EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/120064/2013
Veterinary Medicines and Product Data Management

CVMP assessment report for ZULVAC 1 Ovis (EMEA/V/C/002335/S/003)

Inactivated Bluetongue Virus, serotype 1, strain BTV-1

EU/2/11/131/001, 005-006

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

Authorised presentations

EU Number	Invented name	Strength	Pharmaceutical form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
EU/2/11/131/001	ZULVAC 1 Ovis	Inactivated Bluetongue Virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1	Suspension for injection	Sheep	Subcutaneous use	Type I glass vials with chlorobutyl stopper and aluminium seal	20ml (10doses)	1 vial	Zero days
EU/2/11/131/005	ZULVAC 1 Ovis	Inactivated Bluetongue Virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1	Suspension for injection	Sheep	Subcutaneous use	Type II glass vials with chlorobutyl stopper and aluminium seal	100ml (50doses)	1 vial	Zero days
EU/2/11/131/006	ZULVAC 1 Ovis	Inactivated Bluetongue Virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1	Suspension for injection	Sheep	Subcutaneous use	Type II glass vials with chlorobutyl stopper and aluminium seal	240ml (120 doses)	1 vial	Zero days

RP*>-1 (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 Ovis**
Active substances:	Inactivated Bluetongue Virus, serotype 1, strain BTV-1
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, serotype 1.
Marketing authorisation holder (name and address):	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom
MAH contact point:	Dr Catrina Stirling Tel.: +44 1304 616161
Rapporteur:	Maria Tollis

Table of contents

1. Background information on the annual re-assessment

1.1. Submission of the annual re-assessment application

In accordance with Article 39 of Commission Regulation (EC) No. 726/2004, the marketing authorisation holder (MAH), Pfizer Limited (MAH), submitted to the European Medicines Agency (the Agency) on 30 July 2012 an application for the first annual re-assessment for ZULVAC 1 Ovis vaccine (i.e. re-assessment of the benefit-risk balance of the product).

1.2. Scope of the annual re-assessment

The annual re-assessment relates to the following specific obligations:

1. The marketing authorisation holder (MAH) 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 reassessment.

2. For the first and subsequent annual reassessments the marketing authorisation holder 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 MAH is required to submit 6-monthly Periodic Update Safety reports starting once the marketing authorisation has been approved and, in addition to the legal requirements applicable to reporting of suspected adverse reactions, the MAH 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 reassessment of the product.

In the case that all specific obligations and points for concerns (either major objections or other concerns subject to which, the granting of a marketing authorisation under exceptional circumstances was provided) are considered resolved, then the marketing authorisation which is currently under exceptional circumstances can convert to standard status.

1.3. Documentation submitted

The MAH submitted the following documentation:

- One document called ZULVAC 1 Ovis Centralised Procedure Annual Assessment 2012.
- One document called ZULVAC 1 Ovis Centralised Procedure Annual re-assessment (1) RLoQ containing the responses to the List of Questions made in the first part of this annual re-assessment.

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

- The dossier was submitted on 30 July 2012
- The procedure started on 14 August 2012
- A List of Questions was adopted on 10 October 2012

- An opinion was adopted on 13 December 2012.
- European Commission adopted a Commission Decision on 20 February 2013.

2. Scientific discussion

2.1. Assessment

Specific Obligations

1st specific obligation:

The outstanding issues that that required resolution in order for the authorisation to convert to a normal status were described in the CVMP assessment report of the initial application for the granting of a community marketing authorisation for ZULVAC 1 Ovis and are the following:

Part 2

a) The development of an in vitro batch potency test within an appropriate timeframe.

b) The data on 3 batches between 250-1000 l, when available.

c) The results of the BPT in transgenic mice carried out on the first ten batches of ZULVAC 1 Ovis vaccine are awaited.

d) The data in order to validate the identification and quantification of saponin in the finished product.

e) The batch results for the first three manufacturing scale batches of the 10 dose and 120 dose presentations.

Part 2:

a) Development of an *in vitro* potency test

The MAH confirmed that was developing an *in vitro batch* potency test in order to substitute the *in vivo* batch potency test in transgenic mice.

