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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for ZULVAC 1+8 Bovis (EMEA/V/C/002473/S/0003)

International non-proprietary name: Vaccine to prevent viraemia caused by Bluetongue Virus, serotypes 1 and 8

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

Annex A

EU Number	Invented name	Strength	Pharma-ceutical form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
EU/2/12/139/001	ZULVAC 1+8 Bovis	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	Cattle	Intramuscular use	High density polyethylene (HDPE) vial with chlorobutyl elastomer rubber stopper and aluminum seal	20 ml (10 doses)	1 vial	Zero days
EU/2/12/139/002	ZULVAC 1+8 Bovis	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	Cattle	Intramuscular use	High density polyethylene (HDPE) vial with chlorobutyl elastomer rubber stopper and aluminum seal	100 ml (50 doses)	1 vial	Zero days
EU/2/12/139/003	ZULVAC 1+8 Bovis	Inactivated Bluetongue Virus, serotype 1, strain BTV-1/ALG2006/01 E1 RP* ≥ 1 Inactivated	Suspension for injection	Cattle	Intramuscular use	High density polyethylene (HDPE) vial with chlorobutyl elastomer rubber stopper and	240 ml (120 doses)	1 vial	Zero days

EU Number	Invented name	Strength	Pharma-ceutical form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
		Bluetongue Virus, serotype 8, strain BTV-8/BEL2006/02 RP* ≥ 1				aluminum seal			

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

Product information on the annual reassessment

Invented name:	ZULVAC 1+8 Bovis
Active substances:	BTV-1, strain BTV-1/ALG2006/01 E1 / Inactivated bluetongue virus, serotype 8, strain BTV-8/BEL2006/02
Pharmaceutical form:	Suspension for injection
Strength:	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 *Relative Potency by a mice potency test compared to a reference vaccine that was shown efficacious in cattle
Route of administration:	Intramuscular use
Target species:	Cattle
Therapeutic indication:	Active immunisation of cattle from 3 months of age for the prevention* of viraemia caused by bluetongue virus (BTV), serotypes 1 and 8. *(Cycling value (Ct) ≥ 36 by a validated RT-PCR method, indicating no presence of viral genome).
Marketing authorisation holder (name and address):	Zoetis Belgium SA Rue Laid Burnait, 1 1348 Louvain-la-Neuve BELGIUM
Applicant contact point:	Dr Frederic Descamps
Rapporteur:	Dr Ellen-Margrethe Vestergaard Phone: +45 44 889264 Email: emv@dkma.dk

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1. Background information

1.1. Submission of the application

The marketing authorisation holder (MAH), Zoetis Belgium SA submitted in accordance with Article 39(7) of Commission Regulation (EC) No. 726/2004 to the European Medicines Agency (the Agency) on 6 March 2013 an application for the first annual re-assessment for ZULVAC 1+8 Bovis and requested that the marketing authorisation (MA) of the vaccine currently under exceptional circumstances converts to a normal status 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 first annual re-assessment of the MA for this product ZULVAC 1+8 Bovis (i.e re-assessment of the benefit-risk balance). A marketing authorisation under exceptional circumstances was granted on 8 March 2012 by the European Commission for this veterinary medicinal product.

The CVMP adopted an opinion and CVMP assessment report on 12 September 2013.

On 18 November 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 marketing authorisation holder 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 revert 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 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 revert to normal status.
3. The applicant is required to submit 6-monthly Periodic Safety Update Reports (PSURs) starting once the marketing auhorisation 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.
4. The marketing authorisation holder is required to demonstrate safety in the field including pregnant and lactating cows, using the correct formulation of the vaccine in the present application. The results from this safety study will be assessed at the first annual re-assessment.

