EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

CVMP assessment report for ZULVAC 1 Bovis (EMEA/V/C/002334/S/0002)

Inactivated Bluetongue virus, serotype 1, strain BTV-1

EU/2/11/130/001-003

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

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Authorised presentations

EU Number	Invented Name	Strength	Pharmaceutical Form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
EU/2/11/130/001	ZULVAC 1 Bovis	Inactivated Bluetongue Virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1	Suspension for injection	Cattle	Intramuscular use	Hydrolytic glass vials type I (EP) with butyl stopper (EP) and aluminium seal	20ml (10 doses)	1 vial	Zero days
EU/2/11/130/002	ZULVAC 1 Bovis	Inactivated Bluetongue Virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1	Suspension for injection	Cattle	Intramuscular use	Hydrolytic glass vials type II (EP) with butyl stopper (EP) and aluminium seal	100ml (50 doses)	1 vial	Zero days
EU/2/11/130/003	ZULVAC 1 Bovis	Inactivated Bluetongue Virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1	Suspension for injection	Cattle	Intramuscular use	Hydrolytic glass vials type II (EP) with butyl stopper (EP) and aluminium seal	240ml (120 doses)	1 vial	Zero days

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

Product information on the annual re-assessment

Invented name:	**ZULVAC 1 Bovis**
Active substances:	Inactivated Bluetongue virus, serotype 1, strain BTV-1/ALG2006/01 E1
Pharmaceutical form:	Suspension for injection
Strength:	RP ≥ 1
Route of administration:	Intramuscular use
Target species:	Cattle
Therapeutic indication:	Active immunisation of cattle from 2½ months of age for the prevention* of viraemia caused by Bluetongue Virus (BTV), serotype 1.
Marketing authorisation holder (name and address):	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom
Applicant contact point:	Dr Catrina Stirling Tel.: +44 1304 616161
Rapporteur:	Ellen-Margrethe Vestergaard

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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, submitted to the European Medicines Agency (the Agency) on 30 July 2012 an application for the first annual re-assessment of ZULVAC 1 Bovis 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 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 Bovis Centralised Procedure Annual Assessment 2012 which included all responses to the three specific obligations above.
- One document called ZULVAC 1 Bovis 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 revised benefit-risk assessment was submitted on 6 September 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 normal status were described in the CVMP assessment report of the initial application for the granting of a community marketing authorisation for ZULVAC 1 Bovis and are the following:

Part 2:

a) The development of a validated saponin test,

b) The submission of the results of the batch potency test in transgenic mice carried out on (at least) the first ten batches,

c) The submission of data on 3 batches between 250-1000 l when available,

d) The submission of batch results for the first three manufacturing scale batches of the 10 dose and 120 dose presentations post approval,

e) The submission of the first three manufacturing scale batches (10 doses presentation and 120 doses presentation) into the long-term stability program after approval.

Part 3:

a) The submission of the complete study report, including the results and the analysis of the milk production and reproductive performance of the cows after vaccination at the end of the study.

b) The submission of results from the double dose field study in dairy cattle and the final production results from the overdose study,

c) The complete study report in dairy cows under field conditions at the end of the study.

Part 2:

a) Saponin test

The applicant 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 applicant is currently investigating a method for saponin 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. The MAH will continue the work and finalise the test on the saponin quantification as soon as possible (Recommendation n.1).

b) Results of the batch potency test (BPT) in transgenic mice carried out on (at least) the first ten batches of ZULVAC 1 Bovis vaccine following authorisation

To date, apart from the stability serials (300 l), only 2 batches of the ZULVAC 1 Bovis final product were manufactured (March 2012) and they were tested according to the approved dossier:

Table 1: Results of BPT in transgenic mice of ZULVAC 1 Bovis vaccine

Batch-final Bulk (n. of doses)	RP (Relative Potency)
E16531 (10 doses)	2.8
E16532 (50 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 plus the additional 2 batches above. Moreover the MAH has provided data from 9 batches from a similar vaccine that contained BTV serotype 1 (ZULVAC 1+8 Bovis) and which were found acceptable during the annual re-assessment of that product in 2011.

Conclusion:

The required results were requested in order to further validate the 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 even and the request remains as a recommendation. The MAH will undertake it. (Recommendation n.3 for the marketing authorisation provided under exceptional circumstances to ZULVAC 1 Bovis vaccine to convert to a standard marketing authorisation status).

c) 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 applicant therefore proposed to limit batch size to 250 l and submit a variation if lager batch sizes is required.

