16 May 2013
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for the annual re-assessment of ZULVAC 1+8 Ovis (EMEA/V/C/002251/S/0006)

International non-proprietary name: inactivated bluetongue virus, serotypes 1+8

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

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Authorised presentations

EU (MA) number	Invented name	Strength	Pharmaceutical form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
EU/2/11/120/001	ZULVAC 1+8 Ovis	Inactivated bluetongue virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1 Inactivated bluetongue virus, serotype 8, strain BTV-8/BEL2006/02 RP* ≥ 1	Suspension for injection	Sheep	Subcutaneous use	High density polyethylene vials with chlorobutyl stopper and aluminium seal	20 ml (10 doses)	1 vial	Zero days
EU/2/11/120/002	ZULVAC 1+8 Ovis	Inactivated bluetongue virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1 Inactivated bluetongue virus, serotype 8, strain BTV-8/BEL2006/02 RP* ≥ 1	Suspension for injection	Sheep	Subcutaneous use	High density polyethylene vials with chlorobutyl stopper and aluminium seal	100 ml (50 doses)	1 vial	Zero days
EU/2/11/120/003	ZULVAC 1+8 Ovis	Inactivated bluetongue virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1 Inactivated bluetongue virus, serotype 8, strain BTV-8/BEL2006/02 RP* ≥ 1	Suspension for injection	Sheep	Subcutaneous use	High density polyethylene vials with chlorobutyl stopper and aluminium seal	240 ml (120 doses)	1 vial	Zero days

*Relative potency by a mice potency test compared to a reference vaccine that was shown efficacious in sheep.

Product information on the annual re-assessment

Invented name:	**ZULVAC 1+8 Ovis**
Active substances:	Inactivated bluetongue virus, serotypes 1 and 8
Pharmaceutical form:	Suspension for injection
Strength:	RP* ≥ 1
Route of administration:	Subcutaneous use
Target species:	Sheep
Therapeutic indication:	Active immunisation of sheep from 1.5 months of age for the prevention of viraemia caused by bluetongue virus, serotypes 1 and 8.
Marketing authorisation holder (name and address):	Zoetis Belgium SA (as of 16 May 2013) Rue Laid Burnait, 1 1348 Louvain-la-Neuve BELGIUM
Applicant contact point:	Dr Frederic Descamps
Rapporteur:	Maria Tollis

*Relative potency by a mice potency test compared to a reference vaccine that was shown efficacious in sheep.

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1. Background information

1.1. Submission of the application

On 6 March 2013, the marketing authorisation holder, Pfizer Limited (the applicant), submitted in accordance with Article 39 of Commission Regulation (EC) No. 726/2004 an application for the second annual re-assessment for ZULVAC 1+8 Ovis to the European Medicines Agency (the Agency) and requested that the marketing authorisation for this vaccine currently under exceptional circumstances converts to a normal marketing authorisation in case all the specific obligations are considered as fulfilled.

The product contains inactivated bluetongue virus (BTV), serotype 1 (BTV-1) and serotype 8 (BTV-8).

This is the second annual re-assessment of the marketing authorisation for this product (i.e. re-assessment of the benefit-risk balance). A marketing authorisation under exceptional circumstances was granted on 14 March 2011 by the European Commission for this veterinary medicinal product. The CVMP opinion following the first annual re-assessment was adopted on 12 July 2012 recommending the continuation of the marketing authorisation under exceptional circumstances.

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

On 26 July 2013, the European Commission adopted a Commission Decision for this application.

1.1.1. Scope of the annual re-assessment

The annual re-assessment relates to the following specific obligations (as stated in Annex II of the CVMP opinion adopted for the granting of the marketing authorisation):

1. The applicant is required to submit in 6 months following the authorisation of the product, an action plan together with timelines for all points that require resolution in order for the authorisation to convert to normal status. The above information will be evaluated and approved by the CVMP and will form part of the subsequent annual re-assessment.

