13 March 2025
EMA/110832/2025
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Hepizovac (EMEA/V/C/006592/0000)

Vaccine common name: Epizootic haemorrhagic disease vaccine (inactivated)

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

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Introduction

The applicant CZ Vaccines S.A.U. submitted on 29 November 2024 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Hepizovac, through the centralised procedure under Article 42(2)(c) of Regulation (EU) 2019/6 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 19 June 2024 as Hepizovac contains an active substance which has not been authorised as a veterinary medicinal product within the Union at the date of the submission of the application (Article 42(2)(c)).

Hepizovac suspension for injection for cattle is a vaccine containing 4 x $10^{5.5}$ $CCID_{50}$ (50% cell culture infective dose) of inactivated epizootic haemorrhagic disease virus (EHDV), serotype 8, strain EHDV8 SPA 2022/LCV_03 LCV Cod.:078 as active substance and aluminium hydroxide and purified saponin (Quil A), as adjuvants. The target species is cattle.

The primary vaccination schedule to be given to cattle from 2 months of age consists of two doses of 4 ml to be administered 3 weeks apart by the subcutaneous route. The proposed onset of immunity is 21 days after primary vaccination. No duration of immunity has been established.

At the time of submission, the applicant applied for the following indications:

For the active immunisation of cattle to prevent viraemia and to reduce clinical signs caused by serotype 8 of the epizootic haemorrhagic disease virus. The proposed onset of immunity is 21 days after completion of the primary vaccination scheme. The duration of immunity has not been established.

Hepizovac is presented in packs containing 1 bottle of 52 ml, 100 ml or 252 ml.

The rapporteur appointed is Jacqueline Poot and the co-rapporteur is Leona Nepejchalová.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances.

The CVMP considered that the outbreaks of epizootic haemorrhagic disease (EHD) caused by the serotype 8 in cattle in Europe, the significant impact on animal health and the lack of authorised vaccines in the Union to respond to these outbreaks constituted exceptional circumstances related to animal health as per Regulation (EU) 2019/6.

In Europe, outbreaks of the disease were first confirmed in several cattle farms in Italy in October 2022. Since then, outbreaks of the disease caused by the serotype 8 of the virus have been confirmed in other Member States (Spain, Portugal and France). For example, in France, between 1 June 2024, and 6 March 2025, 3,819 outbreaks of EHD were recorded.

Data collected from the field show that the morbidity is highly variable but can reach 100% in some farms. Clinical signs observed include hyperthermia, anorexia, abatement, muzzle ulcers, nasal discharge and lameness, requiring extensive and prolonged treatment. Severe symptoms can be observed in adult cattle (from 2 years of age) which may lead to mortality (M. Gondard *et al.*, 2024).

In the light of the animal health situation, some EU Member States (e.g. Spain, France, Belgium) have allowed the use of EHDV vaccines against serotype 8 under the Article 110 of Regulation (EU) 2019/6, by which 'a competent authority may, in the interest of animal health and welfare and public health, allow the use of an immunological veterinary medicinal product not authorised within the Union on a case by case basis'. As of March 2025, Belgium has implemented mandatory vaccination programs to combat EHD in cattle.

For the assessment of this procedure, an accelerated timetable was applied for by the applicant and

agreed by the CVMP. In fact, the benefit of the immediate availability on the market of a veterinary medicinal product against EHD virus serotype 8, currently circulating in the European Union (EU), was recognised by the CVMP.

On 13 March 2025, the CVMP adopted an opinion and CVMP assessment report.

On 23 April 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Hepizovac.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF), has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

Manufacture and quality control of the active substance inactivated epizootic haemorrhagic disease virus, serotype 8, strain EHDV8 SPA 2022/LCV_03 LCV Cod.:078 takes place at CZ Vaccines S.A.U., Spain.

A GMP certificate issued by Consellería de Sanidade, Xunta de Galicia is provided that is valid for the production of biological veterinary medicines. The GMP certificate is also available in EudraGMDP.

A declaration has been provided for the active substance manufacturer from the QP at the proposed EU batch release site stating that the active substance is manufactured in compliance with EU GMP.

Finished product

Manufacture, quality control testing (microbiological, chemical/physical, biological), primary packaging, secondary packaging and batch release of the finished product takes place at CZ Vaccines S.A.U., A Relva s/n, Torneiros, O Porriño, Pontevedra, Spain.

Manufacturing Authorisation was issued on 20 November 2024 by the competent authority of Spain (AEMPS).

A GMP certificate issued by Consellería de Sanidade, Xunta de Galicia is provided that is valid for the production of biological veterinary medicines, quality control, packaging and batch release. The GMP certificate is also available in EudraGMDP.

Secondary packaging can also be carried out at two additional sites.

Manufacturing authorisations were issued by the competent Authority for these sites.

Overall conclusions on administrative particulars

The sites involved in manufacturing are appropriately authorised for manufacturing and valid GMP certificates are available for all sites.

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements.