Two alternatives were considered:

a) The development of an ELISA based on the detection of the VP2 protein (antigenically relevant and serotype specific). For that purpose 7 peptides were designed. Four of these peptides were based on the model for BTV-1 VP2 structure and hydrophobicity of the amino acids (aa) sequences.

b) Development of a quantitative RT-PCR for the quantification on the inactivated antigen. A validated quantitative RT-PCR is available for the evaluation of viraemia in blood samples. The same technique was tested for the quantification of the number of Bluetongue virus (BTV) genomes copies/dose in the final product. When using the final product the presence of the adjuvant interfered with the technique, while satisfactory results were obtained when testing the inactivated antigen before blending. That means that such a test would not be possible to be set up for the final product but for the inactivated antigens (prior to blending). The MAH is still working on the development of a quantitative RT-PCR for the quantification on the inactivated antigen and progress will be reported in the next annual reassessment.

Conclusion:

The MAH's progress in developing the recommended *in vitro* potency test was noted. The delay in providing the requested test does not constitute a barrier for the marketing authorisation provided under exceptional circumstances to ZULVAC 1 Ovis vaccine to convert to a standard marketing authorisation status. Nevertheless the MAH was asked to continue/finalise the on-going work (Recommendation n.5 for the marketing authorisation provided under exceptional circumstances to ZULVAC 1 Ovis vaccine to convert to a standard marketing authorisation status) and it will undertake it.

b) Provision of data on 3 batches between 250 – 1000 l when available.

The reason of the wide range in volumes that were submitted during the process of registration of the vaccine was the high variability in demand for BTV vaccines as they are used according to the epidemiological situation which was constantly changing. Due to the current demand of BTV vaccines, to date no antigen batches higher than 250 l have been manufactured. In process control tests of vaccine antigen batches of 250 l were already submitted. The MAH therefore proposed to limit batch size to 250 l and submit a variation if lager batch sizes is required.

Conclusion:

The justifications presented by the MAH for not providing the requested data were acceptable. Due to the current epidemiological situation of BTV, the proposal to limit the batch size of ZULVAC 1 Ovis vaccine to 250 l (for which data was provided during the authorisation process under exceptional circumstances) and submit a variation if larger batch sizes are required was considered as acceptable. (Recommendation n.2 for the marketing authorisation provided under exceptional circumstances to ZULVAC 1 Ovis vaccine to convert to a standard marketing authorisation status).

c) Results of the BPT in transgenic mice carried out on the first ten batches of ZULVAC 1 Ovis vaccine to be provided.

To date, apart from the stability serials (300 l), only 1 batch of ZULVAC 1 Ovis vaccine (vaccine batch E16533 -120 doses- for which manufacturing batch protocols were provided) has been manufactured (March 2012) and tested satisfactorily according to the requirements in the approved dossier. The results of BPT in transgenic mice carried out using batch E16533 of ZULVAC 1 Ovis vaccine are briefly summarised below.

Batch-final Bulk (n. of doses)	RP (Relative Potency)
E16533 (120 doses)	2.8

The MAH argued that for a "normal" marketing authorisation data are only expected to be provided for 3 consistency batches in addition to the potency test validation and in this case the MAH provided data on the stability/consistency serials (3) plus the additional batch with 120 doses. Moreover the MAH has provided data from 9 batches from a similar vaccine that contained BTV serotype 1 (ZULVAC 1+8 Ovis) and which were found acceptable during the annual re-assessment of that product in 2012.

Conclusion:

The required results were requested in order to further validate the batch potency test (BPT) in transgenic mice and not to prove the consistency of production of the vaccine (which is the main purpose of the requirement for the results from 3 batches). The fact that there is limited production of the vaccine batches in order to carry out the requested BPT in transgenic mice and the acceptance of results for the bivalent vaccine ZULVAC 1+8 Ovis) from 9 batches were noted. However the need for the remaining results from the 8 vaccine batches in order to validate the batch potency test could not be waived. Therefore it is considered that the request remained as a recommendation. (Recommendation n.3 for the marketing authorisation provided under exceptional circumstances to

ZULVAC 1 Ovis vaccine to convert to a standard marketing authorisation status). The MAH will undertake the above recommendation.

d) Saponin test

The MAH is still working on the set up and validation of an adequate method for the saponin testing in the finished product. In the preliminary studies using vaccine samples, no satisfactory results were obtained with the available method as some vaccine components interfere with the saponin test. In order to avoid this interference, the MAH is currently investigating a method for saponins extraction and clean-up as a previous step before HPLC testing and saponin determination. Preliminary results were shown and satisfactory saponin chromatogram profiles have been obtained. However preliminary results in finished product have not been satisfactorily and may be attributable to technical issues during the experimental phase. Further investigation of the extraction and clean-up method is needed.

