15 January 2014
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for the annual re-assessment of Bovilis BTV8 (EMEA/V/C/000148/S/0005)

International non-proprietary name: 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 (MA) number	Invented name	Strength	Pharmaceutical form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
EU/2/10/106/001	Bovilis BTV8	500 Antigenic Units*	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber stopper and aluminium cap	10ml	1 vial	Zero days
EU/2/10/106/002	Bovilis BTV8	500 Antigenic Units*	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials with rubber stopper and aluminium cap	20 ml	1 vial	Zero days
EU/2/10/106/003	Bovilis BTV8	500 Antigenic Units*	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials with rubber stopper and aluminium cap	50ml	1 vial	Zero days
EU/2/10/106/004	Bovilis BTV8	500 Antigenic Units*	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials with rubber stopper and aluminium cap	100ml	1 vial	Zero days
EU/2/10/106/005	Bovilis BTV8	500 Antigenic Units*	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terepphthalate (PET) vials, with rubber stopper and aluminium cap	200ml	1 vial	Zero days
EU/2/10/106/006	Bovilis BTV8	500 Antigenic Units*	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber stopper and aluminium cap	250ml	1 vial	Zero days
EU/2/10/106/007	Bovilis BTV8	500 Antigenic Units*	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber stopper and aluminium cap	500ml	1 vial	Zero days
EU/2/10/106/008	Bovilis BTV8	500 Antigenic Units*	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber stopper and aluminium cap	10ml	10 vials	Zero days
EU/2/10/106/009	Bovilis BTV8	500 Antigenic Units *	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber stopper and aluminium cap	20 ml	10 vials	Zero days
EU/2/10/106/010	Bovilis BTV8	500 Antigenic Units *	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber	50ml	10 vials	Zero days

EU (MA) number	Invented name	Strength	Pharmaceutical form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
						stopper and aluminium cap			
EU/2/10/106/011	Bovilis BTV8	500 Antigenic Units *	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber stopper and aluminium cap	100ml	10 vials	Zero days
EU/2/10/106/012	Bovilis BTV8	500 Antigenic Units *	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber stopper and aluminium cap	200ml	10 vials	Zero days
EU/2/10/106/013	Bovilis BTV8	500 Antigenic Units *	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber stopper and aluminium cap	250ml	10 vials	Zero days
EU/2/10/106/014	Bovilis BTV8	500 Antigenic Units*	Suspension for injection	Cattle, sheep	Subcutaneous injection	Polyethylene terephthalate (PET) vials, with rubber stopper and aluminium cap	500ml	10 vials	Zero days

* inducing a virus neutralising antibody response in chickens of ≥ 5.0 $\log_2$

Product information on the annual re-assessment

Invented name:	**Bovilis BTV8**
Active substances:	Bluetongue virus serotype 8
Pharmaceutical form:	Suspension for injection
Strength:	500 Antigenic Units* *inducing a virus neutralising antibody response in chickens of ≥ 5.0 $\log_2$
Route of administration:	Subcutaneous use
Target species:	Cattle, sheep
Therapeutic indication:	To stimulate active immunity against bluetongue virus serotype 8 to reduce viraemia in cattle and prevent viraemia in sheep
Marketing authorisation holder (name and address):	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The NETHERLANDS
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1. Background information on the annual re-assessment

1.1. Submission of the application

On 30 August 2013, the marketing authorisation holder (MAH), Intervet International BV (the applicant), submitted in accordance with Article 39 of Regulation (EC) No 726/2004 an application for the third annual re-assessment of Bovilis BTV8 to the European Medicines Agency (the Agency) 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.

This is the third annual re-assessment for Bovilis BTV8 (i.e. re-assessment of the benefit-risk balance). The CVMP opinion on the previous re-assessment (second one) was adopted on 8 November 2012. A marketing authorisation under exceptional circumstances was granted on 6 September 2010 by the European Commission for this veterinary medicinal product.