Part 2 - Quality

Quality documentation (physico-chemical, biological, and microbiological information)

The vaccine benefits from the reduced data requirements intended for applications in exceptional circumstances under Article 25 of Regulation (EU) 2019/6 and the "Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances" (EMA/CVMP/IWP/251947/2021).

The applicant provided data from the company's bluetongue vaccines already authorised to support some of the quality aspects of Hepizovac. This is considered acceptable in the framework of an Art. 25 application and this data fills some of the data gaps identified by the CVMP.

Qualitative and quantitative composition

The product is a vaccine for cattle presented as a suspension for injection containing inactivated EHDV serotype 8 virus as active substance and aluminium hydroxide and Quil A as adjuvants in phosphate buffered saline (PBS).

The vaccine is intended to be available in multidose presentations and consequently contains thiomersal as a preservative.

The product is packed in 52 ml, 100 ml and 252 ml high-density polyethylene (HDPE) bottles in cardboard boxes. The pack sizes are consistent with the dosage regimen and duration of use.

Container and closure system

The product is packed in 52 ml, 100 ml and 252 ml HDPE bottles in accordance with Ph. Eur. 3.1.5 requirements. Bottles are closed with a butyl rubber stopper (in accordance with Ph. Eur. 3.2.9) and an aluminium seal. Bottles are washed with water for injections and subsequently sterilised. The stoppers are also sterilised. Sterilisation is considered adequate.

Product development

The antigen is an inactivated EHDV serotype 8 that was isolated by the national reference laboratory for EHD in Spain in 2022. The strain is considered relevant for the emergency situation since it is the same that is causing the current EHDV outbreak in Europe. The vaccine is formulated based on the pre-inactivation virus titre; this is acceptable in principle, for an emergency situation. Virus is grown on baby hamster kidney -21 (BHK-21) cells, the same cell line that is used to culture the (related) bluetongue viruses (BTV) for the Bluevac BTV range of vaccines. Like for BTV, EHDV virus is inactivated using binary ethylenimine (BEI) which is a highly effective, standard method.

The adjuvants, aluminium hydroxide and Quil A, are well known in the field as these are used in several licensed vaccines for bovines. The bluetongue virus vaccine range by the applicant (Bluevac BTV) contains the same adjuvants in the same concentrations. Since this concerns a multidose product, thiomersal is added as a preservative at the same concentration as for Bluevac BTV.

The proposed posology of the vaccine is two injections of 4 ml given subcutaneously (s.c.), three weeks apart. This vaccination schedule is very similar to that of Bluevac BTV in cattle.

Considering the emergency situation and the high similarity of the BTV and EHDV viruses, the development of Hepizovac using Bluevac BTV vaccines as a blueprint is considered logical and acceptable.

Description of the manufacturing method

The manufacturing process consists of two main steps: production of the antigen and manufacturing of the finished product. The process is considered to be a standard manufacturing process, highly comparable to the processes for the Bluevac BTV range of vaccines.

Briefly, BHK-21 cells are grown in suspension in medium supplemented with bovine serum, by passages of increasing volume. When sufficient cells are grown, these are transferred to a tank and the medium is replaced by serum-free medium. Cells are inoculated with virus and incubated. The culture is clarified, the supernatant is collected and filtered into a container. Inactivation is performed by addition of BEI solution. The culture is transferred to a new container and inactivation is continued. The viral antigen is purified and concentrated. The excess BEI is neutralised by addition of sodium thiosulphate. The antigen is stored.

For preparation of the bulk vaccine, aluminium hydroxide gel and Quil A solution are mixed and the calculated amount of antigen is added, followed by the diluent (PBS) and thiomersal. Stirring is started and continued for a certain time. After this time, a sample is taken to perform tests for appearance, thiomersal, sterility, aluminium, Quil A and pH. The bulk is stored until QC results are available.

Filling is automatic; fill volume is checked throughout the filling process. Containers are closed and capped. Filled vials are stored until QC approval. Labelling and secondary packaging is performed and the presentation is checked prior to batch release.

Major steps of the manufacturing process have been validated by three consecutive batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible and consistent manner. The in-process controls are adequate for this type of manufacturing process.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Certificates of analysis (CoAs) have been provided for the substances listed in pharmacopoeias. They conform to relevant Ph. Eur. monograph requirements.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

Starting materials not listed in pharmacopoeias and of biological origin are: BHK-21 seeds, EHDV-8 seeds, bovine serum albumin (BSA) and Quil A.

Master cell seed (MCS) suspension cells: the cell line was originally established in 1962, cloned, adapted, cultured and stored in liquid nitrogen to lay down the MCS. The seed was tested for culture characteristics, identity, sterility, mycoplasma, karyology, general tests and specific tests for

extraneous agents (EA). Testing of EA was performed in accordance with the historic requirements; recently, further testing was performed in accordance with Ph. Eur. chapter 5.2.5. Absence of testing for endogenous retrovirus is acceptable for this Art. 25 procedure, based on the inactivation method and the use of the cell seeds in the manufacturing of authorised vaccines. Absence of tumorigenicity testing is justified considering the nature and composition of the product.