Conclusion:

The justifications provided 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 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 considered as acceptable.

(Recommendation n.2 for the marketing authorisation provided under exceptional circumstances to ZULVAC 1 Bovis vaccine to convert to a standard marketing authorisation status).

d) Batch results for the first three manufacturing scale batches of the 10 dose and 120 dose presentations

The results for the pilot scale batches (300 l) of the 10 dose and 120 dose presentations included in the stability study were submitted in the original dossier.

To date, only two more batches of ZULVAC 1 Bovis vaccine were manufactured (March 2012) and tested according to the approved dossier. The results for 10 and 50 dose presentations were provided. So far the MAH provided data on 3 pilot scale (300 l) of consistency/stability serials and 1 full scale batch. The batches themselves are identical whether filled in 10 or 120 dose presentations therefore in terms of product consistency at release they represent equivalent data. Potential differences in stability were addressed in the stability study presented below satisfactorily.

Conclusion:

The applicant'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 authorisations.

e) On-going stability study; pending tests results to be provided when available

Final product stability

The stability study of ZULVAC 1 Bovis 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 GMP's and tested for stability in Pfizer Olot, S.L.U.

The results obtained indicated that when stored in the conditions specified in the SPC, the product keeps its characteristics in terms of appearance, pH, thiomersal and aluminum content for at least 15 months in the 6 batches tested. 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 Bovis stability batches was not investigated beyond 15 months. Therefore, the claimed shelf-life for the final product ZULVAC 1 Bovis is 1 year.

The final stability report was provided.

Antigen stability

The final Report for the inactivated BTV-1 antigen stability study was provided. 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 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 F37659 was used to blend ZULVAC 1 Ovis vaccine at a concentration of $10^{6.5}$ $TCID_{50}$/dose in order to produce the batch FT090157.

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 and potency at least until 15 months after being manufactured when stored in the conditions indicated in the SPC. These results support a shelf life of 12 months for the Bluetongue virus serotype 1 inactivated antigen when stored at 2 - 8 ºC and protected from light.

The results obtained support a shelf life of 12 months for the BTV-1 inactivated antigen when stored at 2 - 8 °C and protected from light for a final product of a shelf life of 12 months.

Although indicated in the submitted protocol, the stability of the vaccine ZULVAC 1 Ovis batch FT090157 was not investigated beyond 15 months as the applicant only generated data in order to demonstrate a 12 months shelf-life of the final product.

Conclusion: Final product: The results obtained for the finished product 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 the 6 batches tested. Overall the data support a 12 month shelf-life for both the antigen and finished product.

The MAH provided manufacturer's batch protocols of the 6 vaccine batches used in the stability report and they were acceptable.

Vaccine antigen: 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.

Safety was tested at T0 and this was considered satisfactory. Furthermore, the MAH provided manufacturer's batch protocols of vaccine batch FT090157 which was acceptable.

Part 3:

The safety of ZULVAC 1 Bovis was assessed in Part 3 of the initial dossier taking into account the guidance on combined vaccines (CVMP/IWP/52/97) and using data of a bivalent vaccine containing BTV-1 and BTV-8 in order to demonstrate safety of the monovalent BTV-1. Both vaccines contain the same amount of BTV-1 antigen ($10^{6.7}$ $TCID_{50}$/2 ml), adjuvant, and excipients. Therefore data were directly relevant.

The safety of administration of an overdose (although no longer required under Annex I to Directive 2001/82/EC as amended) and repeated administration of one dose was documented under laboratory conditions in calves of the minimum recommended age for vaccination (from 2.5 - 3 months).

The safety of the product under field conditions was not fully documented in Part 3 of the initial dossier as according to relevant legislation regarding authorising of vaccines under exceptional circumstances field studies are not necessary. The applicant addressed all points under Part 3 (a, b, c) of the 1st specific obligation by providing the final report regarding a double dose field study in dairy cows using ZULVAC 1+8. The study is summarised below.

Safety of the vaccine ZULVAC 1+8 Bovis, in dairy cows under field conditions.

The objective of this study was to evaluate the safety of the administration of an overdose (4 ml) of ZULVAC 1+8 Bovis to dairy cows under field conditions (European Pharmacopoeia (Ph. Eur.) section 5.2.6 - Evaluation of Safety of Veterinary Vaccines and Immunosera).