2. For the first and subsequent annual re-assessments the applicant should provide annually an updated risk assessment on the continuous use of the vaccine taking into account the continued need for the vaccine, its history of use over the previous twelve months and progress made in addressing the items that require resolution in order for the authorisation to convert to normal status.

3. The applicant is required to submit 6-monthly periodic safety update reports (PSURs) starting once the marketing authorisation has been approved and, in addition to the legal requirements applicable to reporting of suspected adverse reactions, the applicant is required to specifically monitor and evaluate the following suspected adverse reactions in the PSURs: abortions, spontaneous death, effects on milk production, local reactions, pyrexia, lethargy and hypersensitivity reactions, including severe allergic reactions. The frequency of submissions of PSUR reports will be assessed at the annual re-assessment of the product.

Following the first annual re-assessment the following specific points of concern remained, in relation to the above specific obligation No. 1:

1. The applicant is requested to provide data on process control tests carried out on at least 3 vaccine antigen batches of different sizes, produced within the range of 250–1,000 l.

2. The results obtained support a shelf life of 12 months for the bluetongue virus serotype 8 inactivated antigen when stored at 2 °C – 8 °C and protected from light. Overall, based on the applicant's statement, it is understood that the applicant is not intended to claim a longer stability of vaccine batches when formulating using a combination of inactivated BTV-1 and BTV-8 antigens having a 12 months stability. The applicant is requested to confirm such an interpretation. Moreover, the applicant is requested to address the apparent discrepancy noted between the initial results of potency test in mice carried out at T0 (BTV-1: relative potency (RP)=1.5; BTV-8: RP=1.3) and those obtained with the new data presented with this renewal application (BTV-1: RP ≥1.1; BTV-8:RP ≥1.3).
3. The applicant is requested to amend the title of the study relating to testing efficacy of antimicrobial preservation at time 6 (months) according to the actual time point at which the test was carried out.
4. The results obtained from the majority of the stability tested parameters allowed to support a stability of the finished product up to 12 months. The applicant is requested to clarify the apparent discrepancy noted in the values provided the pH and thiomersal content a T6 for vaccine batch 13926 (pH 7.3 in the initial table against 7.4 in the updated table; thiomersal: 0.0094% in the initial table against 0.0093% in the updated table).
5. Data are still awaited in order to comply with the request to the applicant to provide a test for saponin quantification.

1.1.2. Documentation submitted

The applicant submitted the following documentation:

- ZULVAC 1+8 Ovis annual report 2013.

1.2. Steps taken for the assessment of this annual re-assessment

- The application was submitted on 6 March 2013.
- The procedure started on 20 March 2013.
- An opinion was adopted on 16 May 2013 by the CVMP

2. Scientific discussion

2.1. Assessment

The applicant submitted the document *ZULVAC 1+8 OVIS – ANNUAL REPORT 2013* focusing on the above mentioned list of specific obligations and, in particular, specific obligation No. 1 addressing the list of remaining points of concern on the quality of this vaccine.

Specific obligations

1st specific obligation

At the time when the marketing authorisation was granted to ZULVAC 1+8 Ovis, the applicant had been requested to submit, as a matter of priority, data relating to the following outstanding issues:

Part 2 (Quality):

1. In process control tests carried out on at least 3 vaccine antigen batches of different sizes, produced within the range of 250–1,000 l.
2. Final data supporting the 12 months storage time at 2 °C – 8 °C of vaccine antigen(s).
3. Final data for testing the efficacy of antimicrobial preservation.
4. Full set of data, according to the reported timelines, in order to demonstrate the claimed stability of finished product.
5. A validated test to quantify the saponin content in the finished product is awaited.

The above points were revisited during the first annual re-assessment and concerns remained for further annual re-assessment.

1. In process control tests carried out on at least 3 vaccine antigen batches of different sizes, produced within the range of 250–1,000 litres

In the context of the first annual re-assessment, the CVMP concluded that the applicant gave plausible justifications for not providing the requested data, relating to the unpredictability of the market size at the time. Indeed, at that time, no antigen batches higher than 250 l had been manufactured. However, as a matter of principle, the point for concern remained and the data were again requested in order to fulfill the specific obligation.