The points that required resolution in order for the authorisation to convert to normal status (see

above specific obligation 1) were listed in the CVMP assessment report of the original application for granting a community MA for ZULVAC 1+8 Bovis and were the following seven recommendations:

1. The applicant will provide the T15 data as soon as available. The data is expected in January 2013. The applicant will also blend two more 10 dose presentation and two more 50 dose presentation batches and will include them into the real-time stability study.
2. The applicant will test one stability batch of each presentation (10 dose and 50 dose) for preservative efficacy at end of shelf-life (T15 months). The data will be presented when completed.
3. The applicant will develop a test for Saponin quantification A timeline for the implementation of the test could not be given, but updates will be provided annually until completed.
4. The applicant will provide batch results for two batches of BTV-8 antigen produced in bioreactors at the current maximum batch size when available post authorisation.
5. The applicant will provide batch results for three consecutive batches of BTV-1 and BTV-8 antigen produced in 1000 l bioreactors when available post authorisation to demonstrate the validity of this bioreactor size.
6. The applicant will blend 2 more 10 dose presentation and 2 more 50 dose presentation batches and will provide the data of these serials as soon as available or at first annual re-assessment whichever is first.
7. The applicant will include two pilot-scale batches each of the 10 and 50 dose presentations in the stability study. After approval the applicant will place the first three manufacturing scale batches into long-term stability programme.

1.1.2. Documentation submitted

The MAH submitted the following documentation:

- Administrative data including revised product information (Parts 4.6 and 4.7).
- ZULVAC 1 + 8 Bovis annual assessment 2013 including responses to specific obligations 1-4 relates references and responses to recommendations 1–7 including an updated benefit-risk assessment.

1.2. Steps taken for the assessment of this annual reassessment

- The application for the first annual re-assessment was submitted on 8 July 2013.
- The procedure started on 16 July 2013.
- An opinion was adopted on 12 September 2013.

2. Scientific discussion

2.1. Assessment

Specific Obligations

1st Specific obligation

An action plan was not submitted 6 months following the authorisation of the vaccine as the MAH needed additional time to compile all data required for this first reassessment with a view for the authorisation to revert to normal status. This was considered acceptable by the CVMP. A total of seven Part 2 (Quality) recommendations under the first obligation were required to be fulfilled by the MAH in order for the authorisation given under exceptional circumstances to ZULVAC 1+8 Bovis to convert to a normal status. They are listed in section 1.1 of this report. A summary of the assessment of the new data to address these points is presented below:

1. **The applicant will provide the T15 data as soon as available. The data is expected in January 2013. The applicant will also blend two more 10 dose presentation and two more 50 dose presentation batches and to include them into the real-time stability study.**

The MAH detailed the stability program and provided T15 data from 10 and for 50 doses presentations (2 different batches) respectively. Safety was also tested at T17. The CVMP concluded that overall the point of concern was satisfactorily addressed. However as the pH results exceeded the limit of the specification for pH, an evaluation of the pH specification limit is considered appropriate.

2. **The applicant will test one stability batch of each presentation (10 dose and 50 dose) for preservative efficacy at end of shelf-life (T15 months). The data will be presented when completed.**

The efficacy of antimicrobial preservative in ZULVAC vaccines filled in HDPE plastic bottles during all their shelf life was already demonstrated. However this vaccine differs from the rest of the Zulvac vaccines against the Bluetongue virus in the concentrations of antigens present.

While the same preservative and concentration are used as well as same filling components and volumes filled, the saponin concentration in ZULVAC 1+8 Bovis has been increased from 0.2 to 0.5 mg /ml.

The APE was tested in just one additional batch of ZULVAC 1+8 Bovis (10 dose vial, 25 ml HDPE bottle irradiated) at the end of its shelf life (T15 months) and not in two additional batches as initially indicated. The result was satisfactory and it showed that a higher saponin concentration did not affect the efficacy of the antimicrobial preservative. Although the point was not resolved as originally requested in two batches the MAH demonstrated in one type of bottle that a higher saponin concentration has no influence on the efficacy of the APE.

The information provided was considered sufficient as there is no indication that an increase of the saponin concentration will affect the antimicrobial preservative effect. Thus the CVMP concluded that the point of concern was satisfactorily addressed. The specific obligation is fulfilled for this point.