Conclusion:

The efforts made by the MAH in order to comply with the request above were noted. The CVMP is of the opinion that, the absence of such a test should not preclude the conversion of the marketing authorisation to normal status. However, it was recommended that the MAH continues the work and finalizes the test on the saponin quantification as soon as possible (Recommendation n. 4)

e) Batch results from first three manufacturing scale batches of the 10 dose and 120 dose presentations.

Results for the pilot scale batches (300 l) of the 10 dose and 120 dose presentations were included in the stability study were submitted in the original dossier. To date, only one batch (16533) of ZULVAC 1 Ovis vaccine has been manufactured (March 2012) and it was tested satisfactorily according to the approved dossier. The Manufacture Batch Protocols (MBPs) were provided. So far the MAH has provided overall data on 3 pilot scale (300 l) consistency/stability serials and one full scale batch (batch E16533 of ZULVAC 1 Ovis vaccine). The batches themselves are identical whether filled in 10 or 120 dose presentations therefore in terms of product consistency at release represent equivalent data. The MAH argued that on the basis of the above data the only concern should be whether or not there is any difference in stability between presentations; however this has been satisfactorily addressed in the latest stability results provided for this procedure

Conclusion:

The MAH's justifications for the omission to provide the requested data due to limited production were noted. Based on the additional clarifications provided, considering that the consistency of production has been satisfactorily demonstrated, the difference in volumes of the batches were not considered as a barrier for recommending the conversion of the marketing authorisation.

Conclusion on 1st specific obligation

Part 2:

The test for the quantification of saponin is not ready yet but work is continuing in finalising it. This was considered acceptable. It was also clarified that due to the current demand the MAH is willing to limit the batch size to 250 l and submit a variation should there be a need to use a larger batch size. As a result no new data were presented on this issue. This was considered acceptable.
Batch potency test results in transgenic mice from only one final product batch were submitted due to the limited production of the vaccine. The justification for these limited results was considered acceptable but the need to further validate the batch potency test on the basis of the remaining first 8 production batches is still relevant. This request is a recommendation for the MAH following a

conversion of the marketing authorisation and the MAH will undertake it.
Due to limited production of the vaccine results from only one full scale batch were presented instead of the required three. The remaining results cannot be waived and their provision is now one of the recommendations which the MAH will undertake.

2nd specific obligation:

In order to support the continued need for the product in the field, the MAH presented an overall review of the current situation concerning the circulation of BTV serotypes in Europe. 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 Europe. Vaccination against BTV is still performed in some EU countries. 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 Bluetongue serotype 1) is important to ensure rapid response should any re-introductions occurred again.

Introduction and summary of the product and claims

Part 2: Quality

ZULVAC 1 Ovis is an inactivated vaccine containing inactivated strain of BTV serotype 1. 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 were adequately documented. The stability of the antigen and vaccine were demonstrated. Potency of the vaccine for release was established against as reference vaccine shown to be efficacious in calves and given a relative potency of 1. For a vaccine batch to be release as potent it must demonstrate a relative potency with respect to the reference batch of ≥ 1.

The remaining outstanding points which still need to be resolved such as the saponin quantification test, remaining batch and BPT results from full scale production batches, are considered as having no additional impact on the risk of the product and should not constitute a barrier for the authorisation given under exceptional circumstances to the concerned vaccine, to be converted to a standard status.

The MAH will undertake work on all the above in order to fulfil the relevant recommendation.

Part 3: Safety

The safety of ZULVAC 1 Ovis has been demonstrated in lambs of 6 weeks of age (1.5 months) after a single, repeat and overdose injection of the vaccine. In addition safety has also been fully demonstrated in pregnant ewes. ZULVAC 1 Ovis vaccine has been demonstrated to be well tolerated by the target species and presents a low risk for users and the environment and, as a consequence, the safety statements in the relevant sections of the SPC are considered fully supported and appropriate.

Part 4: Efficacy

The efficacy of the product has been presented in laboratory challenge studies. The SPC claim statements are considered fully supported and appropriate. No new information on the efficacy of the vaccine was presented in this annual re-assessment; therefore no new risks were identified.

Conclusion on 2nd specific obligation

The 2nd specific obligation has been satisfactorily addressed.