For the second annual re-assessment the applicant reiterated that due to the current demand of BTV vaccines, to date no antigen batches higher than 250 l have been manufactured and declared the intention to limit batch size to 250 l and to submit a variation if larger batch sizes will be required in the future.

The CVMP concluded that the point of concern was finally and satisfactorily addressed. The applicant would need to submit a variation if larger batch sizes will be required in the future. The specific obligation is fulfilled for this point.

2. Final data supporting the 12 months storage time at 2 °C – 8 °C of vaccine antigen(s)

In the context of the first annual re-assessment, the applicant claimed that a shelf life of the final product of 12 months has been demonstrated although, according to the batch potency test results in mice, potency for the BTV-8 inactivated antigen at time 15 months (RP ≤ 0.92) was shown to be slightly below the expected threshold (RP ≥ 1).

The CVMP concluded in the context of the first annual re-assessment that the results obtained support a shelf life of 12 months for BTV serotypes 1 and 8 inactivated antigens when stored at 2 °C – 8 °C and protected from light. It was understood that the applicant did not intend to claim a longer stability of vaccine batches, when formulating using a combination of inactivated BTV-1 and BTV-8 antigens having a 12 months stability. However, the applicant was requested to confirm such an interpretation and moreover to address an apparent discrepancy noted between the initial results of potency test in mice carried out at T0 (BTV-1: RP=1.5; BTV-8: RP=1.3) and those obtained with the new data presented with this renewal application (BTV-1: RP ≥ 1.1; BTV-8: RP ≥ 1.3).

For the second annual re-assessment the applicant confirmed that it is not intended to claim a longer stability of vaccine batches, when formulating using a combination of inactivated BTV-1 and BTV-8 antigens having a 12 months stability. Regarding the discrepancy noted between the initial results of the potency test in mice carried out at T0 (BTV-1: RP=1.5; BTV-8: RP=1.3) and those obtained with the new data presented with the 2012 renewal application (BTV-1: RP ≥ 1.1; BTV-8: RP ≥ 1.3), the

applicant confirmed that an error occurred in the original calculation for BTV-1 titre and that the correct results are the last reported, i.e. BTV-1: RP ≥ 1.1; BTV-8: RP ≥ 1.3.

The CVMP concluded that the point of concern was finally and satisfactorily addressed. The specific obligation is fulfilled for this point.

3. Final data for testing the efficacy of antimicrobial preservation

In the context of the first annual re-assessment, the applicant provided the protocol of a study designed to proof that the selected concentration of thiomersal is effective against the growth of representative bacterial and fungal species in accordance with the European Pharmacopoiea (Ph. Eur.) monograph on efficacy of antimicrobial preservatives. The antimicrobial preservation effectiveness tests demonstrated the effectiveness of the antimicrobial used until the end of the 12 months shelf life.

The CVMP concluded in the context of the first annual re-assessment that the point for concern was satisfactorily addressed and the applicant's conclusions were considered as reasonably sustainable. However, the request to the applicant to amend the title of the study relating to testing efficacy of antimicrobial preservation at time 6 (months) according to the actual time point at which the test was carried out, was reiterated.

For the second annual re-assessment the applicant clarified that the title of each report is based on the actual time point when the testing was initiated.

The CVMP concluded that the point of concern was satisfactorily addressed. The specific obligation is fulfilled for this point.

4. Full set of data, according to the reported timelines, in order to demonstrate the claimed stability of finished product

In the context of the first annual re-assessment, the applicant provided a final report including the results of the testing of the 6 stability batches kept at 2 °C – 8 °C.

The CVMP concluded in the context of the first annual re-assessment that overall, the point for concern was satisfactorily addressed. The results obtained from the majority of the stability tested parameters supported a stability of the finished product up to 12 months. However, the applicant was requested to clarify the apparent discrepancy noted in the values provided for the pH and thiomersal contents at T6 for vaccine batch 13926 (pH 7.3 in the initial table against 7.4 in the updated table; thiomersal: 0.0094% in the initial table against 0.0093% in the updated table).

