 Ovis studies confirmed the DoI and demonstrated that full protection from infection is guaranteed 3 weeks after (onset of immunity) a

single booster vaccination given 12 months after the primary course. A summary is provided below of the design and the results of the two additional studies.

Duration of immunity study of ZULVAC 1+8 Ovis 2-shots vaccine in lambs

The objective of the study was to evaluate the ability of ZULVAC 1+8 Ovis vaccine to prevent viraemia (no detection of viral genome by qRT-PCR technique during 27 days post challenge) in sheep challenged 12 months after completion of the primary vaccination scheme. Two of ZULVAC 1+8 Ovis vaccine were used, which were formulated at a concentration of $10^{6.7}$ and $10^{6.5}$TCID50/2ml dose for both antigen serotypes for each batch respectively. The Manufacturer's Batch Protocols (MBPs) were provided for the two batches of ZULVAC 1+8 vaccine used.

Study design

Healthy 8-9 weeks old, crossbred lambs, without antibodies against BTV, were included in the study. Almost half of those lambs were used for the 12 months DoI challenge study, whereas the remaining animals were kept for the anamnestic response study. The lambs were allocated to 3 treatment groups (1-2-3). In groups 1 and 2, lambs were vaccinated with batches containing $10^{6.7}$ and $10^{6.5}$TCID50/2ml dose for both antigen serotypes, respectively, according to the recommended scheme of vaccination and route of administration (one vaccination followed by a second dose given 3 weeks later, was administered by subcutaneous route on Day 0 (D0) and Day 21 (D+21), respectively). Lambs in group 3 were left as unvaccinated controls. After vaccination, sheep were monitored for the appearance of any systemic reaction associated with the vaccine administration (anaphylactic shock, anorexia, etc.).

Twelve months after completion of the primary vaccination scheme the vaccinated sheep were submitted to an experimental challenge given by subcutaneous route using a virus suspension of BTV-1and BTV-8 respectively. In both cases the challenge virus strain was homologous to the vaccine strain. This condition was not considered ideal for such type of experiment, however both challenge virus strains were considered relevant to the epidemiologic situation in Europe, therefore acceptable in order to demonstrate the efficacy of the two batches of ZULVAC 1+8 vaccine. The efficacy of the vaccine batches was assessed based on the definition of protection: consistent absence of viral load detectable by qRT-PCR (segment 7, according to Toussinant et al, 2007) in all vaccinated animals during the monitoring period of 4 weeks. The defining viral load detectable by qRT-PCR was a Ct value <36.0.

One year after completion of the basic 2 shots vaccination scheme, some lambs from each group were included in an anamnestic response study for the evaluation of viraemia after challenge. Lambs in groups 1 and 2 received a booster vaccination, whereas lambs in group 3 were still left as unvaccinated controls. Three weeks later, half of the lambs from each group were submitted to a virulent challenge with BTV-1 or BTV 8.

The monitored clinical signs were rectal temperature increase; lameness; prostration; death. In order to obtain the daily clinical score, a value of 1 was attributed to each clinical sign that the lambs presented, except for death when value of 3 was attributed. At the end of the study, i.e. after 27 days after challenge, all lambs were euthanised.

Bleeding was also carried out on D0 before the 1st vaccination, and frequently thereafter.

Results

The vaccine was well tolerated by all lambs which never manifested systemic reactions such as anaphylactic shock, anorexia, prostration, after the 1st and 2nd vaccination. At D0, none of the lambs selected for the study presented antibodies against any of BTV serotypes by ELISA. Also, at D0, in none of the lambs viral genome was detected by qRT-PCR. The evolution of the geometric mean titres (GMTs) of serum neutralising antibodies against BTV-1 and BTV-8 from vaccination until challenge was presented.

Statistically significant differences were recorded, concerning the increase of rectal temperatures between vaccinated and control groups on D+5, 7 and 10 after challenge coinciding with the period of maximal viraemia recorded in the unvaccinated sheep. The clinical outcome of both BTV-1 and BTV-8 challenge was of very limited extent. Vaccinated sheep in group 1 did not manifest any clinical sign attributable to BTV infection at any time point during the monitoring period after challenge. Most animals in group 2 did not manifest, at any time after challenge, any clinical sign attributable to BTV infection. A small number of control sheep (from each BTV serotype) died after challenge. Evidence was provided that the death of some controls was due to BTV-1 and BTV-8 infection. The remaining control lambs presented very mild, unspecific clinical signs of BTV infection after challenge. No statistical significant differences were recorded among groups. In none of the vaccinated sheep of both groups 1 and 2 challenged with both BTV-1 and BTV-8, viral genome detected by qRT-PCR at any time point checked during 27 days after challenge. Contrary, in all the unvaccinated sheep the viral genome was detected from D+3 after challenge with BTV-1 and from D+5 after challenge with BTV-8 up to 27 days after challenge when the study terminated.

Conclusion

The efficacy of ZULVAC 1+8 Ovis vaccine in terms of prevention of viraemia in vaccinated and challenged sheep for 12 months was supported by the results of the study.

Anamnestic response study of ZULVAC 1+8 Ovis in sheep

The objective of this study was to test the anamnestic response in sheep, after the administration of a booster vaccination of ZULVAC 1+8 Ovis vaccine given to sheep 12 months after completion of primary vaccination scheme. The anamnestic response was measured in terms of capability of the vaccine to prevent the viraemia (detection of viral genome by qRT-PCR) caused by a homologous BTV-1 and BTV-8 experimental challenge.