3. **The applicant will develop a test for saponin quantification. A timeline for the implementation of the test could not be given, but updates will be provided annually until completed.**

A new approach for the saponin quantification in ZULVAC BTV vaccines is under investigation. The MAH confirmed that apart from the study of the typical validation parameters for an analytical method, markers for saponin quantification in the finished product will be identified and release criteria will be established. The CVMP acknowledged that the extraction of component attached to alhydrogel has significant challenges in order to determine the contents of these components. The MAH will continue the development of a quantitative method for determination of saponin in the finish product – a concept which have been accepted for ZULVAC 1 Ovis and ZULVAC 1 Bovis vaccines by the CVMP. The higher concentration of saponin was not considered a disadvantage for the development of a method.

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 MAH is recommended to continue and finalise the test on the saponin quantification as indicated in the list of recommendations below.

4. **The applicant will provide batch results for two batches of BTV-8 antigen produced in bioreactors at the current maximum batch size when available post authorisation.**

Due to the current demand of BTV vaccines to date no BTV-8 antigen batches were produced in bioreactors. The MAH will provide the data on 2 additional batches made in bioreactors when available.

The CVMP concluded that the above were acceptable and the point of concern was satisfactorily addressed.

5. **The applicant will provide batch results for three consecutive batches of BTV-1 and BTV-8 antigen produced in 1000 lt bioreactors when available post authorisation to demonstrate the validity of this bioreactor size.**

The MAH confirmed that due to the current demand of BTV vaccines, to date no antigen batches higher than the current maximum batch size have been manufactured.

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

6. **The applicant will blend 2 more 10 dose presentation and 2 more 50 dose presentation batches and will provide the data of these serials as soon as available or at first annual reassessment whichever is first.**

Data on three 50 dose presentation serials and three 10 dose presentation serials were provided and were considered satisfactory. Therefore the CVMP concluded that the above were acceptable and the point of concern was satisfactorily addressed. The specific obligation is fulfilled for this point.

7. **The applicant will include two pilot-scale batches each of the 10 and 50 dose presentations in the stability study. After approval the applicant will place the first three manufacturing scale batches into long-term stability programme.**

The VICH GL17 guideline states “stability information should be provided on at least three batches of the finished product representative of that which will be used at manufacturing scale. Where possible, batches of finished product included in stability testing should be derived from different batches of bulk material.” Eudralex Vol 4 (GMP) gives that “unless otherwise justified, at least one

batch per year of product manufactured in every strength and every primary packaging type, if relevant should be included in the stability programme (unless none are produced during that year)".

The CVMP concluded that the batches introduced into the stability programme were in agreement with the guidelines and thus the point of concern is satisfactorily addressed. The specific obligation is fulfilled for this point.

Overall the information provided regarding the 1st specific obligation addressed all related recommendations satisfactorily. However the analytical test for the determination of saponin remains to be finalized. It should also be noted that the MAH should consider changing the pH specification by variation application in order to avoid future out of specification (OOS), as indicated in the list of recommendations below. It is also expected that batch results from BTV-8 antigens produced in bioreactors will be provide when available. None of the above three recommendations should preclude the conversion of the marketing authorisation to normal status as they do not affect the safety and efficacy of the product. Therefore, the 1st specific obligation can be considered as fulfilled.

2nd Specific obligation

To address this specific obligation the MAH provided an updated risk assessment including a summary of the product and claims. The only changes from the original MA are the new proposed safety wordings in Sections 4.6 and 4.7 of the summary of product characteristics (SPC). These safety statements (modifications highlighted in bold italics) are considered appropriate and fully supported by the data provided from a new study on pregnant and lactating animals using the correct vaccine formulation.

4.6 Adverse reactions (frequency and seriousness)

A transient increase in rectal temperature, not exceeding **2.7 °C**, may occur during the 48 hours following vaccination***. Local reactions of < 2 cm are common while reactions of up to 5 cm may occasionally occur after administration, these resolve within a maximum of 25 days. Local reactions may increase slightly following the second dose in this case lasting up to 15 days and usually <2 cm, reactions between 2-5 cm are occasional(ly) observed and in rare cases reactions >5 cm may occur.***

4.7 Use during pregnancy, lactation and lay

Can be used during pregnancy and lactation.