The general adverse reactions or side effects, rectal temperatures, local reactions, milk production and reproduction parameters were compared with the data obtained from the cows inoculated with Phosphate Buffer Saline (PBS) only (control animals). The vaccine teste was a bivalent product containing Bluetongue virus 1 and 8 antigens, (batch:FT010083) with a concentration of Bluetongue virus (BTV), serotype 1, of $1x10^{6.7}$TCID50/2 ml dose, and serotype 8 of $1x10^{7.3}$TCID50/2 ml dose before inactivation, adjuvanted with aluminum hydroxide gel at 3% and saponin1%. A total of 182 Friesian dairy cows different physiological phase (not pregnant, lactating and at different stage of gestation) were included in the study. 93 cows received 4 ml of the vaccine (overdose), and 89 control cows were inoculated at the same time with 4 ml of placebo (PBS). Different safety parameters were evaluated after the vaccine administration such as adverse reactions or side effects, rectal temperatures, local reactions, milk production and reproduction parameters (returns to oestrus, confirmed gestations, abortions and dystocias).

The main results of the safety trial were as follows:

- General adverse reactions or side effects were not observed.
- A transitory rectal temperature increase for up to 2.1 ºC was recorded. This maximum increase occurred in one cow at 1 day after the injection and then rectal temperatures returned to normal values.
- Slight local reactions (nodules of diameter < 2 cm) appeared at the injection site in 37.5% (9 out of 24) vaccinated animals. Moderate reactions (nodules of diameter up to 5 cm) were observed in 4.2% (1 out of 24) of the animals. Local reactions totally disappeared 57 days after vaccination.
- Effects on dairy cows milk production were not observed.
- Effects on the reproduction parameters, regardless the physiological phase of the cows and parity were not observed.

Conclusion:

The results of the trial demonstrated that an overdose of the vaccine appears safe in the field in previously vaccinated cows. Differences in reproductive performance parameters between the two groups were not easily detectable due to the low total number of analysed animals and the extent of the expected variation in the reproductive responses measured. However no negative effect was demonstrated in pregnant and lactating cows due to vaccination. A number of questions on this study remain to be addressed by the applicant before a final conclusion can be made (they are listed in section 5 of this report) and before the final SPC wording on safety can be agreed. The detailed assessment of the final report on this study is enclosed in Annex I. On the basis of the above findings the SPC should be updated in order to reflect the frequency of local reactions observed.

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 will 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. The final results from

the ongoing stability study on the final product and on the vaccine antigen were submitted and supported satisfactorily for both a shelf life of 12 months.

Batch potency test results in transgenic mice from only two final product batches 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 now kept as a recommendation for the applicant following a conversion of the marketing authorisation. 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.

Part 3 (a, b and c):

A final study report from a filed study was submitted in order to fulfill the Part 3 section of the 1st specific obligation. This was acceptable; additionally the applicant provided satisfactory responses to all questions that were raised from this study.

2nd specific obligation:

An updated benefit-risk assessment was provided by the MAH. 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 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.

Part 2: Quality

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 documented in Part 2. 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, remaining batch and BPT results from full scale production batches, are considered as having no additional impact on the risk assessment 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 Bovis has been demonstrated in calves of 2.5 - 3 months of age after and single, repeat and overdose. This trial, was performed on a single farm in Spain and involved the vaccination with a double dose of ZULVAC 1+8 Bovis in 182 mostly seropositive dairy cows. Vaccination against serotype 1 and 8 has been mandatory in Spain from year 2008 to 2011. The safety of an overdose of the vaccine from this field trial in previously vaccinated cows was considered acceptable.

Following the submission of the final report from the field study and receipt of the satisfactory responses to additional questions by the CVMP, an update of section 4.10 of the SPC was recommended to reflect the findings on local reactions after overdose.

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. As result of the safety study provided to address local reactions observed at the overdosing and changes to section 4.10 of the SPC were recommended to reflect the findings concerning local reactions in an overdose study.

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 Bovis vaccine were sold in the EU/EEA countries (the product is not sold in any third country). Most of sales of Zulvac 1 Bovis 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. The MAH was requested to provide alternative information. The MAH provided a thorough PSUR from the use of this vaccine under national emergency licenses in Belgium, France and Spain during a one year period (2010). Around 11.750.000 doses/animals were treated and the overall conclusion regarding safety was in agreement with the information specified in the SPC. These pharmacovigilance data from the national emergency vaccine licenses supported the safety also for the centrally approved product,

Pharmacovigilance data for the 2012 period from the sales of the centrally authorised product was subsequently submitted with data lock point on the 31 Aug 2012. The assessment of the report is scheduled on the CVMP agenda for discussion in January 2013. The MAH confirmed that reports of adverse events will continue to be monitored and investigated as necessary, and steps will be taken to revise the SPC as data so indicate.