On 15 January 2014, the CVMP adopted an opinion and CVMP assessment report.

On 14 March 2014, the European Commission adopted a Commission Decision for this application.

1.1.1. Scope of the annual reassessment

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

1. The applicant is required to submit data as requested in post-authorisation commitments and 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 reassessment.

2. For the first and subsequent annual reassessments the applicant 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 (PSUR) starting once the MA 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 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) The applicant is requested to provide evidence for the consistency of the proposed batch potency test, by submitting, once available, the results obtained from the proposed batch potency test carried out on a significant (according to the number of vaccine batches actually produced in order to respond to the request from the market) number of commercially produced vaccine batches. A recommendation should also be agreed by the applicant to provide the results obtained also from any rejected batches of the vaccine, accompanied by plausible justifications for such negative results.

2) The progress on the development of the antigen quantification test at the formulation step (and on the finished product) is noted. The final data is awaited.

3) Concerning the applicant's proposed development and introduction of a post-inactivation antigen quantification step, the applicant should commit to provide the corresponding relevant results after a consistent number of commercial batches have been produced at both manufacturing sites following the introduction of the proposed post-inactivation antigen capture enzyme-linked immunosorbent assay (ELISA). A time line should also be presented.

4) At present stage, under exceptional circumstances, a provisional 12 month shelf life can be agreed. The applicant should provide the full stability data package once available.

1.1.2. Documentation submitted

The applicant submitted the document entitled: Bovilis BTV8 Annual Re-assessment 2013 where the following points in response to specific obligations 1, 2 and 3 were addressed:

- Specific obligation 1: Responses to the issues remaining in the CVMP assessment report for the 2nd annual reassessment of Bovilis BTV8 (EMA/CVMP/671778/2012, please, refer to the four recommendations above) and appendixes 1, 2, and 3.
- Specific obligation 2: benefit-risk assessment.
- Specific obligation 3: PSURs from 1 April 2012 to 30 September 2012 and from 1 October 2012 to 3 March 2013 (appendix 4).

1.2 Steps taken for the assessment of this annual reassessment

- The application for the Bovilis BTV8 annual re-assessment was submitted on 30 August 2013.
- The procedure started on 10 September 2013.
- A list of questions was adopted on 7 November 2013.
- An opinion was adopted on 15 January 2014 by the CVMP.

2. Scientific discussion

2.1. Assessment

Specific obligations

1st specific obligation

During the second annual re-assessment a number of concerns remained for a further annual re-assessment regarding specific obligation 1; they are listed in section 1.1.1 of this report. In this third annual re-assessment these points were revisited by the applicant and the assessment of the new information is presented below:

Part 2 (Quality):

1. Evidence for the consistency of the proposed batch potency test should be provided, by submitting, once available, the results obtained from the proposed batch potency test carried out on a significant (according to the number of vaccine batches actually produced in order to respond to the request from the market) number of commercially produced vaccine batches.

Results obtained also from any rejected batches of the vaccine, accompanied by plausible justifications for such negative results should also be provided.

In the context of the second annual re-assessment, the CVMP acknowledged the efforts of the applicant to fulfil this recommendation, as well as the difficulties encountered and which will be still encountered in the future due to the epidemiological situation of bluetongue virus (BTV) outbreaks. However, the CVMP recommended to retain this recommendation for the third annual re-assessment in order to obtain further data and thus confidence on the batch potency test.

For the third annual reassessment the applicant therefore provided an overview of potency results obtained so far. The applicant argued that the control of BTV8 disease under field conditions, further supported the suitability of the current batch potency test to guarantee that only efficacious product is released for the market.

By means of the overview of the requested data, the consistency of the production process and the product's potency test has been demonstrated.

On the basis of the provided data the CVMP concluded that the consistency of the production process and the suitability of the batch potency test were satisfactory and overall the point for concern was satisfactory addressed.

2. The progress on the development of the antigen quantification test at the formulation step (and on the finished product) is noted. The final data is awaited.