Working cell seed (WCS) suspension cells: the BHK-21 WCS was prepared from the MCS by culture; the culture was concentrated and frozen in liquid nitrogen. WCS was tested for identity, growth, sterility, mycoplasma and extraneous agents; in addition, growth, sterility, identity and karyotype were tested on the highest passage.

Master cell seed, monolayer cells: the BHK-21 monolayer cell line is used for the preparation of the viral seeds for EHDV-8.

Master seed virus (MSV): the original seed was received from the national reference laboratory for EHDV in Spain in November 2023. The virus was isolated from a bovine in 2022 on a Spanish farm. The virus was identified by RT-qPCR, isolated passaged on BHK-21 monolayers before laying down the MSV. The MSV was tested for identity, titre, residual water, sterility, mycoplasma, and specific tests for extraneous agents. The list of EAs in the risk assessment appears not to be fully complete in accordance with Ph. Eur. 5.2.5.

Working Seed Virus (WSV): the WSV was prepared from the MSV and tested for identity, titre, sterility, mycoplasma, mycobacteria, brucella, BTV, porcine circovirus type 2 (PCV2) and porcine parvovirus (PPV). This is considered acceptable for this inactivated vaccine.

Bovine serum albumin is derived from bovine blood from New Zealand and has a certificate of suitability. BSA is considered to have been adequately tested for absence of extraneous agents through testing of the seeds.

A CoA for Quil A is provided. Quil A is free of polyvinylpyrrolidone /polyvinylpolypyrrolidone (PVP/PVPP).

Starting materials of non-biological origin

Starting materials of non-biological origin are antifoam, material used to prepare the BEI solution, material used in the cell culture, component of the freezing medium. Specifications in the respective CoA are provided. All of these substances are well-known starting materials.

In-house preparation of media and solutions consisting of several components

Information regarding the qualitative and quantitative composition of all culture media, their treatment processes and their storage conditions is provided in the dossier. All components are either tested for or treated to ensure that there are no contaminants, and further assurance is given that there is no potential risk.

Control tests during the manufacturing process

During the manufacturing of the antigen, tests are performed for sterility (at several points), cell count, cell viability/CPE, virus titre, inactivation, residual thiosulphate and identity. The timing of the testing is summarised in a flow chart.

During manufacturing of the bulk, tests for aluminium hydroxide and Quil A content (prior to addition of antigen) and pH (of the antigen bulk prior to addition of the antigen and of the vaccine bulk),

appearance, thiomersal content and sterility are performed.

Tests are sufficiently described and validated and, where appropriate, acceptance limits are indicated.

The in-process tests are deemed to be sufficient to control all the critical steps in the manufacturing.

The maximum limit for virus titre prior to inactivation is in line with the maximum titre used in the inactivation kinetics study.

Control tests on the finished product

Information concerning the control tests on the finished product is presented. The description of the methods used for the control of the finished product and the specifications are provided, and, where applicable, the test validations were extrapolated from Bluevac BTV as the tests are considered the same.

The finished product is tested for filling volume, appearance, identity, sterility and presentation (packaging).

Identity of the antigen is tested by RT-qPCR. The method is sufficiently described, has adequate controls and is considered fit for purpose.

The potency of the vaccine is based on the pre-inactivation virus titre. A test for potency in the final product is under development. This is acceptable for this emergency situation. The applicant has indicated the expected timeframe for the development of the test (specific obligation - SOB).

The adjuvant content is determined in the bulk; acceptable limits are set. The aluminium hydroxide content is tested in the "mix of adjuvants" and in the bulk preparation in accordance with Ph. Eur. 2.5.13; the method was validated for Bluevac BTV final vaccine. Both methods are considered fit for purpose and acceptable for this Art. 25 procedure.

Thiomersal is tested in the bulk. The method was validated for the Bluevac vaccines; acceptable limits are set. The method is considered fit for purpose and acceptable for this Art. 25 procedure.

The pH is tested in the bulk, this is acceptable, and acceptable limits have been set. Sterility is tested on each bulk batch and on each batch of finished product. The method is in accordance with the Ph. Eur. method by direct inoculation. The product must be sterile.

Filling volume is tested during the filling process in previously weighed vials. Fill volume is calculated from the density value. Acceptable limits have been set; the method is considered fit for purpose.

Batch-to-batch consistency

The applicant presented finished product data for the manufacture of three consecutive finished product batches, using two antigen batches. The vaccine batches complied with all in-process and finished product testing. The data support the consistency of production.

Stability

The antigen is stored and a shelf life is proposed. To prepare the consistency batches, antigen batches that had been stored for 1 or 3 months were used. The proposed storage period for the EHDV antigen at the lower end of the range of storage periods for the BTV antigens is acceptable. The applicant is requested to provide data for the proposed stability when they become available. This is considered a specific obligation (SOB).