For the second annual re-assessment the applicant clarified that an error occurred in reporting the original results. The applicant confirmed that the correct results are 7.4 and 0.0093% for pH and thiomersal content, respectively, as reported in the updated table.

The CVMP concluded that the point of concern was satisfactorily addressed. The specific obligation is fulfilled for this point.

5. A validated test to quantify the saponin content in the finished product is awaited

In the context of the first annual re-assessment, the applicant confirmed that the set up and validation of an adequate method for the saponin testing in the finished product was under development. In the preliminary studies some vaccine components interfered with the saponin test.

The CVMP acknowledged during the first annual re-assessment that the efforts made by the applicant investigating a method for saponins extraction and clean-up as a step before HPLC testing and saponin determination in order to fulfil the specific obligation. However, although the absence of a validated

method would not preclude the continuation of the marketing authorisation granted to ZULVAC 1+8 Ovis given under exceptional circumstances, the request for relevant data was reiterated.

For the second annual re-assessment the applicant reiterated similar arguments provided in the first annual re-assessment, i.e. no updated information on the validation of an adequate method for saponin quantification has been provided.

Taking into account that the product has an *in vivo* potency test the CVMP considered that, in view of the fact that current legislation requires an adjuvant assay only insofar as testing procedures are available, the absence of such a test should not preclude the conversion of the marketing authorisation to normal status. Indeed, the absence of the outstanding saponin quantification test does not affect the safety and efficacy of the product. The applicant is recommended to continue and finalise the test on the saponin quantification as indicated in the List of Recommendations below.

Overall, the CVMP concluded that the 1st specific obligation is fulfilled.

2nd specific obligation

Concerning specific obligation 2, an updated benefit-risk assessment, based on pharmacovigilance data, was provided for the first annual re-assessment. The CVMP concurred in the context of the first annual re-assessment with applicant's conclusions that the benefit-risk profile remained favourable for the product ZULVAC 1+8 Ovis.

For the second annual re-assessment an updated benefit-risk assessment was provided by the applicant in order to fulfill this second specific obligation. In order to support the continued need for the product in the field, the applicant presented an overall review of the current situation concerning the circulation of BTV serotypes in Member States. Specifically, it was stated that BTV-1 is still circulating in Spain along with BTV-4, whereas BTV-8 appears now to no longer be present in European Union (EU). Vaccination against BTV is still performed in some Member States. However, although BTV-8 does not appear to circulate in EU any longer, risks persist on reintroduction of BTV-8 to the EU and/or other serotypes from the Middle East, Asia and Africa. As a result the availability of this category of vaccines (i.e. against BTV-1) is important to ensure rapid response should any re-introductions occurred again.

In the following a summary of the product and claims is presented:

Part 2: Quality

ZULVAC 1+8 Ovis is an inactivated vaccine containing inactivated strains of BTV-1 and BTV-8 serotypes. The manufacturing of the product, including control of all starting materials and control tests (in process and on the final product) as well as stability are fully documented in Part 2 of the dossier. Data have been provided with the present re-assessment which, overall, demonstrate the stability of the antigen and of the finished product (12 months, respectively).

The saponin quantification test method development and validation remains to be finalised. Similarly to the decision taken by the CVMP for other vaccines, the absence of such a test on the finished product is considered as having no additional impact on the risk of the product and should not constitute a barrier for the authorisation granted under exceptional circumstances for ZULVAC 1+8 Ovis to be converted to a normal status.

Part 3: Safety

The safety of the product has been fully documented in Part 3 of the dossier. The safety of ZULVAC 1+8 vaccine has been demonstrated in lambs of 6 weeks of age (1.5 months) after a single, repeat and an overdose. Evidence was also provided concerning the safe use of the vaccine which has now been administered to approx 94,000 animals. Moreover, pharmacovigilance data do not indicate that

any revision of the summary of product characteristics (SPC) warnings is required and the safety of the vaccine and therefore risks remain the same.