In the context of the second annual re-assessment, the CVMP concluded that the *in vitro* approach for the validity of the antigen quantification on the finished product that was presented by the applicant (relating to an antigenic mass ELISA), could be potentially effective, but no evidence was provided in order to support it. The difficulties encountered or which will be encountered in the future due to the epidemiological situation of BTV outbreaks) were acknowledged. Therefore, the CVMP recommended to retain the request on this recommendations for the third annual re-assessment given the importance of the antigen quantification and in view of the fact that it was done for other centralised bluetongue serotype 8 vaccines.

The antigen quantification at the formulation stage was addressed in the 3rd recommendation.

Concerning the development of the antigen quantification test in the finished product, the applicant argued that taking into account the suitability of the current batch potency test and the current absence of any demand from the market for the vaccine there is no need to change over to an alternative *in vitro* test. In addition, validation of such a test would require additional animal experiments for which there is currently no justification.

The CVMP concluded that as there is a valid *in vivo* potency test approved, the absence of an *in vitro* method (as alternative to the currently performed *in vivo* potency test) in the finished product should not preclude the potential for the MA given under exceptional circumstances, to convert to a standard MA. The specific point for concern relating to the development of the antigen quantification test in the finished product was considered as solved.

3. Development and introduction of a post-inactivation antigen quantification step. The applicant should commit to provide the corresponding relevant results after a consistent number of commercial batches have been produced at both manufacturing sites following the introduction of the proposed post-inactivation antigen capture ELISA. A time line should also be presented.

In the context of the second annual re-assessment an ELISA test was proposed; the CVMP concluded that there was no evidence for the validity of the test but noted the difficulty to proceed with a validation test. However the CVMP recommended to retain the request on this recommendation for the

third annual re-assessment and allow the applicant to complete the validation should the produced vaccines allow it.

In order to address this point for concern in the third annual reassessment the applicant provided a number of documents. A standard operating procedure (SOP) on an antigenic mass ELISA for inactivated BTV serotype 8 was submitted. This SOP describes a post-inactivation antigenic mass ELISA developed and used to quantify the amount of inactivated BTV serotype 8 in aqueous suspension.

The applicant also submitted data on the "comparison of the potency of Bovilis BTV8 vaccines" where the potency of batches was compared by using the test method described in the SOP to determine the antigenic mass content of BTV8 antigen before or after inactivation. In this study, the equivalence of the potency of batches of Bovilis BTV8 vaccine was demonstrated. The batches were formulated after the antigenic mass content of two BTV8 commercial antigen batches was determined using the pre- and post-inactivation antigenic mass ELISA (standard dose of 500 AU/ml). The immunogenicity of the batches of vaccine was investigated by using the *in vivo* test in chickens. The serological response was determined by a virus neutralization test and statistically analysed. It was concluded that the assumption that blending based on the pre- or post-inactivation antigenic mass ELISA is different, can be rejected.

The report of a dose-response study, in chickens, where Bovilis BTV8 vaccines blended based on bluetongue virus post-inactivation antigenic mass ELISA was also provided. In this report, the results were provided from testing the potency of batches formulated using different amounts of post-inactivation quantified antigen. The discriminatory ability of the current potency test for Bovilis BTV8 was investigated for its capacity to identify sub-potent Bovilis BTV8 vaccine batches for which the antigen content was determined using the post-inactivation antigenic mass ELISA.

The above study was designed to test the serological response induced by Bovilis BTV8 vaccines containing different antigen content. The immunogenicity of each vaccine batch was investigated, alongside with the reference batch, in two independent potency tests in chickens. The serological response was determined by a virus neutralization test and statistically analysed. The statistical analysis showed no significant difference between the reference vaccine compared to vaccines containing antigen at the double and the standard doses, whereas vaccines containing the half, quart and eighth of the full standard antigen doses induced virus neutralizing titre levels significantly lower than the standard level. From the results obtained, it was concluded that the potency of BTV8 vaccine batches formulated based on the antigenic mass determined in the post-inactivation ELISA, containing the standard 100% antigen dose (500 AU/ml) showed no significant difference compared to the reference standard vaccine. Furthermore, it was demonstrated that it is possible to discriminate statistically Bovilis BTV8 vaccines batches containing the standard antigen dose (500 AU/ml, 100%) from batches containing the quart antigen dose (125 AU/ml, 25%) in the *in vivo* potency test.