Regarding 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 EU. 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 the Union. However, although BTV-8 does not appear to circulate in the Union any longer, risks persist for reintroduction of BTV-8 and/or other serotypes from the Middle East, Asia and Africa to the Union. As a result, the availability of this category of vaccines is important to ensure a rapid response should any re-introductions occur. In order to support the continued use of ZULVAC 1+8 Bovis, a table was also provided showing that 29,980 and 16,300 doses were sold in France and Spain respectively in 2012. In 2013 a total of 7930 doses were sold in France. It is to be noted, that this vaccine was sold under national emergency type licenses prior to the centralised authorisation.

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

Part 2: Quality

ZULVAC 1+8 Bovis is an inactivated vaccine containing strains BTV serotypes 1 and 8. 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. Follow-up measures have been fulfilled to fully demonstrate the stability of the antigen and vaccine. Potency of the vaccine for release was established against a reference vaccine shown to be efficacious in cattle 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.

The saponin quantification test method development remains to be finalised. Similarly to the decision taken by CVMP for ZULVAC 1 Ovis, ZULVAC 1 Bovis, and ZULVAC 1+8 Ovis 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 to ZULVAC 1+8 Bovis to be converted to a normal status.

The pH was exceeded by 0.1 units during stability testing. Summarizing all pH data values submitted, no pH value were measured below 7.0. Although this was seen in a limited number of data, it is likely that the pH of the ZULVAC 1+8 Bovis will increase during further stability time points. The MAH should consider to justify the optimisation of the pH specification (by a variation) to prevent future stability testing to be out of specification.

Part 3: Safety

The safety of the product is fully documented in the safety dossier. The safety of ZULVAC 1+8 Bovis was demonstrated in 3 months old calves after single, repeat dose and overdose injections. In addition a new safety study in pregnant cattle has now been completed using the correct formulation of Zulvac 1+8 Bovis (saponin content 1ml/dose for ZULVAC 1+8 Bovis versus 0.4ml/dose for ZULVAC 1 Bovis and ZULVAC 8 Bovis). Results showed no negative effects on reproductive parameters (return to oestrus, confirmed gestations, abortions) nor on milk production regardless the physiological phase and parity of the cows at the time of vaccination. Adverse reactions regarding the local injection site swelling and the increase in rectal temperatures have correctly been reflected in the updated SPC at Section 4.6. The vaccine did not induce general adverse reactions. Evidence was also provided concerning the safe use of the vaccine which has now been administered to approx. 54,000 animals in 2012 and 2013. Moreover, there is no need to revise the SPC on the basis of already submitted pharmacovigilance data 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 demonstrated that the use of ZULVAC 1+8 Bovis prevents viraemia in cattle vaccinated twice from 3 months of age. No evidence was observed through pharmacovigilance concerning any lack of efficacy of the vaccine and therefore its benefits remain unaltered.

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

The CVMP concluded that the MAH's conclusions were sustainable overall. Although a limited number of doses of ZULVAC 1+8 Bovis has been sold in the Union in 2012 and 2013, 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 MAH 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 Bovis. The specific obligation is fulfilled.

3rd Specific obligation

The MAH provided no updated PSUR, but the PSURs which had already been submitted so far (3 in total) supported the safe and efficacious use of the product in the field. No update of the SPC and product literature was deemed necessary as a result of safety concerns from these 3 reports.

The CVMP concluded that although no new pharmacovigilance data concerning the use of ZULVAC 1+8 Bovis in cattle were provided in this first annual re-assessment of the vaccine, the 3rd specific obligation can be considered as fulfilled as the safe and efficacious use of ZULVAC 1+8 Bovis vaccine in the field has been appropriately demonstrated and the updating of the safety statements in the product's information due to a new study was considered adequate.