The finished product is stored at 2-8 °C; a shelf life of 18 months is proposed. No data on stability of the finished product have been provided. A study protocol is provided for three batches of the finished product that will be stored for 27 months. The Bluevac vaccines have shelf lives ranging between 18 months (BTV 1) and 24 months (BTV 4 and 8); no deterioration was observed in the batches put on stability for these vaccines. The proposed shelf life for the finished product of 18 months is in accordance with the lower end of the Bluevac vaccine range and as such acceptable. The applicant is requested to provide to the authorities the results of stability testing to support the proposed shelf life as soon as they become available and report any confirmed out-of-specification results. This is considered a specific obligation (SOB).

An in-use stability of 10 hours is claimed. No data have been provided, however based on the highly similar composition of Hepizovac and the Bluevac BTV range of vaccines (including the thiomersal content), the same in-use stability period of 10 hours can be accepted for this Art. 25 procedure.

New active substance (NAS) status

The applicant requested the active substance inactivated epizootic haemorrhagic disease virus, serotype 8, strain EHDV8 SPA 2022/LCV_03 LCV Cod.:078 contained in Hepizovac to be considered a new active substance as it is novel and not hitherto authorised in a veterinary medicinal product in the European Union.

Based on the review of the data provided, the CVMP considered that the active substance inactivated epizootic haemorrhagic disease virus, serotype 8, strain EHDV8 SPA 2022/LCV_03 LCV Cod.:078 contained in the veterinary medicinal product Hepizovac is to be qualified as a new active substance considering no EHDV antigen is included in any authorised vaccine in the EU at the time of the application.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The manufacturing process including appropriate in-process controls and quality controls on the finished product are described in sufficient detail to give confidence that the manufacture will yield a consistent immunological product. The potency of the finished product is calculated based on the pre-inactivation virus titre; the product is blended to a standard target potency. This potency corresponds to the potency of batches that were shown to be effective in pre-clinical studies. This is acceptable for this Art. 25 procedure. A potency assay for the finished product needs to be developed, this is a specific obligation. Consistency of production is supported by the data on three consecutive batches. Based on the review of the data on quality, and taking into account the status of an application under Art. 25 of Regulation EU 2019/6, the manufacture and control of Hepizovac are considered acceptable.

As a post-authorisation measure, the applicant is requested to provide the results of remaining stability data for the antigen and the finished product and report any confirmed out-of-specification results without delay. This is considered a SOB.

Part 3 – Safety documentation (safety and residues tests)

General requirements

The active substance of Hepizovac is inactivated epizootic haemorrhagic disease virus, serotype 8, strain EHDV8 SPA 2022/LCV_03 LCV Cod.:078. Inactivated epizootic haemorrhagic disease virus, serotype 8 is a new active substance not authorised for a veterinary medicinal product in the EU before. A full safety file in accordance with Article 8(1)(b) has been provided.

EHDV-8 is circulating in Europe since 2022, causing bluetongue-like symptoms in cattle and severe disease with high mortality in deer. The EHD virus is related to bluetongue virus (genus: Orbivirus) and is transmitted mainly through the bites of cullicoides midges.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances. A full safety file in accordance with Article 8(1)(b) has not been provided. The applicant holds marketing authorisations for BTV vaccines (Bluevac-1, -4 and -8 and, recently, Bluevac-3). The qualitative and quantitative composition of Hepizovac is highly similar to these Bluevac vaccines, the only difference being the antigens. The safety of Hepizovac was investigated in a pre-clinical study in calves and further supported by studies performed with the Bluevac range of products. Clinical data are not provided yet and this is in line with the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances.

Safety documentation

Safety of the administration of one dose and a repeated dose was investigated in a combined safety and efficacy study in calves. The product contains a fixed amount of antigen; thus, no minimum or maximum dose batches exist and safety and efficacy can be tested with the same standard batch of vaccine.

Supportive data on the safety of a single and a repeated dose as well as an overdose are also provided in the form of studies performed with the Bluevac-range of vaccines. Safety of vaccination for reproductive performance was studied in pregnant cows vaccinated with the Bluevac range of vaccines. All of these studies were performed and assessed in the frame of the authorisation procedures for the Bluevac vaccines.

Pre-clinical studies

Safety of the administration of one dose

In the combined safety and efficacy study four groups of 9-week-old EHDV- and BTV seronegative and PCR negative calves were included. Three groups were vaccinated with 4 ml of Hepizovac, formulated with three different concentrations (an antigen payload of $10^{5.5}$ $CCID_{50}$/ml (G1, n=10) and two higher doses (G2, n=8), (G3, n=11)) and group 4 (n=10) was injected with PBS. All groups were vaccinated twice with a three-week interval. After each dose, animals were observed for local and systemic signs for 14 days. Rectal temperatures were recorded two days before each vaccination, at the time of vaccination and 4 hours later and then daily for 4 days.