The lack of further progress on the full development and validation of the post-inactivation antigen quantification test was justified by the absence of a demand for the vaccine from the market (no batches are produced). It is unknown when such data may become available however a post-inactivation antigen quantification test will be implemented by the applicant once the test will be fully validated.

The justifications provided by the applicant for the lack of further progress towards the full development and validation of the post-inactivation antigen quantification test were noted by the CVMP. Furthermore the efforts of the applicant were acknowledged in view of the above supportive data that partially qualify the post-inactivation antigenic mass ELISA. Therefore, this point for concern could be considered as resolved.

For the discriminatory value of the acceptance criteria and the corresponding results obtained in the dose response study report, in chickens, of Bovilis BTV8 vaccines blended based on bluetongue virus post-inactivation antigenic mass ELISA, the applicant provided reasonable justifications to support the fact that there could indeed be a chance that batches containing less than 500 AU/ml (based on either pre- or post-inactivation ELISA) will not be rejected in the potency test because the virus neutralisation titre results passed the criteria. In order to further substantiate the justifications provided, the applicant stated that further information will be provided on the validity of the potency test on batches blended based on post-inactivation antigenic mass ELISA (not yet implemented as no batches of finished product have been produced so far as there is currently no demand from the market). The applicant reassured that without this information no data for a variation application are available. As stated before, the post-inactivation ELISA will not be used for in-process control of the antigen until approved with a formal variation application. Only after this, batches will be blended based on the post-inactivation antigenic mass ELISA.

As a consequence, for the request expressed by the applicant of the MA for the vaccine currently under exceptional circumstances to convert to a normal status the CVMP concluded on the need for a condition of the normal authorisation with a timeline for being fulfilled after the production of 10 commercial batches.

4. At present stage, under exceptional circumstances, a provisional 12 month shelf life can be agreed. The applicant should provide the full stability data package once available

In the context of the second annual re-assessment, the CVMP concluded that the stability data provided indicated a trend which would guarantee the fulfilment of this recommendation. The applicant confirmed that final data will be provided.

For the third annual reassessment stability data were provided that supported the applicant's proposal for an antigen shelf life at a maximum of 3 months and an overview of all the stability data which were presented so far.

In summary, data to support a shelf life of 24 months for batches of finished product for the 10, 20 and 50 ml presentations made with antigen within 3 months after its manufacture were provided.

Data to support a shelf life of 12 months for batches of finished product for the 100, 200 and 500 ml presentations and made with antigen within 3 months after its manufacture, were submitted and considered satisfactory. In case of an extension of the shelf life up to 24 months for finished product presentations larger than 50 ml, a full set of stability data needs to be provided.

2nd specific obligation

In the second annual re-assessment the CVMP concluded that despite the absence of an updated risk assessment, the analysis conducted by the applicant was sustainable. The "low" numbers and figures evaluated in the latest PSUR supported the reduced use of the vaccine which could justify the omission of an updated benefit-risk assessment. In the meantime the benefit-risk balance of the product was considered as unchanged.

For the third annual reassessment the applicant noted that the need of the vaccine was even further reduced. In the absence of a significant need of the vaccine, the applicant considered that no change or update in the benefit-risk assessment of the product was necessary, especially in view of satisfactory PSUR reports that confirmed the safety profile of the product. No evidence was observed through pharmacovigilance concerning any lack of efficacy of the vaccine and therefore its benefits remain unaltered. The efficacy of the vaccine was established according to the requirements of the CVMP Guideline EMEA/CVMP/IWP/220193/2008, European Pharmacopoeia and Directive 2001/82/EC.

