11 April 2013
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for the annual re-assessment of ZULVAC 8 Bovis (EMEA/V/C/000145/S/0009)

International non-proprietary name: inactivated bluetongue virus, serotype 8

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/2/09/105/001	ZULVAC 8 Bovis	RP ≥ 1*	Suspension for injection	Cattle	Intramuscular	Type I hydrolytic glass vial with butyl stopper and aluminium seal	20 ml (10 doses)	1 vial	Zero days
EU/2/09/105/002	ZULVAC 8 Bovis	RP ≥ 1*	Suspension for injection	Cattle	Intramuscular	Type II hydrolytic glass vial with butyl stopper and aluminium seal	100 ml (50 doses)	1 vial	Zero days

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

Product information on the annual re-assessment

Invented name:	**ZULVAC 8 Bovis**
Active substances:	Inactivated bluetongue virus, serotype 8
Pharmaceutical form:	Suspension for injection
Strength:	RP ≥1*
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, serotype 8.
Marketing authorisation holder (name and address):	Zoetis Belgium SA (as of 16 May 2013) Rue Laid Burnait, 1 1348 Louvain-la-Neuve BELGIUM
Applicant contact point:	Dr Frederic Descamps
Rapporteur:	Maria Tollis

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1. Background information

1.1. Submission of the application

The Marketing Authorisation Holder (MAH), Pfizer Limited submitted on 28 January 2013 an application for the annual re-assessment for ZULVAC 8 Bovis to the European Medicines Agency (the Agency) and requested that the marketing authorization (MA) of the vaccine currently under exceptional circumstances converts to a normal MA in case all the specific obligations are considered as fulfilled.

This is the third annual re-assesment of the marketing authorisation for this product (i.e re-assessment of the benefit-risk balance) and the CVMP opinion on the previous one was adopted on 12 July 2012. A MA under exceptional circumstances was granted on 15 January 2010 by the European Commission for this veterinary medicinal product.

The CVMP adopted an opinion and CVMP assessment report on 11 April 2013.

On 13 September 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 of the marketing authorisation:

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 MAH 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.

Following the second annual re-assessment the following specific points of concern remained, in relation to the above specific obligation 1:

1. Data are still awaited in order to comply with the request to the MAH to provide a test for saponin quantification.
2. The results obtained support a shelf life of 12 months for the bluetongue virus serotype 8 inactivated antigen when stored at 2-8 °C and protected from light. Overall, based on the MAH's statement, it is understood that the MAH does not intend to claim a longer stability of vaccine batches when formulating using an inactivated BTV-8 antigen having a 12 months stability. The MAH is requested to confirm such an interpretation.

3. The MAH is requested to provide further data on the so called “matrixing concept” also likely applied in order to demonstrate the stability of the finished product (ZULVAC 8 Bovis and ZULVAC 8 Ovis).

4. Overall, the results of the study demonstrate that the administration of an overdose (4 ml) of ZULVAC 1+8 Bovis vaccine is safe with respect to the induction of local reactions and the potential increase of rectal temperature in pregnant/lactating cows. Concerning the outcome on reproductive performance and on the potential impact on milk production, a discrepancy is noted as the (satisfactory) results have been reported following the use of ZULVAC 1 Bovis monovalent vaccine in a study. Therefore, the extrapolation of the results obtained from this study to ZULVAC 8 Bovis (and to ZULVAC 1+8 Bovis) is questioned. The MAH is requested to address this point and provide justification for a potential extrapolation of the results obtained using ZULVAC 1 Bovis vaccine to ZULVAC 8 Bovis vaccine.

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

1.1.2. Documentation submitted

The MA submitted the following documentation:

- ZULVAC 8 Bovis Annual Report 2013

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

- The dossier was submitted on 28 January 2013.
- The procedure started on 12 February 2013.
- The CVMP adopted an opinion on 11 April 2013.

2. Scientific discussion

2.1. Assessment

Specific Obligations

1st specific obligation

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.