No systemic adverse events were observed. No statistically significant increases in rectal temperatures were observed. Mean temperature increases did not exceed 1.5 °C, individual

temperature increases did not exceed 2.0°C. In G1, a slight increase in rectal temperature (around 1 °C) was seen in two calves for one day on day 1 or 2 after vaccination. After the first injection, local reactions were observed in 90% of calves, consisting of swelling up to 8 cm diameter and developing into nodules around up to 5 cm which decreased in size from 21 days post vaccination. In some cases, the swelling was found to be painful. After the second injection, a similar picture was seen, with injection site swelling in 90% of calves and nodules developing in 90% of calves (up to 6 cm).

The study results support the safety of Hepizovac in calves of the lowest age for vaccination. While the study was not performed under GLP, the quality of the study is considered to be adequate and acceptable for this Art. 25 procedure. Research batches were used in the study, this is acceptable for this Art. 25 procedure. The observed adverse events are as expected for the type of vaccine. There was no indication for an increased reaction after repeated vaccination. Appropriate warnings are given in the SPC with respect to injection site reactions and elevated temperature.

Safety of the administration of one dose and a repeated dose is further supported by the results of safety studies performed with Bluevac-3, Bluevac BTV8, Bluevac-1, Bluevac-4 and Bluevac 4+8. Except for Bluevac-3, this concerns centrally authorised vaccines for which the studies have been assessed previously. In these studies, no systemic adverse events were observed and generally no temperature increases were found. Local reactions were observed that are similar in size and duration to what was found for Hepizovac. There was no indication for an increased reaction after a repeated vaccination.

Safety of one administration of an overdose

No overdose testing was performed for Hepizovac and this acceptable since this is not required for inactivated vaccines. However, a study report is included on the safety of an overdose of Bluevac-8. After an overdose (8 ml, s.c.) of Bluevac BTV8 in 2,5-month-old calves, no systemic reactions or temperature increases were observed. Injections site nodules up to 4.5 cm were found. The results indicate that it is unlikely that other adverse events than those observed after a single dose will occur after an overdose.

Safety of the repeated administration of one dose

Safety of a repeated dose was tested in the pivotal study since the proposed vaccination schedule prescribes two injections with a three-week interval. Temperature increases and local reactions were very similar after the first and second dosing.

The studies performed with the Bluevac range vaccines also do not indicate an increase of adverse reactions after the second dosing.

Based on the combined data, there is no reason to expect severely enhanced adverse events after repeated administration of the vaccine. The safety of a third (booster) injection was not investigated for Hepizovac (or for Bluevac vaccines). This is considered acceptable for this Art. 25 procedure. The risk of enhanced adverse reactions occurring after a third vaccination is considered very small based on the available data. It is indicated in the SPC that no data are available concerning booster vaccinations.

Examination of reproductive performance

No data have been generated on the reproductive performance after vaccination with Hepizovac. However, data on the reproductive safety of the Bluevac range of vaccines have been provided as

supportive evidence. No data has been provided on safety for breeding males.

In a field study in Spain, 85 pregnant cows divided over the three trimesters were vaccinated with Bluevac-1, no abortions occurred that were attributed to vaccination and all calves were born normal. In another field study in Spain, 38 cows with pregnancies divided over the three trimesters were vaccinated with Bluevac-4, no abortions, abnormal births or teratogenic effects were observed.

Two pre-clinical safety studies were performed, one with cows in the third trimester of pregnancy and vaccinated with Bluevac 1+8 the other with cows in the first trimester of pregnancy and vaccinated with Bluevac 4+8. Both were controlled studies with 8 cows per group. No abortions were observed, and calves were born normal.

The data on the Bluevac-range of vaccines are considered relevant due to the highly similar composition and posology. With Bluevac vaccinations, no negative effect on pregnancy was observed in any of the four studies. The warning sentences in the SPC: "No negative impact is expected in pregnant cows. No negative impact on the milk-yield using the vaccine in lactating cows is expected." and: "The safety of the vaccine has 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" are considered acceptable based on the data provided. These sentences are considered to provide valuable information to the user and are sufficiently supported by data for this Art. 25 procedure. The risk to pregnant animals is considered to be very small.

Examination of immunological functions

No specific studies on immunological functions after vaccination were carried out. This is accepted since this concerns a conventional inactivated vaccine containing only substances with no known adverse effects on the immunological function.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/IWP/54533/2006. The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely route is accidental self-injection. The active substance is an inactivated virus and is not infectious; therefore, does not pose a risk for the user. The excipients including adjuvants are commonly used in other vaccines and do not pose an unacceptable risk for the user albeit accidental injection may lead to reactions due to the composition of the vaccine.

As a result of the user safety assessment the following advice to users/warnings for the user are considered appropriate:

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Study of residues

No study of residues was performed.

MRLs

The active substance being a principle of biological origin intended to produce active immunity is not within the scope of Regulation (EC) No 470/2009.

The excipients, including adjuvants, listed in section 2 of the SPC are either allowed substances for which Table 1 of the Annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

The applicant has not provided data investigating interactions of the vaccine with any other veterinary medicinal product and therefore proposes to include a statement in Section 3.8 of the SPC that 'No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case-by-case basis.'