The CVMP concluded that the low number of Bovilis BTV8 vaccines sold and evaluated in the latest PSUR supported the reduced use of the vaccine due to the improved BTV8 epidemiological situation in Europe which could therefore justify the omission of an updated benefit-risk assessment. In the meantime the benefit-risk balance of the product was considered as unchanged. Moreover although a limited number of doses of Bovilis BTV8 has been sold in the European Union (EU) in 2012 and in 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. The specific obligation is fulfilled.

3rd specific obligation

In the second annual re-assessment the CVMP concluded that the information included in the provided PSUR (covering the time between 01.10.2011 and 31.03.2012) was acceptable. Based on these data, no update of the summary of product characteristics (SPC) and other product information was deemed necessary due to safety concerns.

For the third annual reassessment the applicant provided the PSURs covering the time between 01.04.2012 and 30.09.2012 and from 01.10.2012 to 31.03.2013. The reports supported the safe and efficacious use of the product in the field. No update of the SPC and other product information was deemed necessary as a result of safety concerns.

The CVMP concluded that the information included in the above PSUR was acceptable. Based on these data, no update of the SPC and other product information is deemed necessary due to safety concerns. 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.

2.2. Summary and conclusions

In accordance with Article 39 of Commission Regulation (EC) No. 726/2004, on 30 August 2013, the applicant submitted to the Agency an application for the third annual re-assessment of Bovilis BTV8 vaccine (i.e. re-assess the benefit-risk balance of the product).

During this third annual re-assessment the evidence for compliance with the specific obligations described in the beginning of the report were re-investigated. The information provided confirmed the positive benefit-risk balance of the product and justified the maintenance of the MA in the EU.

During this current procedure, the 3 specific obligations, including their sub-points as applicable, were addressed by the applicant. The four recommendations of specific obligation 1 were addressed by the applicant and are summarised below.

For the third annual reassessment the applicant provided the results of a valid potency test carried out for all the batches that were produced for the market. On the basis of the submitted results the consistency of the production process and the suitability of the batch potency test was considered satisfactory and overall the point for concern was satisfactory addressed.

Concerning the development of the antigen quantification test in the finished product the CVMP concluded that as there is a valid *in vivo* potency test approved, the absence of an *in vitro* method (as alternative to the currently performed *in vivo* potency test) should not preclude the potential for the MA given under exceptional circumstances, to convert to a standard MA. The specific point for concern relating to the development of the antigen quantification test in the finished product was considered as resolved.

The antigen quantification at formulation stage was discussed by the applicant under the 3rd recommendation. The applicant provided a SOP for a post-inactivation antigenic mass ELISA developed

and used to quantify the amount of inactivated BTV serotype 8 in aqueous suspension with acceptable clarifications.

The lack of further progress on the full development and validation of the post-inactivation antigen quantification test was justified by the absence of a demand for the vaccine from the market (no batches are produced). A post-inactivation antigen quantification test will only be implemented once the test will be fully validated.

The justifications provided by the applicant for the lack of further progress towards the full development and validation of the post-inactivation antigen quantification test were noted by the CVMP. Furthermore the efforts of the applicant were acknowledged in view of the above supportive data that partially qualify the post-inactivation antigenic mass ELISA.

However, on the basis of the provided information the relevant point for concern could not be considered as resolved. As a consequence, for the MA to convert to a normal status the CVMP agreed to include this as a condition of the normal authorisation with a timeline for being fulfilled after the production of 10 commercial batches.

The applicant provided stability data that supported the applicant's proposal for an antigen shelf life and an overview of all submitted stability data. Taking into account the above and the inclusion of a condition to address remaining concerns, specific obligation 1 is considered fulfilled.

Concerning the second specific obligation the low number of Bovilis BTV8 vaccines sold and evaluated in the latest PSUR supported the reduced use of the vaccine due to the improved BTV epidemiological situation in Europe and thus justified the omission of an updated benefit-risk assessment. In the meantime the benefit-risk balance of the product was considered as unchanged. Moreover it was acknowledged that BTV-8 does not appear to circulate in EU any longer, however the 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. The specific obligation is fulfilled.