Two batches of the ZULVAC 1+8 vaccine were used for this study formulated, respectively, at a concentration of $10^{6.7}$ and $10^{6.5}$TCID50/2ml dose of both antigen serotypes for each batch. The Manufacturer's Batch Protocols were provided, and the composition of one dose was detailed.

Healthy sheep from the study on duration of immunity in lambs with ZULVAC 1+8 Ovis 2-shots described above, were used for this anamnestic response study. Specifically, some from group 1, some from group 2 and some from group 3.

The sheep received a different treatment depending on the groups they were allocated in the duration of immunity study and specifically:

Group 1: Sheep vaccinated according to the primary vaccination scheme 1 year before with a batch containing $10^{6.7}$ TCID50/2ml dose of ZULVAC 1+8 Ovis, were vaccinated (one 2ml/dose) by subcutaneous route with another batch also containing $10^{6.7}$ aTCID50/2ml dose of ZULVAC 1+8 Ovis.

Group 2: Sheep vaccinated according to the primary vaccination scheme 1 year before with a batch containing $10^{6.5}$ TCID50/2ml dose ZULVAC 1+8 Ovis, were vaccinated (one 2ml/dose) by subcutaneous route with another batch containing $10^{6.5}$TCID50/2ml dose ZULVAC 1+8 Ovis vaccine.

Group 3: Control sheep were left as unvaccinated controls.

After vaccination, sheep were monitored for the appearance of systemic reactions associated with the vaccine administration (anaphylactic shock, anorexia, etc.). Blood samples were taken from all the sheep at Day 0 (before booster vaccination) and 21 days later at challenge (D+21), in order to measure the serum neutralising antibody titres in the animals selected for this study.

On day D+21, some sheep of each group (1, 2, and 3) were challenged with BTV-1 and some other sheep of each group (1, 2 and 3) were challenged with BTV-8.

In both cases, the challenge strain was homologous to the vaccine strain. This condition was not considered ideal for this type of experiment, however both challenge virus strains were considered relevant to the epidemiologic situation in Europe and therefore acceptable in order to demonstrate the efficacy of the two batches of ZULVAC 1+8 vaccine. The efficacy of the vaccine batches was assessed based on the definition of protection as consistent absence of viral load detectable by qRT-PCR (segment 7 according to Toussinant et al, 2007) in all vaccinated animals during the monitoring period of 4 weeks. The viral load which was detectable by qRT-PCR was defined as the one that provides, a result of a Ct value <36.0.

Blood samples were taken from all the animals just before challenge (D0 post infection) and frequently thereafter, for the evaluation of the presence of the BTV genome by qRT-PCR.

The animals were monitored on days 0, 4, 6, 8, 11, 14, 18, 21, 25 and 28 after challenge for the appearance of clinical signs associated with the disease.

Results

None of the sheep manifested any systemic reactions (anaphylactic shocks, anorexia, prostration) after vaccination.

At Day 0, all the sheep from vaccinated groups presented antibodies against BTV serotype 1 and 8 whereas none of the control sheep had antibodies. The booster (D+21) vaccination on D+21 resulted in an increase of neutralising antibody titres against BTV-1 and BTV-8 in all the vaccinated sheep. In none of the sheep, BTV genome was detected on the day of challenge.

The evolution (geometric mean titres-GMTs) of neutralising antibody titres against BTV-1 and BTV-8 in sheep of groups 1, 2 and 3, from vaccination to challenge is presented below:

GROUP	GMTs of neutralising antibodies against BTV-1 and BTV-8			
	D0		D+21	
	BTV-1	BTV-8	BTV-1	BTV-8
1	45.9	19.0	724.1	175.9
2	44.6	16.4	362.0	128.0
3	<2	<2	<2	<2

In none of the sheep from group 1 and group 2 challenged with BTV serotype 1 and BTV serotype 8, viral genome was detected by real time RT-PCR during 28 days after challenge. In all the unvaccinated and challenged sheep of group 3, the viral genome was detected from D+4 after challenge with BTV-1 and BTV-8.

With regard to BTV-1 serotype a statistically significant difference was recorded in relation to the increase of rectal temperatures between vaccinated and control groups on D+8 after challenge. Similarly a significant statistical difference was recorded with regard to BTV-8 serotype, in relation to the increase of rectal temperatures between vaccinated and control groups on D+6 and D+8 after challenge. In both cases the controls had higher values.

Clinical signs attributable to BTV infection were practically absent during the monitoring period after challenge although a control was euthanised due to severe infection indicative of BTV.

Conclusion

The results obtained from this study demonstrated that the administration of a booster vaccination of ZULVAC 1+8 Ovis one year after a primary vaccination course induced an anamnestic response in the sheep able to prevent viraemia in the vaccinated sheep challenged 21 days (coinciding with the established onset of immunity) after the booster vaccination with BTV serotypes 1 and 8. However any further duration of the booster effect cannot be extrapolated.

3. Benefit-risk assessment

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

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 booster effect of re-vaccination was only demonstrated in terms of memory response mediated by serum neutralising antibodies. As antibodies are not indicator of efficacy against BTV infection, although prevention of viraemia was demonstrated 3 weeks after the one dose booster, in principle, the revaccination scheme still remains undetermined. The following statement in section 4.9 of the SPC should therefore remain unchanged: any revaccination scheme should be agreed by the Competent Authority or by the responsible veterinarian, taking into account the local epidemiological situation.