Part 4: Efficacy

The efficacy of the product was presented in laboratory challenge studies in the dossier. Data provided in this section have demonstrated that the use of ZULVAC 1+8 Ovis prevents viraemia in lambs vaccinated twice from 6 weeks of age as demonstrated by a fully validated real time polymerase chain reaction assay (RT-PCR). No evidence was observed through pharmacovigilance concerning any lack of efficacy of the vaccine and therefore its benefits remain unaltered.

Overall, the applicant considered that the efficacy of ZULVAC 1+8 Ovis has been fully established according to the requirements of the CVMP Guideline EMEA/CVMP/IWP/220193/2008, Ph. Eur. and Directive 2001/82 and the minimum titres are fully supported.

The potency of the vaccine for release has been established against a reference vaccine shown to be efficacious in lambs and given a relative potency of 1. For a vaccine batch to be released as potent, it must demonstrate a relative potency with respect to the reference batch of ≥ 1 (please see Part 2.E for full details of the method and validation of the potency test.

The CVMP concluded that the applicant's conclusions are sustainable overall. Although a very limited number of doses of ZULVAC 1+8 Ovis has been sold in the Union (only in France) in 2012, it is thought that there is still a benefit of having this category of vaccines available in case or re-incursion of BTV in EU. Furthermore, the applicant provided appropriate data included in the SPC regarding the composition of the product, safety warnings and the expected efficacy of the vaccine. Thus, it can be concluded that the benefit-risk balance remains favorable for ZULVAC 1+8 Ovis. The specific obligation is fulfilled.

3rd specific obligation

Concerning this specific obligation for the first annual re-assessment, the CVMP concluded that no update of the SPC and product literature was deemed necessary as a result of the safety assessment based on the PSURs submitted including the specific monitoring of certain suspected adverse reactions.

For the second annual re-assessment, the applicant has confirmed that PSURs have been submitted in line with the agreed timetable and that no revision to the SPC has been requested as a result of the assessment of these data.

The CVMP confirmed the applicant's conclusions. No update of the SPC and product literature is deemed necessary as a result of safety concerns from the PSURs submitted during the concerned period. The specific obligation is fulfilled.

2.2. Summary and conclusions

In the first annual re-assessment the evidence for compliance with the specific obligations described in the beginning of the report was investigated. The CVMP concluded that while the benefit-risk balance remained positive, points of concern remained in relation to the specific obligations that therefore were not fulfilled. As a consequence the CVMP recommended for the marketing authorisation to continue under exceptional circumstances, therefore to be subject to further annual re-assessments.

In accordance with Article 39 of Commission Regulation (EC) No. 726/2004, the applicant submitted to the European Medicines Agency on 6 March 2013 an application for the second annual re-assessment of ZULVAC 1+8 Ovis. An annual report focusing on the list of specific obligations and, in particular, specific obligation No. 1 was provided by the applicant.

During this second annual re-assessment the evidence for compliance with the specific obligations described in the beginning of the report were re-investigated. The three specific obligations, including the subpoints as applicable, were addressed by the applicant. The five subpoints of specific obligation No. 1 were successfully addressed by the applicant and are summarised below.

The CVMP considered the applicant's intention to limit batch size to 250 l, due to the current demand of BTV vaccines that has lead to that no antigen batches higher than 250 l have been manufactured. The applicant would however submit a variation if larger batch sizes will be required in the future. The CVMP considers the approach acceptable.

The CVMP noted the applicant's intention not to claim a longer stability of vaccine batches when formulating using a combination of inactivated BTV-1 and a BTV-8 antigen with 12 months stability. Regarding the discrepancy noted between the initial results of potency test in mice carried out and those obtained with the new data presented with the 2012 application, the applicant corrected an error in the original calculation for BTV-1 titre and confirmed that the correct results are the last reported, i.e. BTV-1: RP ≥ 1.1; BTV-8: RP ≥ 1.3. The CVMP considers that this has been satisfactorily addressed.

