College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

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PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Butafosal 100 mg/ml + 0.05 mg/ml solution for injection for cattle, horses and dogs

PRODUCT SUMMARY

EU procedure number	NL/V/0418/001/DC
Name, strength and pharmaceutical form	Butafosal 100 mg/ml + 0.05 mg/ml solution for injection for cattle, horses and dogs
Applicant	Alivira Animal Health Limited 2ndFloor, 1-2 Victoria Buildings, Haddington Road, Dublin 4, 004 XN32, Ireland
Active substance(s)	Butaphosphan, Cyanocobalamin (Vitamin B12)
ATC vetcode	QA12CX99
Target species	Cattle, horses and dogs
Indication for use	<u>All target species:</u> - Supportive treatment and prevention of hypophosphatemia and/or cyanocobalamin (vitamin B12) deficiency. <u>Cattle:</u> - Supportive treatment to restore rumination following surgical treatment of displaced abomasum associated with secondary ketosis. - Complementary treatment of parturient paresis in addition to Ca/Mg therapy. - Prevention of ketosis development, if administered before calving. <u>Horses:</u> Adjunctive therapy in horses suffering from muscular exhaustion.

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Alivira Animal Health Limited	MRP/DCP
Publicly available assessment report	

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	Generic application in accordance with Article 18 of Regulation (EC) 2019/6 as amended.
Reference product (RP)	CATOSAL, Oplossing voor injectie
Marketing authorisation holder	Elanco Animal Health GmbH
MS where the RP is or has been authorised	NL
Marketing authorisation number EU procedure number	REG NL 6025
Date of authorisation	7th of June 1995
Date of completion of the original decentralised procedure	30th of April 2025
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	BE, DE, ES, FR, IT
Concerned Member States for subsequent recognition procedure	-
Withdrawn CMS during original decentralised procedure	-

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The veterinary medicinal product is a parenteral aqueous solution that contains Bustaphosphan (100 mg/mL) and Cyanocobalamin (0.050 mg/mL) as active substances. The excipients are Benzyl alcohol, Sodium hydroxide and Water for injections.

The container/closure system is an amber colour glass vial, closed with a rubber stopper and an aluminium overseal. No relevant differences are observed in respect to the container closure system of the reference product. The product is packed in a multidose container and presented in 3 filling volumes: 50, 100 and 250 mL.

The generic VMP is an established pharmaceutical form and, overall, its development is adequately described in accordance with the relevant European guidelines. The choice of the formulation is well justified. The qualitative composition is not the same as the one the reference product. The preservative of the reference product, n-butanol, has been replaced by Benzyl alcohol in the generic VMP. The change of the preservative and the concentration of Benzyl alcohol in the generic VMP have been properly justified during development studies and it is supported by data from preservative efficacy tests conducted as per Ph.Eur. 5.1.3. It is demonstrated that the osmolality, pH and viscosity of the test product is similar to those of the reference product.

A Bioequivalence study is not necessary from a quality point of view as per section 7.1.a and 7.1.b of the EMA Guideline on the conduct of bioequivalence studies for veterinary medicinal products. Additional comparison demonstrates that the relevant physicochemical properties of test and reference product are similar in spite of the differences in composition. Therefore, the waiver of a bioequivalence study can be granted.

B. Description of the manufacturing method

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

The manufacturing process description, including IPCs, has been adequately provided.

A batch range from 100L to 1000L has been proposed for commercial-scale manufacturing and information on batch formula for both the lowest and the highest batch size has been provided. The applicant has adequately justified that the non-standard manufacturing process can be actually considered as standard in this particular case, in view of the experience of the manufacturing site with similar aseptic products. The proposed batch size range can be, hence, accepted.

Process validation data on 3 commercial-size batches (100 L) of the VMP packed in 50 mL bottles and 3 commercial-size batches (100 L) of the VMP packed in 250 mL bottles have been provided. Overall, the manufacturing process is considered well validated for the aseptic manufacturing of the VMP in batches of 100 L. The applicant will validate the first three commercial batches of the 1000 L batch size post-authorisation. This is accepted as the manufacturing can be considered as standard.

The aseptic manufacturing involves a sterile filter, which has been well validated.

C. Control of starting materials

The VMP has two active substances: Butaphosphan and Cyanocobalamin.

Butaphosphan is not described in any relevant Pharmacopoeia. This active substance is manufactured in accordance with the principles of good manufacturing practice. An ASMF is used for the drug substance. The latest available version of the AP-ASMF is provided by the DPM.

The specification of the active substance Butaphosphan is acceptable and in line with the ASMF. CoA's for three batches of the drug substance Butaphosphan controlled by the DPM have been presented. Compliance with the proposed specification is demonstrated.