Four outstanding issues that required resolution in order for the authorisation given under exceptional circumstances to ZULVAC 8 Bovis to convert to a normal status were listed in the CVMP assessment report of the second annual re-assessment application for the granting of a Community MA for ZULVAC 8 Bovis. Three issues were related to Part 2 and one issue to Part 3 of the dossier as follows.

Part 2

1. Data are still awaited in order to comply with the request to the marketing authorisation holder to provide a test for saponin quantification.

The MAH informed of the ongoing work 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. As a first step, a method for the saponin extraction based on protein precipitation by an organic solvent and clean-up/concentration by solid phase extraction has been tested. Preliminary results are shown in an interim report included in the 2012 annual re-assessment. Satisfactory saponin chromatogram profiles have been obtained. However, the recovery percentage in experimental samples (77-79%) has still to be improved and the suitability of the extraction and clean-up method is under investigation using ZULVAC vaccines samples. Preliminary results in finished product have not been satisfactory but the non-satisfactory results may be attributable to technical issues during the experimental phase.

Although promising results have been obtained, further investigation of the extraction and clean-up method is on-going. Once the suitability of the method (sample pre-treatment is demonstrated), in a second step, the new method will be fully developed and validated. Apart from the study of the typical validation parameters for an analytical method such as reproducibility and repeatability, saponin peaks suitable to be used as markers for saponin quantification in the finished product will be identified and release criteria will be established. Depending on the outcome of this saponin method investigation and the existence of irreversible interactions in the finished product that could still interfere in the saponin determination, the release criteria will be quantitative or qualitative. However, the MAH also reiterated that as the product has an *in vivo* potency test and Annex I to Directive 2001/82/EC states that an adjuvant assay is required only in the context of there being available tests this should not be a barrier to grant a full marketing authorisation.

The CVMP noted the attempts (and the difficulties encountered) by the MAH in order to comply with the request to develop a quantification of the saponin adjuvant in the finished product. Considering that the delay in providing the requested test has recently been considered not to constitute a barrier for the marketing authorisation granted under exceptional circumstances to be converted to a normal status.

The CVMP concluded that the point for concern was sufficiently clarified and resolved to provide fulfilment of the specific obligation on this aspect.

However, the MAH would be recommended to continue and finalise the on-going work as indicated in the List of Recommendations below.

2. The results obtained support for a shelf life of 12 months for the bluetongue virus serotype 8 inactivated antigen when stored at 2–8 °C and protected from light. Overall, based on the MAH's statement, it is understood that the MAH does not intend to claim a longer stability of vaccine batches when formulating using an inactivated BTV-8 antigen having a 12 months stability. The MAH is requested to confirm such an interpretation.

The MAH has confirmed that it is not intended to claim a longer stability of vaccine batches when formulating by using an inactivated BTV-8 antigen that has a 12 months stability.

The CVMP concluded that the point for concern was clarified and resolved.

3. The MAH is requested to provide further data on the so called “matrixing concept”, also likely applied in order to demonstrate the stability of the finished product.

For the stability testing the bracketing approach was used. The use of this approach is based on the Note for Guidance On bracketing and matrixing designs for stability testing of drug substances and Drug Products” (CPMP/ICH/4104/00):

- Bracketing is the design of a stability schedule such that only the extremes of certain design factors are tested at all-time points: different strengths and/or different container size and/or fill.
- Matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point and at a subsequent time point, another subset of samples for all factor combinations is tested.

As both ZULVAC 8 Ovis and ZULVAC 8 Bovis vaccines have exactly the same composition with the exception of antigen content, in order to demonstrate the stability of both products a bracketing/matrixing approach was proposed in the approved stability protocol. The testing of 3 batches of each product and 2 batches for each presentation was considered as an acceptable approach. Therefore, the following batches were tested for stability:

- ZULVAC 8 Bovis: 1 batch of 50 doses + 2 batches of 10 doses;
- ZULVAC 8 Ovis: 1 batch of 50 doses + 2 batches of 120 doses.

The results obtained with the 3 batches of each product tested support a shelf life for the final product of at least 12 months when stored at 2°C – 8 °C and protected from light, as all the tested parameters were satisfactory after a minimum storage period of 15 months.