The CVMP considered the clarification given by the applicant that the title of each report concerning the set of studies relating to testing efficacy of antimicrobial preservation is based on the actual time point when the testing was initiated. The CVMP considers that this point for concern has been satisfactorily addressed.

The CVMP considered the confirmation of correct results 7.4 and 0.0093% for pH and thiomersal content, respectively, as reported. The CVMP considers that this point for concern has been satisfactorily addressed.

Concerning the development and validation of a method for saponin quantification, no updated information has been presented. Similarly to the decision taken by the CVMP for other vaccines, the absence of such a test on the finished product is considered as having no additional impact on the risk of the product and should not constitute a barrier for the authorisation granted under exceptional circumstances for ZULVAC 1+8 Ovis to be converted to a normal status. The absence of such a test does not affect the safety and efficacy of the product. The applicant is expected to finalise the work on the saponin quantification test method development.

Taking the above issues and conclusions into account, the CVMP considered that the specific obligation No. 1 was fulfilled however that the applicant would be expected to finalise the work on the saponin quantification test method development.

Concerning the second specific obligation an overall review of the current situation concerning the circulation of BTV serotypes in Europe was considered by the CVMP. In summary, it was acknowledged that BTV-1 is still circulating in Spain along with BTV-4, whereas BTV-8 appears now to no longer be present in Europe. Vaccination against BTV is still performed in some Member States. However, although BTV-8 does not appear to circulate in EU any longer, risks persist on reintroduction of BTV-8 and/or other serotypes from the Middle East, Asia and Africa to the EU. The CVMP agreed that as a result the availability of this category of vaccines (i.e. against BTV-1) is important to ensure rapid response should any re-introductions occurred again. In addition, the CVMP also reviewed the applicant's summary of the dossier and the product and the benefit-risk assessment and concluded that the remaining points for concern related to the dossier were satisfactorily addressed. The CVMP considered that the specific obligation No. 2 was fulfilled.

Considering the pharmacovigilance data submitted for this vaccine, no safety concerns were identified during the concerned period. The CVMP considered that specific obligation 3 was now fulfilled however

recommends that the submission of future PSUR should follow the standard timetable, following the conversion of the marketing authorisation.

On the basis of the above, the CVMP considered that the specific obligations have been fulfilled and there are no remaining grounds to maintain the marketing authorisation for ZULVAC 1+8 Ovis under exceptional circumstances.

In addition, concerning the saponin quantification test, the attempts (and the difficulties encountered) made by the applicant in order to comply with the request to develop a quantification of the saponin adjuvant in the finished product were noted. The delay in providing the requested test does not constitute a barrier for the marketing authorisation provided under exceptional circumstances to ZULVAC 1+8 Ovis to convert to a normal marketing authorisation status. The applicant is expected to continue and finalise the on-going work.

3. Benefit-risk assessment

ZULVAC 1+8 Ovis is an inactivated vaccine against bluetongue virus (BTV) serotypes 1 (BTV-1) and 8 (BTV-8). The product has been authorised in 2011 under exceptional circumstances due to the epidemiological situation at the time. This is the second annual re-assessment of this product.

3.1. Benefit assessment

Direct benefits

The benefit of the product is prophylactic immunisation to protect sheep against infection with BTV serotypes 1 and 8. The vaccine has been proven to prevent viraemia in immunised animals. Prevention of viraemia directly benefits the animal in that this ensures no clinical signs or loss of condition. Pharmacovigilance data do not indicate a lack of efficacy in the field and therefore the benefits remain the same.

Additional benefits

In addition to the direct benefit to the immunised animal, there is a benefit to herd health both locally and regionally. As BTV is an arthropod borne disease an animal needs to be viraemic for the insect vector to pick up the BTV, therefore as ZULVAC 1+8 Ovis prevents viraemia it is also able to prevent disease transmission and spread. The use of ZULVAC 1+8 Ovis is important for animal health at Community level as it is considered the most effective way to control disease spread as there are no efficient ways to control the insect vector and no therapeutic treatment for BTV infections. Vaccination has been shown to be an efficient tool for disease control.