Clinical studies

No clinical trials were performed with Hepizovac. This is acceptable, in accordance with the status of application in the frame of Art. 25 of Regulation (EU) 2019/6.

The applicant provided the report of an independent clinical trial performed by German authorities with the related vaccine Bluevac BTV8 as supportive information. The field study included 200 adult cattle per group. For Bluevac-BTV8 no effect of vaccination on milk yield was observed. Based on this study and taking into account the high comparability in composition of the Bluevac BTV vaccines and Hepizovac, the conclusion by the applicant that effects on milk yield are not expected for Hepizovac, can be accepted.

Environmental risk assessment

An environmental risk assessment has been provided in accordance with the CVMP Note for Guidance on the environmental risk assessment of immunological veterinary medicinal products (EMEA/CVMP/074/95). Based on the data provided, the ERA can stop at Phase I. Hepizovac is expected to pose a negligible risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The applicant has provided one pivotal pre-clinical study to investigate the safety of one dose and repeated administration of one dose to the target animal species of the minimum recommended age using a standard potency vaccine via the recommended route. Experimental batches were used in the study.

Additional studies performed with the Bluevac-BTV range of vaccines are presented. These vaccines are highly comparable in composition and posology. The results of studies on safety of one dose and a repeated dose are highly comparable between Hepizovac and Bluevac vaccines. An overdose of Bluevac

vaccine was shown to be safe, this is acceptable support for this Art. 25 procedure.

On the basis of the results, it was concluded that the safety of Hepizovac in the target animals when the product is administered according to the recommended schedule and via the recommended route is acceptable. A combined safety and efficacy study is acceptable in principle for a product with a fixed dose. It is noted the study was not performed under GLP and research batches were used. However the quality of the study is considered to be adequate to conclude on safety and thus acceptable for this Art. 25 procedure. A warning concerning the occurrence of local adverse reactions and elevated temperature is included in the SPC.

Reproductive safety of Hepizovac was not investigated. Supportive data on reproductive safety of the Bluevac vaccines indicate that these products are safe when used in pregnant animals at all stages of gestation. No data on safety in male breeding animals is available. The safety for lactating animals is supported by the results of a large clinical study with Bluevac BTV8 where no effect of vaccination on milk yield was observed. The use of data derived from highly similar vaccines from the same MAH is acceptable for this Art. 25 procedure. Appropriate warning sentences are included in the SPC.

The product is not expected to adversely affect the immune response of the target animals or of its progeny, and therefore no tests on the immunological functions were carried out. This is acceptable.

Based on the assessment presented, the product does not pose an unacceptable risk to the user when used in accordance with the SPC. The appropriate warnings for the user have been included in the product literature. Hepizovac is not expected to pose a risk for the environment or to the consumer when used according to the SPC.

Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)

General requirements

The claimed efficacy of the product is for active immunisation of cattle to prevent viraemia and to reduce clinical signs caused by serotype 8 of the Epizootic Haemorrhagic Disease virus, with an onset of immunity of 21 days after completion of the primary vaccination scheme. A duration of immunity has not been established.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances. A full efficacy file in accordance with Article 8(1)(b) has not been provided. However, data on onset of immunity for the target species from a combined safety/efficacy study in calves vaccinated according to the recommended schedule are provided. No data on duration of immunity are provided yet. This is in line with the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances.

Challenge model

A challenge model was tested in calves using the homologous EHDV-8 vaccine strain. Challenge of 12-week-old calves with 2 x $10^{6.0}$ $CCID_{50}$ s.c. resulted in clear viraemia (as detected by RT-qPCR) and slight clinical signs. This is in accordance with the expectations for EHDV infections in cattle. Clear serological responses were observed in all animals. The RT-qPCR for EDHV-8 was appropriately validated, the limit of detection was determined. The anti-VP7 ELISA is a commercial assay. The challenge model and tests used are considered to be fit-for-purpose. Use of the homologous strain is considered appropriate in the framework of exceptional circumstances.

Efficacy parameters and tests

The efficacy parameters, as chosen by the applicant and investigated in the efficacy studies, are viraemia, humoral response and clinical signs. The tests performed are considered appropriate for evaluating the efficacy of the product. Validation results were presented for the EHDV RT-qPCR and confirm that the tests chosen are adequately validated to provide reliable results.

Efficacy documentation

Pre-clinical studies

One pivotal combined safety and efficacy study was performed in calves. Since the vaccine is blended using a fixed antigen content there are no minimum and maximum potency batches, hence safety and efficacy can be investigated in one study.

Dose determination

The proposed dose of 4 x $10^{5.5}$ $CCID_{50}$ for Hepizovac was established based on the findings of a combined safety and efficacy study that was designed to determine onset of immunity and dose. This study is summarised below.