3rd specific obligation:

The MAH confirmed that one PSUR has been submitted covering the period from 5 August 2011 to 29 February 2012. During this period, no doses of centralised authorised ZULVAC 1 Ovis vaccine were sold in the EU/EEA Countries (the product is not sold in any third country). Most of sales of ZULVAC 1 Ovis were made under national licenses only, while only the sales for 2012 were made under the centralised license. Therefore no pharmacovigilance data were available for assessment from the submitted PSUR. Thus the history of the use of the vaccine over the last twelve months has not yet been provided by the MAH. The MAH confirmed that reports of adverse experiences will continue to be monitored and investigated as necessary, and steps will be taken to revise the SPC as data so indicate. It is expected that pharmacovigilance data from the 2012 sales will be reported in the next PSUR, which is expected shortly.

Conclusion on 3nd specific obligation

No pharmacovigilance data from the use of the vaccine in sheep has been presented in the first PSUR period, as the vaccine has not been sold / used anywhere under its central authorisation. No updates of the SPC are considered necessary due to any safety concerns during the period covered from the first PSUR.

Additional Information

In the CVMP assessment report of the initial authorisation under exceptional circumstances in 2011 it was stated in Part 2 under stability that the MAH committed to place the first three manufacturing scale batches (10 doses presentation and 120 doses presentation) into the long-term stability program after approval. The results obtained to date indicated that when stored in the conditions specified in the SPC, the finished product keeps its characteristics in terms of appearance, pH, thiomersal and aluminum content for at least 9 months in the 6 batches tested. Potency results for the 6 batches are only available at T0. Data were provided in order to support the claimed stability characteristics of the vaccine under application.

Final product

The final stability report GC015-619-T15/01 was submitted in the context of the current procedure.

The stability study of ZULVAC 1 Ovis was conducted with samples of 6 batches of final product (3 batches of 10-dose presentation and 3 batches of 120-dose presentation) manufactured in Pfizer Olot, S.L.U. (formerly Fort Dodge Veterinaria, S.A, Olot site), following good manufacturing practices (GMP's) and tested for stability in Pfizer Olot, S.L.U. Potency, safety and sterility parameters were tested at T0 and T15 months providing also satisfactory results for the 6 batches tested. The results obtained with the 6 batches tested support a shelf life for the final product of at least 12 months when stored at 2 – 8 °C and protected from light. Although indicated in the submitted stability protocol, the stability of the ZULVAC 1 Ovis batches was not investigated beyond 15 months. For that reason, the claimed shelf-life for the final product ZULVAC 1 Ovis is 1 year. The results of the 6 tested batches and they were acceptable.

Conclusion:

The results indicated that when stored in the conditions specified in the SPC, the product keeps its characteristics according to the relevant specifications in the approved dossier for at least 15 months in all the 6 batches tested. Upon specific request, the manufacturer's batch protocols for the 6 vaccine batches used in the stability report were provided and they were satisfactory.

Vaccine antigen

Data supporting a 12 month storage time at 2 - 8 °C of inactivated/ neutralised antigens, data were provided from a 24 months stability study of the vaccine batch FT090157 of ZULVAC 1 Ovis were provided. The final report on the stability of BTV serotype 1 inactivated antigen was submitted in the context of the current application. The same inactivated antigen is used for both ZULVAC 1 Ovis and Bovis vaccines formulation. Due to the fact that the efficacy for the ovine vaccine was demonstrated with a lower antigen content (min. $10^{6.4}$ $TCID_{50}$ per 2 ml dose) than for the bovine vaccine (min. $10^{6.7}$ $TCID_{50}$ per 2 ml dose), ZULVAC 1 Ovis was selected to demonstrate the vaccine antigen stability. ZULVAC 1 Ovis batch FT090157 was manufactured in order to support a 12 months stability for the inactivated BTV-1 antigen when stored at 2 - 8°C. Twelve months after its production, the inactivated BTV-1 antigen batch F37659was used to blend ZULVAC 1 Ovis vaccine at a concentration of $10^{6.5}$ $TCID_{50}$/dose in order to produce the batch FT090157 (manufacturing date: August 2009, vial size, 50 doses= 100 ml). ZULVAC 1 Ovis batch FT090157 samples were stored and analysed according to the planned schedule described in protocol. The results obtained until time 15 months indicated that the vaccine formulated with a 12 month old antigen keeps its characteristics in terms of appearance, sterility, physical-chemical properties (pH, thiomersal and Al^{3+} content) and potency in mice at least until 15 months after being manufactured when stored in the conditions indicated in the SPC. These results supported a shelf life of 12 months for the Bluetongue virus serotype 1 inactivated antigen when stored at 2 - 8°C and protected from light. In the table below, the results of the tested batch are reported.