The onset of immunity 21 days after completion of the primary vaccination scheme has been fully documented. A duration of immunity of 12 months has been demonstrated.

3.2. Risk assessment

Main potential risks:

For the target animals:

1. Extraneous agents or contaminants in starting materials or from incomplete inactivation of the live virus.

The production process and starting materials are controlled to ensure no contaminants are present and that all in-process and final product tests are fully validated and that a validated inactivation

process is used. All starting materials are either tested or treated in order to ensure that no contaminants are present or that the treatment process ensures that any potential risk is alleviated. Both the master seed virus for BTV-1 and BTV-8 and the production cell line (baby hamster kidney cells, BHK-21) have been fully tested according to EU requirements. In addition a full TSE risk assessment has been provided.

2. Adverse reactions in the target animal in response to vaccination and lack of efficacy.

There are limited local reactions after vaccination, and these are appropriately indicated on the SPC. These local reactions have no effects on the general systemic health of the animals and are in line or less than those observed with other vaccines for sheep. Pharmacovigilance data following field use do not indicate an increased risk.

For the user:

The CVMP concluded that the vaccine does not present a risk to the user when used as indicated in the SPC.

For the environment:

ZULVAC 1+8 Ovis does not contain any ingredients which are considered harmful to the environment when used as recommended in the SPC.

For the consumer:

Any risks to the consumer with respect to vaccines administered to food producing species, relate to any potential residual live organism or vaccines residues in meat. As ZULVAC 1+8 Ovis is an inactivated vaccine, there are no risks of residual live virus. It has been demonstrated that there are no residues left in meat which would present a risk to the consumer. A zero withdrawal period is considered adequate.

Specific potential risks:

In respect to the potential reversion to virulence and spread of vaccine strain, there are no risks associated to its use as ZULVAC 1+8 Ovis is an inactivated product.

3.3. Risk management or mitigation measures

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

3.4. Evaluation of the benefit-risk balance

The information provided in the dossier and in response to the specific obligations for ZULVAC 1+8 Ovis was adequate to confirm that the benefit-risk balance for the product remains positive.

The product has been shown to be efficacious for the indication of prevention of viraemia in sheep with an onset of immunity of 21 days and duration of immunity demonstrated for 12 months.

The formulation and manufacture of the product is clearly described and specifications have been set to ensure consistent quality. All starting materials are fully EU compliant and documented. Data have been provided regarding attempts to quantify the saponin adjuvant and while this has not been possible the absence of such a test should not preclude the conversion of the marketing authorisation to normal status as the product has an *in vivo* potency test and in view of the fact that current legislation requires an adjuvant assay only insofar as testing procedures are available. The applicant is expected to finalise the work on the saponin quantification test method development.

The product is well tolerated by the target species and presents a low risk for users and the environment and appropriate warnings have been included on the SPC. A sufficient withdrawal period has been set.

Following use of the product in the field no increased risk has been observed therefore all points above remain fully valid. No safety concerns were raised in the pharmacovigilance data provided so far.

3.5. Overall conclusion on the benefit-risk balance

The CVMP considered that this application, accompanied by the submitted documentation, demonstrated that the benefit-risk profile remains favourable for the product.

4. Overall conclusions of the evaluation and recommendations

The CVMP reviewed the documentation submitted by the applicant for evidence of compliance with the specific obligations and for re-assessment of the benefit-risk balance of this veterinary medicinal product.

The specific obligations have been fulfilled.

The applicant is expected to finalise the work on the saponin quantification test method development.

Since all the specific obligations have been fulfilled, there are no remaining grounds to maintain the marketing authorisation of ZULVAC 1+8 Ovis under exceptional circumstances and thus the CVMP recommends the conversion of the marketing authorisation to a normal status.

The CVMP considers it necessary to restart the PSUR cycle for ZULVAC 1+8 Ovis according to the standard rules, following the conversion of the marketing authorisation to a normal status.

4.1. Changes to the community marketing authorisation

Changes are required in the annexes of the Community marketing authorisation, also to take into account recent changes in the relevant templates.