The CVMP concluded that the approach followed by the MAH is acceptable, thus the stability results obtained by the bracketing and matrixing methods can be validated.

The CVMP concluded that the point for concern was clarified and resolved.

Part 3

4. Overall, the results of the safety study demonstrated that the administration of an overdose (4 ml) of ZULVAC 1+8 Bovis vaccine is safe with respect to the induction of local reactions and the potential increase of rectal temperature in pregnant/lactating cows. Concerning the outcome on reproductive performance and on the potential impact on milk production, a discrepancy is noted as the (satisfactory) results have been reported following the use of ZULVAC 1 Bovis monovalent vaccine in a relevant study. Therefore, the extrapolation of the results obtained from this study to ZULVAC 8 Bovis (and to ZULVAC 1+8 Bovis) was questioned. The MAH was requested to address this point and provide justification for a potential extrapolation of the results obtained using ZULVAC 1 Bovis vaccine to ZULVAC 8 Bovis vaccine. The MAH clarified that the field trial was conducted with ZULVAC 1+8 Bovis vaccine as indicated in the final report and therefore all the results are fully extrapolated to ZULVAC 8 Bovis. An addendum to the final report changing the headline of the annex was provided as annex 2 included in the documentation provided with the current re-assessment.

The CVMP concluded that the point for concern was clarified and is resolved.

Conclusion on 1st specific obligation

All of the four remaining points for concern pending from the second annual re-assessment in relation to the 1st specific obligation have been clarified and resolved. Concerning the test for the quantification of saponin work is continuing in order to set the test. This ongoing method development would not prevent the conversion of the MA to a normal status. This approach has been considered acceptable for

similar products of the same manufacturing line in order for the MA provided under exceptional circumstance to revert to normal status, therefore the same principle should also apply for ZULVAC 8 Bovis vaccine.

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

2nd specific obligation

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.

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 bluetongue virus (BTV) serotypes in the 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. Vaccination against BTV is still performed in some Member States. 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 EU. As a result, the availability of this category of vaccines is important to ensure a rapid response should any re-introductions occur again and this was considered by the MAH of crucial importance especially for products for which conversion to full MA is feasible. In order to support the continued use of ZULVAC 8 Bovis vaccine, a table was also provided showing that 68,400, 35,660 and 1,300 doses of ZULVAC 8 Bovis vaccine were sold in France, Germany and The Netherlands, respectively, in 2012.

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

Part 2: Quality

ZULVAC 8 Bovis is an inactivated vaccine containing inactivated strain of BTV serotype 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 lambs and given a relative potency of 1. For a vaccine batch to be released as potent, it must demonstrate a relative potency with respect to the reference batch of ≥ 1.

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

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

Part 3: Safety

The safety of the product is fully documented in Part 3 of the dossier and the following summary of the safety warnings is provided. The safety of ZULVAC 8 Bovis has been demonstrated in calves of 6 weeks of age (1.5 months) after a single, repeat dose and overdose. In addition a safety study using the “old” formulation of ZULVAC 1+8 Bovis (the same saponin content as ZULVAC 8 Bovis and 1 Bovis) in pregnant cattle has been completed and showed no negative effects, therefore fully justifying the use during pregnancy. In addition as considered for ZULVAC 1 Bovis, the vaccine has been tested in

seropositive and lactating cattle. The information concerning injection site reactions should be revised based on the data from the field trial as suggested below.

The following SPC safety statements are considered appropriate:

4.4 Special warnings

If used in other domestic and wild ruminant species that are considered at risk of infection, its use in these species should be undertaken with care and it is advisable to test the vaccine on a small number of animals prior to mass vaccination. The level of efficacy for other species may differ from that observed in cattle.

No information is available on the use of the vaccine in animals with maternally derived antibodies however the vaccine has been shown safe and efficacious in seropositive cattle.

4.7 Use during pregnancy, lactation or lay

The vaccine can be used during pregnancy.