Stability results of vaccine batch FT090157 up to 15 months were provided. Although indicated in the submitted protocol, the stability of the batch has not been investigated beyond 15 months as the MAH decided to generate data in order to demonstrate a 12 months shelf life of the finished product only.

Conclusion:

The results obtained indicated that when stored in the conditions specified in the SPC, vaccine batch FT090157 keeps its characteristics in terms of appearance, sterility, pH, thiomersal and Al^{3+}content and potency for at least 15 months. Upon specific request, the manufacturer's batch protocols of vaccine batch FT090157 were provided. It was confirmed that this batch was tested for safety at T0 according to the approved release specifications and results were satisfactory. Additionally, it was clarified that the following parameters were further investigated in the selected batch: appearance, potency, pH, thiomersal, Al^{3+}content, sterility. For that reason, after T0 safety was not further investigated. This clarification was considered acceptable.

2.2. Summary and Conclusions

In accordance with Article 39 of Commission Regulation (EC) No. 726/2004, the MAH, Pfizer Limited, submitted to the European Medicines Agency on 30 July 2012 an application for the annual re-assessment of ZULVAC 1 Ovis vaccine. This is the first annual re-assessment since the authorisation under exceptional circumstances was granted to the vaccine. Associated to the current annual re-assessment application, the MAH has requested CVMP to consider the conversion of the given authorisation to a normal marketing authorisation status.

In this first annual re-assessment the evidence for compliance to the specific obligations described in the beginning of the report was investigated. The information provided confirmed the positive benefit-risk balance of the product and justified the maintenance of the marketing authorisation in the EU/EEA countries.

During the current procedure, the 3 specific obligations were addressed by the MAH. In particular, the MAH provided information regarding the progress of the development of the *in vitro* potency test and

the saponin quantification test. Results from the BPT in transgenic mice carried out in one ZULVAC 1 Ovis final product batch were presented. Moreover, batch results from one full scale batch of the vaccine were presented. Stability data were also provided which support a 12 month shelf-life for both the antigen and finished product.

No pharmacovigilance data were presented in the PSUR submitted as the product has not been sold under its central authorisation until 2012 but the MAH provided alternative information from nationally approved vaccines.

On the basis of the above the CVMP considered that the specific obligations have been fulfilled as far as possible at this moment considering also the current epidemiological situation in EU. Moreover the MAH will undertake a number of recommendations included in the list of recommendations As a result of the above the CVMP considered that a conversion of the authorisation to normal status could be recommended.

3. Benefit-risk assessment

Introduction

ZULVAC 1 Ovis is an inactivated vaccine against bluetongue virus serotype 1. The vaccine is formulated to contain aluminium hydroxide and saponin as an adjuvant system. The product has been authorised in 2011 under exceptional circumstances due to the epidemiological situation at the time. This is the first annual re-assessment and the MAH has requested the conversion of the authorisation to a normal one on the basis of having fulfilled all specific obligations.

Benefit assessment

Direct Benefit

The benefit of the product is the prophylactic immunisation to protect sheep against infection with BTV serotype 1. The vaccine has been proven to prevent viraemia in sheep. Prevention of viraemia directly benefits the animal, in that this ensures no clinical signs or loss of condition.

Vaccines are a well established and effective method to control the spread of bluetongue virus.

Clinical trials demonstrated that the product is capable of inducing an immune response which prevents transmission of the virus in cattle and reduces clinical signs caused by bluetongue virus serotype 1.

Additional Benefits

ZULVAC 1 Ovis is a standard inactivated vaccine and as such fits in with accepted vaccination practices in the field.

A duration of immunity of 12 months has been demonstrated.

No negative effect was demonstrated in pregnant ewes due to vaccination, which is valuable during a widespread vaccination programme usually necessary to control the spread of disease.

Risk assessment

Main potential risks:

Risk to the target animal

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

   This risk is mitigated by the control of the production process and starting materials to ensure no contaminants are present and that all in-process and final product tests are full validated and that a validated inactivation process is used. All starting materials are either tested for treated to ensure there are no contaminants or that the treatment process ensures any potential risk is alleviated, full details on starting materials were provided. Both the MSV for BTV-1 and the production cell line (BHK-21) have been tested according to EU requirements.