Conclusion on 3nd specific obligation

No pharmacovigilance data from the use of the vaccine in cattle were presented in the first PSUR period, as the vaccine has not been sold / used anywhere under its central authorisation until 2012.

Available national post marketing data on use of the vaccine in the field were provided and supported the safety of the vaccine.

Additional Information

In the CVMP assessment report of the initial authorisation provided under exceptional circumstances in 2011 it was stated that taking into account the substantial variability observed for the reference vaccine, the scope of the *in vivo* test (prevention of mortality) and the 3R principle into consideration, the applicant was strongly encouraged to develop an *in vitro* batch potency test within an appropriate timeframe (i.e. 2 years).

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 acid (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 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 applicant is still working on the development of a quantitative RT-PCR for the quantification on the inactivated antigen.

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 Bovis vaccine to convert to a standard marketing authorisation status. Nevertheless the MAH will continue/finalise the on-going work (Recommendation n.5 for the marketing authorisation provided under exceptional circumstances to ZULVAC 1 Bovis vaccine to convert to a standard marketing authorisation status).

2.2 Summary and Conclusions

In accordance with Article 39 of Commission Regulation (EC) No. 726/2004, Pfizer Limited, submitted to the European Medicines Agency on 30 July 2012 an application for the annual re-assessment of ZULVAC 1 Bovis vaccine. This is the first re-assessment since the authorisation under exceptional circumstances was granted to the vaccine and the MAH has requested CVMP to consider the conversion of the 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, full stability data have been provided which support a 12 month shelf-life for both the antigen and finished product (minor details are expected to be clarified which should not have a major impact on the suitability of the information provided). The applicant also provided information regarding progress of the development of the saponin quantification test and *in vitro* potency test. Results from the BPT in transgenic mice carried out in two Zulvac 1 Bovis final product batches were presented. Moreover, batch results from one full scale batch (10 and 50 dose presentations) of the vaccine was presented.

The final study report on field safety in dairy cattle was provided. A number of clarifications were satisfactorily provided by the MAH and an appropriate warning for the SPC (section 4.10) was recommended.

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

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 all 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 can be recommended.

3. Benefit-risk assessment

Introduction

ZULVAC 1 Bovis is a conventionally produced, liquid and ready-to-use, binary ethylenimine (BEI) inactivated, and aluminium hydroxide /saponin adjuvanted vaccine against bluetongue virus (BTV) serotype 1 infection. 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 Benefits

The benefit of the product is prophylactic immunisation to protect cattle from 2.5 months of age against infection with BTV serotype 1. The vaccine has been proven to prevent viraemia. Prevention of viraemia directly benefits the animal in that this ensures reduction of 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 Bovis 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 cows 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.

   No adverse reactions were observed after the first injection of a single dose of vaccine to calves.

After the second injection of a single dose, a slight and transient but significant increase in the mean rectal temperature of 0.4 ºC was recorded in the vaccinated calves during the first 24 hours. On day 2 after vaccination, rectal temperatures had returned to normal values

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

For the consumer

Zulvac 1 Bovis 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 Bovis 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 Bovis 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 Bovis 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 re-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 considered that this application, 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 considering the epidemiological situation in EU.

Moreover the MAH will undertake the following recommendations:

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 8 first production batches of the product
4. the need to provide stability results from the first three manufacturing scale batches
5. the need to continue the development of the *in vitro* batch potency test.

The CVMP considers that there are no remaining grounds to maintain the marketing authorisation of ZULVAC 1 Bovis under exceptional circumstances.

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

Changes are required in the Community marketing authorisation as a consequence of the CVMP proposal to convert the current marketing authorisation to a normal status. The SPC should also be updated in accordance with the latest information provided by the MAH on safety of an overdose (section 4.10 Overdose).

5. List of Recommendations

Part 2:

1. 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 on-going work.
2. Provision of data on 3 batches between 250-1000: 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 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 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. The MAH will submit stability batch results from the first three manufacturing scale batches (10 doses presentation and 120 doses presentation) if out of specification results are observed during the stability studies.
5. *In vitro* potency test: the progress in the development of the test was noted. The MAH will continue/finalize the on-going work.