11 April 2013
EMA/276752/2013
Committee for Medicinal Products for Veterinary Use

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CVMP assessment report for the annual re-assessment of ZULVAC 8 Ovis (EMEA/V/C/000147/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/2/09/104/001	ZULVAC 8 Ovis	RP ≥ 1*	Suspension for injection	Sheep	Subcutaneous	Type II hydrolytic glass vial with butyl stopper and aluminium seal.	100ml (50 doses)	1 vial	Zero days
EU/2/09/104/002	ZULVAC 8 Ovis	RP ≥ 1*	Suspension for injection	Sheep	Subcutaneous	Type II hydrolytic glass vial with butyl stopper 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 sheep.

Product information on the annual re-assessment

Invented name:	**ZULVAC 8 Ovis**
Active substances:	Inactivated bluetongue virus, serotype 8, strain btv-8/bel2006/02
Pharmaceutical form:	Suspension for injection
Strength:	RP >1*
Route of administration:	Subcutaneous use
Target species:	Sheep
Therapeutic indication:	Active immunisation of sheep from 1.5 months of age for the prevention of viraemia caused by bluetongue virus, sereotype 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 Ovis 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-assessment 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:

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 Safety Update 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 marketing authorisation holder 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 Ovis and ZULVAC 8 Bovis).

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 standard status.

1.1.2. Documentation submitted

The MAH submitted the following documentation:

- ZULVAC 8 Ovis 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.

Three outstanding issues that required resolution in order for the authorization given under exceptional circumstances to ZULVAC 8 Ovis 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 Ovis. They were all related to Part 2 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 ongoing. Once the suitability of the method (sample pre-treatment is demonstrated) is confirmed, 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 ongoing work as indicated in the List of Recommendations below.

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.

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 having 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.

Conclusion on 1st specific obligation

All of the three remaining points for concern of Part 2 still 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 Ovis 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 Union. 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 EU Countries. 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 rapid response should any re-introductions occurred 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 214,350 doses of ZULVAC 8 Ovis vaccine were (only) sold in France in 2012.

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

Part 2: Quality

ZULVAC 8 Ovis 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. The stability of the antigen and vaccine were demonstrated. 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 final 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 Ovis vaccine, to be converted to a normal status.

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

Part 3: Safety

The safety of ZULVAC 8 Ovis vaccine has been demonstrated in lambs of 6 weeks of age (1.5 months) after a single, repeat and overdose injection of the vaccine. In addition safety has also been fully demonstrated in pregnant ewes. ZULVAC 8 Ovis vaccine has been demonstrated to be well tolerated by the target species and presents a low risk for users and the environment and, as a consequence, the safety statements in the relevant sections of the SPC are considered appropriate. The safety of the product is further supported by the fact that since the product has been used in the field, and therefore, administered to a large number of animals, pharmacovigilance data did neither indicate any need for revision of the SPC warnings (then the safety of the vaccines remains unchanged), nor give evidence for any unrecognized risks (no additional data on the safety of the vaccine was presented in this third annual re-assessment, therefore no new risks were identified).

Part 4: Efficacy

The efficacy of the product has been presented in laboratory challenge studies which demonstrate that ZULVAC 8 Ovis prevents viraemia in sheep vaccinated twice from 1.5 months 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 Ovis vaccine to a normal status.

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. In the PSURs provided during the full year period from 1 February 2011 to the end of January 2012, neither abortions nor effects on milk production were reported. The observed adverse reactions and their frequency are in line with the indications on the SPC and therefore no changes are required.

Conclusion on 3rd specific obligation

Although no pharmacovigilance data concerning the use of the concerned vaccine in sheep 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 Ovis vaccine in the field has been widely demonstrated. 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 Ovis.

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 three specific obligations still pending 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 of the same line, the finalisation of this test is not considered as an obstacle to the conversion of the MA provided under exceptional circumstances to ZULVAC 8 Ovis vaccine to a normal status. The remaining points for concern related to Part 2 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 Ovis 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 Ovis is an inactivated vaccine against bluetongue virus 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 sheep against infection with Bluetongue Virus serotype 8 (BTV8). The vaccine has been proven to prevent viraemia. Prevention of viraemia directly benefits the animal in that this ensures no clinical signs or loss of condition. Pharmacovigilance data do not indicate a lack of efficacy in the field and therefore the benefits remain the same.

Additional benefits

In addition to the direct benefit to the 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 Ovis vaccine prevents viraemia it is also able to prevent disease transmission and spread. The use of vaccines such as ZULVAC 8 Ovis 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 Ovis 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 have been provided in Part 2B. All starting materials are either tested or treated in order to ensure there are no contaminants or that the treatment process ensures that 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 vaccine (MSV BTV8) and the production cell line (BHK-21) have been fully tested according to EU requirements. In addition a full TSE risk assessment has been 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 as set out in the introduction. These local reactions have no effects on the general systemic health of the animals and are in line or less

than those observed with other vaccines for sheep. Pharmacovigilance data so far, do not indicate an increased risk derived from the licensed product.

3. Risk of lack of efficacy.

The onset of immunity has been fully documented using challenge studies and these have been presented in Part 4.B.2. The duration of immunity has been proven for 12 months. Pharmacovigilance data do not indicate an increased risk following one year's use of the vaccine in the field.

Risk to the user

A full user risk assessment provided in Part 3.B.7 has concluded 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, ZULVAC 8 Ovis vaccine does not contain any ingredients which are considered harmful to the environment.

Risk to 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 8 Ovis is an inactivated vaccine, there are no risks of residual live virus. With respect to residues from vaccination, this point for concern has been addressed in details 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 risks associated with vaccines are reversion to virulence and spread of vaccine strain. ZULVAC 8 Ovis is an inactivated product, therefore, in this respect, there is no risk associated with its use.

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 sheep with an onset of immunity of 21 days and duration of immunity demonstrated for 12 months.

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

The product is well tolerated by the target species and presents a low risk for users and the environment and appropriate warnings have been included on the SPC. A zero withdrawal period is justified. Following use of the product for 3 years in the field no increased risk has been observed therefore all points above remain fully valid.

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 been provided to validate the potency test.

No safety concerns were raised during the periods covered by the PSURs provided so far. Although no additional pharmacovigilance data has been 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.

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 Ovis vaccine under exceptional circumstances.

The CVMP recommends restarting the Periodic Safety Update Report cycle for ZULVAC 8 Ovis vaccine following the conversion of the MA under exceptional circumstances to a normal.

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 Ovis 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 Ovis 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 Ovis vaccine to convert to a normal marketing authorisation status. The MAH will continue and finalise the ongoing work.