The safety and the efficacy of the vaccine have not been established in breeding males. In this category of animals the vaccine should be used only according to the benefit/risk assessment by the responsible veterinarian and/or national competent authorities on the current vaccination policies against bluetongue virus.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

After administration of a double dose, a slight and transient but significant increase in the mean rectal temperature of 0.7 ^{o}C was recorded in the vaccinated calves during the first 24 hours. On day 2 after vaccination, rectal temperatures had returned to normal values. Local reactions of >2cm are common after 2 fold overdose while reactions of up to 5 cm may occasionally occur after overdose administration, these resolve within a maximum of 57 days.

Part 4: Efficacy

The efficacy of the product has been presented in laboratory challenge studies which demonstrated that ZULVAC 8 Bovis prevents viraemia in calves vaccinated twice from 12 weeks of age as demonstrated by a fully validated RT-PCR. The SPC recommendations are considered fully supported and appropriate. No new information on the efficacy of the vaccine was presented in this third annual re-assessment. No emerging risks deriving from any suspected lack of efficacy were identified.

Conclusion on 2nd specific obligation

The 2nd specific obligation has been satisfactorily addressed and overall considered as fulfilled, thus supporting the conversion of the MA provided under exceptional circumstances to ZULVAC 8 Bovis vaccine to a normal status, providing the above modifications are introduced to the SPC.

The MAH will finalise the work on the saponin quantification test method development.

3rd specific obligation:

Concerning the 3rd specific obligation, no updated PSUR was provided.

PSURs which have been submitted so far, as required, have however widely supported the safe and efficacious use of the product in the field.

Conclusion on 3rd specific obligation

Although no new pharmacovigilance data concerning the use of the concerned vaccine in cattle has been provided in this third annual re-assessment of the vaccine, the 3rd specific obligation can be considered as fulfilled as the safe and efficacious use of ZULVAC 8 Bovis vaccine in the field has been widely demonstrated and provided PSURs support the safe use of the product. The information available so far can be considered suitable in order to allow the MA provided under exceptional circumstances to be converted to a normal status. No further updates of the SPC are considered necessary as no safety concerns were raised during the periods covered by the PSURs provided so far.

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 28 January 2013 an application for the annual re-assessment of the marketing authorisation for ZULVAC 8 Bovis.

This is the third annual re-assessment since the authorisation under exceptional circumstances was granted to the vaccine. Associated to the current annual re-assessment application, the conversion of the given authorisation to a normal marketing authorisation status is sought to be taken into account by the MAH. During the current procedure, the four specific obligations remaining from the second annual re-assessment were addressed by the MAH.

In particular the MAH provided information regarding the progress of the saponin quantification test which remain the only issue to be finalised. In line with the approach already accepted for other vaccines, the finalisation of this test is not considered as an obstacle to the conversion of the MA provided under exceptional circumstances to ZULVAC 8 Bovis vaccine to a normal status. The remaining points for concern related to Parts 2 and 3 of the dossier were satisfactorily addressed and resolved.

Although it is accepted that BTV-8 does not appear to circulate in the EU any longer, 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 again. Although no pharmacovigilance data were presented in the current annual re-assessment, 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 and do not indicate any need to update the SPC on safety grounds.

On the basis of the above, the specific obligations have been fulfilled and there are no remaining grounds to maintain the marketing authorisation of ZULVAC 8 Bovis vaccine under exceptional circumstances. The MAH will finalise the work on the saponin quantification test method development.

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

3. Benefit-risk assessment

ZULVAC 8 Bovis is an inactivated vaccine against bluetongue serotype 8. The product has been authorised in 2010 under exceptional circumstances due to the epidemiological situation at the time. This is the third annual re-assessment of the conditions of the marketing authorisation of this product.

3.1. Benefit assessment

Direct Benefits

The benefit of the product is prophylactic immunisation to protect cattle against infection with bluetongue virus (BTV) serotypes 8, the vaccine has been proven to prevent viraemia. Prevention of viraemia directly benefit the animal in that this ensure no clinical signs or loss of condition.

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 8 Bovis prevents viraemia it is also able to prevent disease transmission and spread. The use of vaccines such as ZULVAC 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

The main risks associated with ZULVAC 8 Bovis vaccine can be summarised as follows.