The CVMP concluded that the information included in the provided PSUR covering the time between 01.04.2012 and 30.09.2012 and from 01.10.2012 to 31.03.2013, was acceptable. Based on these data, no update of the SPC and product information is deemed necessary due to safety concerns. 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 third specific obligation is fulfilled.

On the basis of the above the CVMP considered that recommendations 1, 2 and 4 and specific obligations 2 and 3 were fulfilled respectively.

On the basis of the above the CVMP concluded that all specific obligations have been fulfilled besides recommendation 3 of specific obligation 1. For the MA to convert to normal status as requested by the applicant a condition related to recommendation 3 of specific obligation 1 should be included for the post-inactivation antigen quantification test to be developed after the production of 10 commercial batches.

Considering the pharmacovigilance data submitted for this vaccine so far, it was recommended that the frequency of PSUR submissions should be restarted to follow the standard timetable, following conversion of the MA.

3. Benefit-risk assessment

3.1. Introduction

Bovilis BTV8 is an inactivated vaccine against bluetongue virus serotype 8. The vaccine is formulated to contain aluminium hydroxide and saponin as an adjuvant system. 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.

3.2. Benefit assessment

Direct therapeutic benefit

Bovilis BTV8 is a vaccine containing inactivated bluetongue virus serotype 8 antigen combined with an adjuvant intended to induce an immune response in sheep and cattle, with the aim to prevent viraemia (cycling value (Ct) >30 by a validated rRT-PCR method, indicating absence of infectious virus) in sheep and to reduce viraemia in cattle caused by bluetongue virus serotype 8.

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

The objective is to stimulate active immunity in sheep from 1 month of age against bluetongue virus serotype 8 in order to prevent viraemia and to stimulate active immunity in cattle from 6 weeks of age against bluetongue virus serotype 8 in order to reduce viraemia.

Clinical trials demonstrated that the product is capable of inducing an immune response which prevents viraemia in sheep and reduces viraemia in cattle caused by bluetongue virus serotype 8.

Additional benefits

Bovilis BTV8 is a standard inactivated vaccine and as such fits in with accepted vaccination practices in the field.

A duration of immunity of 6 months has been demonstrated for both cattle and sheep.

The effect of maternally derived antibodies has been investigated and the efficacy of the vaccines in animals from 1 month has been shown.

Vaccination has also been shown to be safe for use during pregnancy in cattle, which is valuable during a widespread vaccination programme usually necessary to control the spread of disease.

3.3. Risk assessment

Main potential risks:

For the target animals:

For sheep and cattle vaccination may be followed by a slight rise in temperature (usually not more than 0.5 °C, in individual cases up to about 2 °C) for up to three days after vaccination, and temporary swellings at the injection site. In sheep these swellings typically last for up to three weeks. In cattle small palpable swellings may still be present up to six weeks after vaccination in approximately one third of the vaccinated animals. Pharmacovigilance data have confirmed the safety of the product in accordance with the SPC.

For the user:

For the user there is a low risk of self-injection. Appropriate warnings and advice on the SPC are included to minimise the risk.

For the environment:

For the environment there is a very low risk that the vaccine components may cause unexpected effects to the environment. However the vaccine is inactivated by a validated inactivation method and therefore is no risk of the spread of live virus. The adjuvants appear to be pharmacologically inert substances. Additionally, no special concern is posed by the final product in light of the safety of packaging, of the limited number of injections and of the maximum quantity administered to animals, of the route and of the method of administration, and disposal.

For the consumer:

For the consumer there are no components which require a maximum residue limit (MRL), therefore there are no concerns over failure to observe a MRL. Withdrawal period of zero days is considered appropriate.