2. Adverse reactions in the target animal in response to vaccination.

A transient increase in rectal temperature, not exceeding 1.2 °C, may occur during the 24 hours following vaccination. Vaccination may be followed in most animals by a local reaction at the injection site. These reactions take the form in most cases of a general swelling of the injection site (persisting for not more than 7 days) or of palpable nodules (subcutaneous granuloma, possibly persisting for more than 48 days).

For the user

The active ingredient and excipients do not present a risk to the user, when used according the SPC information.

For the environment

ZULVAC 1 Ovis contains no ingredients which are considered harmful to the environment when used according to the SPC information.

For the consumer

ZULVAC 1 Ovis contains no components which require an MRL, therefore there are no concerns over failure to observe an MRL. The product contains components found in other marketed products; therefore the risk is no greater than already exists.

Specific potential risks, according to product type and application:

Following this first annual re-assessment, additional information on the product have been provided and no further specific risks have been identified.

Risk management or mitigation measures

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

Evaluation of the benefit-risk balance

ZULVAC 1 Ovis has shown that the benefit risk balance in the target species remain positive. The product has been shown to be efficacious for the indication of preventing viraemia and of reducing clinical signs caused by bluetongue virus serotype 1. The formulation and manufacture of ZULVAC 1 Ovis is clearly described and specifications have been set to ensure consistent quality.

No serious safety issues have been reported in the target animals. ZULVAC 1 Ovis presents a very low risk for users, the environment and the consumers of food from vaccinated animals. Appropriate warnings have been included in the SPC.

Conclusion on benefit risk balance

The information provided in the dossier and in response to the specific obligations and other points raised by the CVMP was adequate to confirm an overall positive benefit risk balance.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the overall benefit risk balance was favourable. The specific obligations have been fulfilled as far as possible at this moment considering the epidemiological situation in EU. Moreover, the MAH will undertake a number of recommendations included in the list of recommendations. As a result the CVMP can recommend a conversion of the marketing authorisation to normal status.

4. Overall conclusions of the evaluation and recommendations

The CVMP reviewed the annual assessment 2012 submitted by the MAH for evidence of compliance with the specific obligations and for re-assessment of the benefit risk balance of this veterinary medicinal product.

The CVMP considers that this annual re-assessment, accompanied by the submitted documentation demonstrated that the benefit-risk profile remains favourable for the product. The specific obligations have been fulfilled as far as possible at this moment considering in particular the epidemiological situation in EU.

Moreover the MAH will undertake a number of recommendations including:

1. the need to finalise the saponin quantification test,
2. the need to submit a variation if larger batch sizes than 250 l are used
3. the need to provide results of BPT in transgenic mice from the remaining 9 first production batches of the product
4. the need to continue the development of the *in vitro* batch potency test.

The CVMP recommends to re-set the periodic safety update report cycle for ZULVAC 1 Bovis according to the standard rules, following the conversion of the marketing authorisation to a normal one.

4.1. Changes to the community marketing authorisation

No changes are required in the following annexes of the Community marketing authorisation:

5. List of Recommendations

1. *In vitro* potency test: the progress in the development of the test was noted. The MAH will continue/finalise the on-going work.

2. Provision of data on 3 batches between 250-1000 l: The justifications provided by the MAH for not providing the requested data were noted. Due to the current epidemiological situation of BTV, the proposal to limit the batch size of ZULVAC 1 Bovis vaccine to 250l (for which data was provided during the authorisation process under exceptional circumstances) and submit a variation if larger batch sizes are required was acceptable.

3. Results of batch potency test (BPT) in transgenic mice: in order to further validate the BPT in transgenic mice results from 10 batches were requested during the initial authorisation of the product. The fact that there is limited production of the vaccine batches in order to carry out the requested BPT in transgenic mice and the acceptance of results from 9 batches of the bivalent vaccine ZULVAC 1+8 Ovis were noted. The MAH will provide the results of BPT in transgenic mice for the remaining first 8 production batches of vaccine, once available.

4. Saponin quantification test: The attempts (and the difficulties encountered) made by the MAH in order to comply with the request to develop a quantification of the saponin adjuvant in the finished product were noted. In the CVMP's opinion, the delay in providing the requested test does not constitute a barrier for the marketing authorisation provided under exceptional circumstances to ZULVAC 1 Bovis vaccine to convert to a normal marketing authorisation status. The MAH will continue and finalise the ongoing work.