Onset of immunity

A combined safety and efficacy study was performed in eight-week-old, EHDV and BTV seronegative and PCR-negative calves. Three groups were vaccinated with 4 ml of Hepizovac, formulated with three different antigen payload of $10^{5.5}$ $CCID_{50}$/ml (G1, n=10), and two higher ones (G2, n=8), (G3, n=11) and group 4 (n=10) was injected with PBS. All groups were vaccinated twice with a three-week interval. Challenge was performed on Day 42 in 8 animals per group, animals were followed up for 14 days.

In the vaccinated animals, none tested PCR positive for EHDV, indicating absence of viraemia after challenge. The control animals were PCR positive (6 of 8) from day 2, all were positive from day 4 and Ct values peaked between days 9 and 11 post-challenge (p.c.).

In all groups, mild clinical signs were observed. However, these were mostly unspecific (i.e. diarrhea). Focusing on more specific clinical signs for EHD (inflammation of oral mucosa, including gingivitis, and ulcerative and/or necrotic lesions of the oral mucosa and/or nose), there were no statistically significant differences in vaccinated groups and control group due to the lack of relevant scores for such clinical signs. A reduction in rectal temperature after challenge was seen in group 1 and group 3.

Vaccination induced an anti-VP7 IgG response in all three vaccinated groups. The mean titres were very similar. Therefore, no dose-response could be demonstrated for the EHDV-8 antigen. After challenge, a booster response was observed in the vaccinates. After challenge, anti-VP7 antibodies were also observed in the controls (14 d.p.c.). Neutralising antibodies (as determined by SNT on the day of challenge) were detected in all the vaccinated groups but not in the controls.

In conclusion, the study was appropriately designed and executed. The lowest dose of antigen tested (G1) is the fixed dose proposed for Hepizovac. Clinical signs were not severe enough to allow analysis of the effect of vaccination, this is not unexpected for EHDV in cattle. The reduction of rectal temperature was statistically significant in the lowest dose group however the rectal temperature increases after challenge were overall minimal and the relevance of the result cannot be determined. Prevention of viraemia is supported by the results.

With respect to selection of the dose, while virus neutralising antibodies were numerically slightly lower in the lowest dose group (G1), it is considered that even in the low dose group neutralising antibodies were detected in almost all animals at three weeks post vaccination and none of the animals exhibited viraemia after challenge. It is therefore considered that the study provides sufficient data to support the claim for prevention of viraemia but not reduction of clinical signs, with an onset of immunity of 21 days for a vaccine formulated with a pre-inactivation EHDV-8 titre of $10^{5.5}$ $CCID_{50}$/ml.

Duration of immunity

No data on duration of immunity has been provided, this is indicated in section 3.2 of the SPC: "Duration of immunity: has not been established". In section 3.9, the following is additionally included: Revaccination: "Not established." This is acceptable for an Art. 25 marketing authorisation procedure since the benefit of the availability of the vaccine outweighs the risk of the absence of these data. Nevertheless, information on the duration of immunity is considered important and therefore the applicant should provide these data post-authorisation (specific obligation-SOB).

Maternally derived antibodies (MDA)

No data have been provided on the influence of maternal antibodies on efficacy of the vaccine. The SPC contains a warning sentence in section 3.4: "No information is available on the use of the vaccine in seropositive cattle, including those with maternal antibodies.". This is acceptable for an Art. 25

marketing authorisation procedure.

Interactions

No data on interactions have been provided, this is acceptable. An appropriate sentence is included in the product literature.

Clinical trials

The absence of clinical efficacy trials can be accepted in the framework of an Art. 25 procedure.

Overall conclusion on efficacy

The dose of $4x10^{5.5}$ $CCID_{50}$ was established based on a combined dose finding/onset of immunity study. The results of this pivotal combined safety and efficacy study in calves show that the product is effective for prevention of viraemia and reduction of clinical signs at the proposed dose of $4x10^{5.5}$ $CCID_{50}$/ml in cattle, with an onset of immunity of 3 weeks after completion of the primary vaccination schedule.

A duration of immunity has not been established, which can be accepted in an Art. 25 application in exceptional circumstances. However, the applicant is requested to provide data on duration of immunity post-authorisation (SOB). Data on the use in EHDV-seropositive animals, including those with maternally derived antibodies, are not available. This can be accepted in the framework of this application.

No clinical studies were undertaken, which is acceptable for an Art. 25 procedure.

In conclusion, the product has been shown to be efficacious for active immunisation of cattle from 2 months of age to prevent viraemia.

The product has been shown to have an onset of immunity 3 weeks after vaccination, which was demonstrated in animals of the minimum recommended age. A duration of immunity was not determined. The applicant is requested to conduct a study on duration of immunity and to provide the corresponding data as soon as available, as a specific obligation (SOB).

Part 5 – Benefit-risk assessment

Introduction

Hepizovac suspension for injection for cattle is a vaccine containing 4 x $10^{5.5}$ $CCID_{50}$ (50% cell culture infective dose) per dose of inactivated epizootic haemorrhagic disease virus (EHDV), serotype 8, strain EHDV8 SPA 2022/LCV_03 LCV Cod.:078, as active substance and aluminium hydroxide and purified saponin (Quil A), as adjuvants. The target species is cattle.