Moreover the available information so far can be considered suitable in order to allow for the MA provided under exceptional circumstances to be converted to normal status. The specific obligation is fulfilled.

4th Specific obligation

To address this specific obligation on safety in pregnant animals the MAH provided a completed study which supported the safe use of the vaccine in pregnant and lactating cattle. As a result of these new data, changes in Section 4.6 and 4.7 of the SPC were proposed.

A total of 120 Friesian dairy cows at different physiological phase (not pregnant and lactating and at different stages of gestation) were included in the safety study. Sixty cows were vaccinated and revaccinated 3 weeks apart with 2 ml of the vaccine and 60 control cows (15 from each treatment group) were administered 2 ml of placebo. The results of the study demonstrated that administration of this vaccine according to the SPC was safe when used under field conditions. Although statistically significant higher rectal temperatures were observed in vaccinated cows 24 hours after both first and second administration only one single animal at each time point showed a temperature increase above 2 ^{o}C. This maximal rise in rectal temperature is correctly reflected in the updated SPC, Section 4.6. Slight to moderate local reactions at the injection site were recorded, and these frequencies have correctly been reflected in the SPC. The vaccine did not induce general adverse reactions and did not have any effect in milk production and reproductive performance regardless the physiological phase and the parity of cows at the time of vaccination.

The CVMP concluded that this point of concern was satisfactorily addressed and the proposed updating of the safety statements in sections 4.6 and 4.7 adequately reflected the new information derived from this study. As a result of the above this specific obligation is considered as fulfilled.

2.2. Summary and Conclusions

In accordance with Article 39 Commission regulation (EC) No. 726/2004, the MAH, Zoetis, submitted to the European Medicines Agency on 8 July 2013 an application for the first annual re-assessment of the marketing authorisation for ZULVAC 1+8 Bovis, proposing also the conversion of the given authorisation to a normal marketing authorisation status. During the current procedure, the four specific obligations remaining from the original authorisation under exceptional circumstances were addressed by the MAH.

The seven subpoints of specific obligation No. 1 were successfully addressed by the MAH and are summarised below.

The Committee considered the data describing stability results from two batches (10 and 50 doses)

satisfactory. However for both batches pH measurements were shown to be out of specification by 0.1 pH unit. Although this deviation is very limited the Committee considered that the MAH should evaluate the pH specification limit and show the true value that the pH starts to affect safety or potency. Nevertheless this should not preclude the conversion of the marketing authorisation to normal status.

The Committee considered data on the efficacy of the antimicrobial preservative for one dose (10 dose) at the end of its shelf life (T15 months). The antimicrobial preservative efficacy was shown and the point was considered resolved.

The Committee also considered the MAH's intention to limit batch size to the current maximum batch size, due to the current demand of BTV vaccines that resulted in no antigen batches higher than the current maximum batch size to be manufactured. The MAH would however need to submit a variation if larger batch sizes will be required in the future. The Committee considered the approach acceptable and thus two related recommendations were considered resolved.

The MAH provided information regarding the progress of the saponin quantification test which remains to be finalised. In line with the approach already accepted for other bluetongue vaccines from the same MAH, finalisation of this test is not considered as an obstacle to the conversion of the MA provided under exceptional to ZULVAC 1+8 Bovis to a normal status.

Batch protocols for two additional 10 doses and two additional 50 doses were provided and the committee considered this point as resolved.

The MAH introduced new batches into the stability program, as required. The batches were produced on manufacturing scale. The point was therefore resolved.

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-8 does not appear to circulate in the EU any longer, however risks persist on reintroduction of BTV-8 and/or other serotypes from the Middle East, Asia and Africa to the EU. As a result, the availability of this category of vaccines is considered important to ensure a rapid response should any re-introductions occur. No new pharmacovigilance data were presented in the current annual re-assessment, but the information gathered so far and the risk assessment of the use of the vaccine support the safe use of the product in the field. The SPC was updated regarding adverse reactions on temperature increase and local injection site reactions in order to reflect a new safety field study provided by the MAH in this first annual re-assessment in order to address specific obligation 4. The results of the study were considered satisfactory. On the basis of the above the Committee considered that specific obligations No. 2, No. 3 and No. 4 were fulfilled respectively.