The Cyanocobalamin drug substance is described in the European Pharmacopoeia and manufactured in accordance with the principles of good manufacturing practice. The quality of this active substance is controlled with a CEP.

The specification of the Cyanocobalamin is adequately set. The validation of the analytical methods is acceptable. CoAs of the drug substance Cyanocobalamin controlled by the DPM are provided and demonstrate compliance with the proposed specification.

All the listed excipients are compendial and a reference to a Ph. Eur. monograph has been provided.

Information about the container of the drug substance Cyanocobalamin has been presented as this is not covered by the CEP. A specification is provided. The analytical method for identification of the aluminium is not accepted and will be replaced. A commitment is submitted.

Specification, technical drawings and CoAs are presented for all materials of the primary packaging of the finished product. The specification of the container closure system of the finished product is accepted. The proposed bracketing approach for the 100 mL container is also accepted.

None of the starting materials used are affected by the Note for Guidance on TSE/BSE.

D. Control tests on intermediates products

N.A.

E. Control tests on the finished product

The finished product specification controls the relevant parameters for the pharmaceutical form, a parental solution, as per VICH GL 39 and Ph. Eur. 0520.

The limits of the specification at release and shelf-life are acceptable and justified with the data provided.

The analytical methods of the drug product specification have been adequately described and validated.

Batch analysis of the finished product at release has been performed with 3 batches of the product in the 50 mL bottles and 3 batches for the product in the 250 mL bottles (100 L each). All batches comply with the specification at release.

F. Stability tests

The information on re-test period of the Butaphosphan is in line with the ASMF of the active substance manufacturer. For the re-test period of Cyanocobalamin reference is made to the CEP, which does not specify any re-test period. Therefore, stability data on Cyanocobalamin was requested and is provided except for the specification limits for microbial control and

bacterial endotoxins. The applicant confirms that compliance with the specification limits for these tests immediately prior to the manufacture of the VMP will be stated. The storage claim for the drug substance can be accepted.

Stability data have been provided on the 50 mL and the 250 mL presentations of the finished product (3 commercial-size batches of 100 L for each presentation) for 6 months under accelerated stability condition, 12 months under intermediate stability condition and 24 months under long-term stability condition. Accelerated and long-term stability testing have been conducted with batches in upright and inverted position. Overall, stability results are within the proposed specification limits. Based on the provided data, the proposed shelf-life of 24 months and the claim that the VMP does not require any special temperature storage condition are accepted.

The claim of 28 days of in-use shelf life after first opening is based on the demonstration of stability for 6 batches (3 batches in 50 mL bottles, 3 batches in 250 mL bottles) at the beginning of shelf life. The provided in-use stability studies have been performed with the batches submitted to accelerated (upright and inverted) and long-term conditions (upright) and a preservative efficacy test (PET) has been included. All results are within the proposed specification limits. The proposed in-use shelf life of 28 days after first opening can be accepted.

A photostability study has been conducted as per conditions of the VICH GL5 on one batch of the finished product. The product remains stable when packed in the proposed amber glass bottle and exposed to light. The storage claim “Store in the original packaging in order to protect from light” can be accepted.

3. SAFETY DOCUMENTATION (safety and residues tests)

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and essential similarity to a reference VMP has been demonstrated, results of safety and residue tests are not required.

The safety and residue aspects of this VMP are identical to the reference VMPs.

Warnings and precautions as listed on the product literature are the same as those of the reference VMP and supplemented with additional statements, based on increased knowledge and the current state of science. This information is considered adequate to ensure safety of the product to users / the environment / consumers.

A. Safety tests

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that the active substance cyanocobalamin and the excipient benzyl alcohol may cause hypersensitivity reactions. Furthermore the risk of accidental self-injection should be taken into account.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the VMP.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because

The VMP will be used to treat a small number of animals in a flock or herd.

B. Residues documentation

Residue tests

No residue depletion studies were conducted because essential similarity to a reference VMP has been demonstrated. Furthermore only IV administration is authorised for cattle and horse, so injections site residues are not applicable.

Maximum Residue Limits

The active substances are included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance	**Marker residue**	**Animal Species**	**MRL**	**Target tissues**	**Other provision**
Butafosfan	Not applicable	All mammalian food producing species	No MRL required	Not applicable	No entry
Cyanocobalamin (vit B12)	Not applicable	All food producing species	No MRL required	Not applicable	No entry

Withdrawal Periods

Based on the data provided above, the following withdrawal periods are justified:

Cattle and horses:

Meat and offal: Zero days.

Milk: Zero hours.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and essential similarity to a reference VMP has been demonstrated, efficacy studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

This section contains information on significant changes, which have been made after the original procedure, which are important for the quality, safety or efficacy of the VMP.

None.