The primary vaccination schedule to be given to cattle from 2 months of age consists of two doses of 4 ml to be administered 3 weeks apart by the subcutaneous route.

At the time of submission, the applicant applied for the following indications:

For the active immunisation of cattle to prevent viraemia and to reduce clinical signs caused by serotype 8 of the epizootic haemorrhagic disease virus.

The proposed onset of immunity is 21 days after primary vaccination. No duration of immunity has been established.

The applicant proposed a withdrawal period of zero days.

Hepizovac is presented in packs containing 1 bottle of 52 ml, 100 ml or 252 ml.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances. Reduced data requirements therefore apply and have been considered in the assessment. These reductions relate to quality, safety and efficacy.

Benefit assessment

Direct benefit

The benefit of Hepizovac is its efficacy in the prevention of viraemia due to infection with EHDV serotype 8, which was investigated in one well designed pre-clinical study.

The onset of immunity is 3 weeks, a duration of immunity has not been established.

Additional benefits

Hepizovac provides a new treatment possibility for an emerging disease.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. There are minor deficiencies in the documentation and testing that can be accepted for this application under Art. 25.

Additionally, specific obligations as post-authorisation measures to the marketing authorisation under

exceptional circumstances are established as follows:

- The applicant is requested to provide information on completion of the development of a potency test on the finished product (specific obligation due by March 2027).
- The results of real-time stability studies for the finished product up to 21 months of storage should be provided to confirm the shelf life of 18 months. Any out of specification detected should be communicated immediately to the European Medicines Agency (specific obligation due by June 2026).
- The results of real-time stability studies for the antigen up to 12 months of storage should be provided. Any out of specification detected should be communicated immediately to the European Medicines Agency (specific obligation due by February 2026).
- A study on the duration of immunity should be conducted and data should be provided as soon as they become available (specific obligation due by February 2027).

Safety

Risks for the target animal

Administration of Hepizovac in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include transient swelling and nodules at the injection site and elevated temperatures.

The safety of Hepizovac in pregnant and lactating cattle is supported by results from studies performed with vaccines from the Bluevac BTV range. These vaccines are highly comparable in composition and posology and application did not result in any adverse effects in cattle in all stages of pregnancy nor was any effect observed on milk yield.

Risk for the user

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment

Hepizovac is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer:

No risks for the consumer have been identified. The withdrawal period is zero days.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal and the use and to provide advice on how to prevent or reduce these risks.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

The veterinary medicinal product is subject to a veterinary prescription.

Post-authorisation measures

Three quality and one efficacy post-authorisation measures (specific obligations) are identified and are considered justified in line with the application under Article 25 'Exceptional circumstances'.

Specific obligations to complete the post-marketing authorisation measures for the marketing authorisation under exceptional circumstances are detailed in Annex II of the product information and mentioned below.

Description	Due date
Completion of the development of a potency test on the finished product. Data should be provided as soon as available.	March 2027
Data from the stability studies (up to 18 months) should be provided upon completion, to confirm the shelf life for the inactivated EHDV antigen. Any out of specification result should be communicated immediately to the European Medicines Agency.	February 2026
Data from the stability studies (up to 21 months) should be provided upon completion, to confirm the accepted shelf life of 18 months for the finished product. Any out of specification detected should be communicated immediately to the European Medicines Agency. As soon as a potency test is available, this is expected to be included in the stability program. Stability data on the 52 ml presentation are expected.	June 2026
A study on the duration of immunity should be conducted and data should be provided as soon as they become available.	February 2027

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:

For the active immunisation of cattle to prevent viraemia and to reduce clinical signs caused by serotype 8 of the epizootic haemorrhagic disease virus.

Onset of immunity: 21 days after completion of the primary vaccination scheme.

Duration of immunity: has not been established.

Based on the data presented to date, the overall benefit-risk balance is considered positive.

The product has been shown to be efficacious for the active immunisation of cattle to prevent viraemia caused by serotype 8 of the epizootic haemorrhagic disease virus.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users when used as recommended.

As the application was submitted under Article 25, certain data on quality, safety and efficacy were not included in the dossier. However, the CVMP considered that the overall benefit of the availability of the veterinary medicinal product would outweigh the risk of absence of these data, also taking into consideration the risk management measures addressed above.

Conclusion

Based on the original data presented on quality, safety and efficacy, the Committee for Veterinary

Medicinal Products (CVMP) considers that the application for Hepizovac is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned veterinary medicinal product.

In addition, based on the review of data on the quality-related properties of the active substance, the CVMP considers that Inactivated epizootic haemorrhagic disease virus, serotype 8, strain EHDV8 SPA 2022/LCV_03 LCV Cod.:078 is to be qualified as a new active substance considering that no products are currently authorised in the EU containing EHDV antigen.