Considering the pharmacovigilance data submitted for this vaccine, so far it is recommended that the submission of future PSURs should follow the standard timetable, following conversion of the MA.

On the basis of the above the CVMP concluded that all specific obligations have been fulfilled and there are no remaining grounds to maintain the marketing authorisation of ZULVAC 1+8 Bovis under exceptional circumstances. The MAH is expected to finalise the work on the saponin quantification test method development.

3. Benefit-risk assessment

3.1. Benefit assessment

Direct Benefits

The benefit of the product is prophylactic immunisation to protect cattle against infection with BTV serotypes 1 and 8. The vaccine has been proven to prevent viremia. Prevention of viremia directly benefits the animal in that this ensures no clinical signs or loss of condition.

Pharmacovigilance data did 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 vaccinated 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 virus, therefore as Zulvac 1+8 Bovis prevents viremia it is also able to prevent disease transmission and spread. The use of vaccines such as Zulvac 1+8 Bovis is important at a community animal health level as they are 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.

3.2. Risk assessment

Main potential risks:

For the target animal

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 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.

Safety studies which demonstrated that the product is safe in both minimum age animals and also in pregnant animals were provided. There are limited local reactions after vaccination, and these are appropriately indicated on the SPC. These local reactions have no effect on the general systemic health of the animals and are in line or less than those observed with other vaccines for cattle. Pharmacovigilance data following field use do not indicate an increased risk.

3. Lack of efficacy.

The onset of immunity has been fully documented using challenge studies. The duration of immunity has been established with the combined product (ZULVAC 1+8), a 12 month duration was demonstrated.

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 Bovis 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 Bovis 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 Bovis is an inactivated product.

3.3. Risk management or mitigation measures

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

The CVMP considers it necessary to restart the periodic safety update report cycle for ZULVAC 1+8 Bovis according to the standard rules, following the conversion of the marketing authorisation to a normal status.

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 Bovis was adequate to confirm that the benefit-risk balance for the product remains positive.

The product was shown to be efficacious with the prevention of viremia indication in cattle, an onset of immunity of 21 days and duration of immunity was demonstrated for the bivalent product for 12 months.

The formulation and manufacture of the product is clearly described and specifications have been set to ensure consistent quality. The pH measurements have shown to be out of specification by 0.1 pH unit. Although this is a very small deviation, the MAH should consider changing the pH specification by a variation application in order to avoid future OOS. 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 MAH is expected to finalise the work on the saponin quantification test method development. The MAH will also provide data on 2 additional batches of BTV-8 antigen made in bioreactors when available. Sufficient data have now been provided to validate the potency test.

ZULVAC 1+8 Bovis was well tolerated in general by the species. The product presented a low risk for users and the environment and appropriate warnings were included in the SPC. No withdrawal period was necessary. The new field data from pregnant animals supported the safe use of the product in line with the SPC statements. No safety concerns were raised in the pharmacovigilance data provided so far. No increased risk has been observed in the field and therefore all points above remain fully valid.

4. Overall conclusions of the evaluation and recommendations

The CVMP reviewed the documentation 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 resolved.

The CVMP considers it necessary to restart the periodic safety update report cycle for ZULVAC 1+8 Bovis 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.

List of Recommendations

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. The delay in providing the requested test does not constitute a barrier for the marketing authorisation provided under exceptional circumstances to ZULVAC 1+8 Bovis to convert to a normal marketing authorisation status. The MAH is expected to continue and finalise the on-going work.

2. The pH specification:

The pH measurements during stability studies were shown to be out of specification (OOS) by 0.1 pH unit. The MAH should consider changing the pH specification by variation application in order to avoid future OOS.

3. Additional batches made in bioreactors

The MAH should provide the data on 2 additional batches of BTV-8 antigen made in bioreactors when available.