Risk to the target animal

The risk to the target animal can come from three sources;

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. Data on the production process and validation are provided in Part 2B. All starting materials are either tested for treated to ensure there are no contaminants or that the treatment process ensure any potential risk is alleviated full details on starting materials are provided in Part 2.C. Both the master seed virus for the bluetongue serotype 8 virus and the production cell line (BHK-21) have been fully tested to EU requirements. In addition a full TSE risk assessment is provided in Part 2.C.4
2. Adverse reactions in the target animal in response to vaccination. This risk is mitigated by the provision of safety studies which demonstrate that the product is safe in both minimum age animals and also in pregnant animals. 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.
3. Risk of lack of efficacy. The onset of immunity has been fully documented using challenge studies presented in Part 4.B.2. The duration of immunity has been proven for 12 months

Risk to the user

A full user risk assessment has been provided in Part 3.B.7 which concludes that the active ingredient and excipients do not present a risk to the user.

Risk to the environment

A full environmental risk assessment has been provided in Part 3.D, which concludes that ZULVAC 8 Bovis vaccine contains no ingredients which are considered harmful to the environment.

Risk to the consumer

Any risk to the consumer with respect to vaccines give to food producing species relate to any residual live organism or vaccines residues in meat, as ZULVAC 8 Bovis is inactivated there are no risks of residual live virus. With respect to residues from vaccination this is addressed in detail in Part 3.B.8 and it has been demonstrated that any there are no residues left in meat which would present a risk to the consumer. Additional risk associated with vaccines are reversion to virulence and spread of vaccine strain, ZULVAC 8 Bovis is an inactivated vaccine therefore there is no risk associated with this product.

3.3. Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall and is considered compliant with full MA requirements.

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

The formulation and manufacture of ZULVAC 8 Bovis is clearly described and specifications have been set to ensure consistent quality. All starting materials are fully EU compliant and documented.

ZULVAC 8 Bovis is well tolerated by the target species and presents a low risk for users and the environment and appropriate warnings have now been included on the SPC. A zero withdrawal period is justified. The field data from pregnant animals together with the pharmacovigilance data support the above analysis and shows no additional risks.

Full stability data to support a 12 month shelf-life for both the antigen and finished product have been provided. Data have been provided regarding attempts to quantify the saponin adjuvant and while this has not been possible this should not be a barrier to a full registration as the product has an *in vivo* potency and Annex I to Directive 2001/82/EC only requires that the adjuvant be quantified in so far as the test methods are available. The MAH is expected to finalise the work on the saponin quantification test method development. Sufficient data have now been provided to validate the potency test. Data on safety in pregnant cattle have been provided and all outstanding points with regards to this data have now been addressed.

No safety concerns were raised during the periods covered by the PSURs provided so far. Although no new additional pharmacovigilance data were provided in this third annual re-assessment, 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.

No change to the impact on the environment is envisaged.

The data supplied to address the outstanding points sufficiently clarify and resolve the remaining concerns related to the specific obligations. Therefore, all specific obligations have been fulfilled.

The benefit-risk balance remains unchanged. Some changes to the SPC will be required.

Conclusion

Based on the original and complementary data presented, the overall benefit-risk balance is favourable. Moreover since all the specific obligations have been fulfilled, there are no remaining grounds to maintain the marketing authorisation of ZULVAC 8 Bovis vaccine under exceptional circumstances.

The CVMP recommends re-starting the Periodic Safety Update Report cycle for ZULVAC 8 Bovis vaccine following the conversion of the MA under exceptional circumstances to a normal one.

Some changes to the SPC are required.

4. Overall conclusions of the evaluation and recommendations

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

The CVMP considered that this third application for 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.

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

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

The CVMP recommends to restart the periodic safety update report cycle for ZULVAC 8 Bovis vaccine following the conversion of the MA under exceptional circumstances to a normal one.

4.1 Changes to the community marketing authorisation

Changes are required in the annexes of the Community marketing authorisation.

5. 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 8 Bovis vaccine to convert to a normal marketing authorisation status. The MAH will continue and finalise the on-going work.