Specific potential risks, according to product type and application:

Following the third annual re-assessment, no further specific risks have been identified from the use of the product but in view of the potential for the conversion of the MA from exceptional circumstances to normal status the following have been identified:

1. Absence of an antigen quantification test at post-inactivation and at final product stage

   A suitable *in vivo* batch potency test is ensuring a consistent batch quality at final product stage. Progress on the development of a post-inactivation antigen quantification test has been made but has been halted due to lack of vaccine demand and thus batch production. As a consequence, for the MA currently under exceptional circumstances to convert to a normal status the CVMP concluded on the need for a condition for such MA, with a timeline for being fulfilled after the production of 10 commercial batches. The pharmacovigilance data have not showed any evidence of lack of safety or efficacy supporting the consistency of production.

2. Stability of the product

   Data to support a shelf life of 24 months for batches of finished product for the 10, 20 and 50 ml presentations made with antigen within 3 months after its manufacture were provided. Stability results have been provided that provide assurance of a stable vaccine for the 12 months of shelf life for the 100, 200 and 500 ml presentations and made with antigen within 3 months after its manufacture. In case of an extension of the shelf life up to 24 months for finished product presentations larger than 50 ml, a full set of stability data needs to be provided. The pharmacovigilance data have not showed any evidence of lack of safety or efficacy supporting the stability profile of the product.

Risk management or mitigation measures

Appropriate warnings have been placed in the SPC to inform on the potential risks to the target animals, the user and the environment and provide advice for reducing these risks. For the conversion of the MA to normal status a condition should be included in the authorisation for the post-inactivation antigen quantification test to be developed after the production of 10 commercial batches.

It was recommended to re-start the PSUR cycle for Bovilis BTV8 to ensure more frequent pharmacovigilance monitoring following conversion of the MA status.

Evaluation of the benefit-risk balance

Bovilis BTV8 has been shown to have a positive benefit-risk balance for use in both sheep and cattle.

The formulation and manufacture of Bovilis BTV8 are well described and specifications are supported. A suitable *in vivo* batch potency test is ensuring a consistent batch quality at final product stage. Progress on the development of a post-inactivation antigen quantification test has been made but has been halted due to lack of vaccine demand and thus batch production. The CVMP agreed on a condition to be fulfilled by the applicant for a post-inactivation antigen quantification test to be developed after the production of 10 commercial batches. Clarifications on the batch potency test, the dose-response study in chickens, where Bovilis BTV8 vaccines were blended based on bluetongue post-inactivation antigenic mass ELISA and on remaining stability data were considered acceptable.

The product has been shown to be efficacious for the indication of stimulation of active immunity in sheep from 1 month of age against bluetongue virus serotype 8 to prevent viraemia and the stimulation of active immunity in cattle from 6 weeks of age against bluetongue virus serotype 8 to reduce viraemia.

The pharmacovigilance data have not showed any evidence of safety concerns or lack of efficacy, therefore supporting the consistency of production and also the stability profile of the vaccine.

Bovilis BTV8 is well tolerated by the target animals and presents a very low risk for users, the consumers and the environment. Appropriate warnings have been included in the SPC.

3.4. Conclusion on benefit-risk balance

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

4. Overall conclusions of the evaluation and recommendations

On the basis of the documentation submitted 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.

Besides recommendation 3 of specific obligation 1, the specific obligations have been resolved.

In view of the fact that specific obligations have been fulfilled and remaining concerns are addressed by a condition for the post-inactivation antigen quantification test to be developed after the production of 10 commercial batches, there are no remaining grounds to maintain the marketing authorisation for this product under exceptional circumstances and thus the CVMP recommends the conversion of the marketing authorisation to a normal status.

The CVMP also considered it necessary to restart the PSUR cycle for this product 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 following annexes of the Community marketing authorisation:

- Annex I, II and III.

5. List of conditions to be included in the full marketing authorisation

1. A post-inactivation antigen quantification test will be developed after the production of 10 commercial batches.

2. The periodic safety update report (PSUR) cycle for is to be re-started for submission of 6 monthly reports (covering all authorised presentations of this product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at three-yearly intervals.