Public Assessment Report

Scientific discussion

Butasal-100
Solution for injection
100 mg/ml + 0,05 mg/ml

Butafosfan
Cyanocobalamin
(Vitamin B12)

Marketing Authorisation Holder:
Interchemie Werken De Adelaar Eesti AS

Updated: 04.03.2025

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, Estonia has granted a marketing authorisation for Butasal-100, solution for injection, 100 mg/ml + 0,05 mg/ml from the marketing authorisation holder Interchemie Werken De Adelaar Eesti AS. A national marketing authorisation was granted 5.05.2020. The Mutual Recognition Procedure EE/V/0106/001/MR was finalised 31.03.2021.

The veterinary medicinal product is indicated for supportive treatment and prevention of hypophosphatemia and/or cyanocobalamin (vitamin B12) deficiency in all target species; for supportive treatment to restore rumination following surgical treatment of displaced abomasum associated with secondary ketosis, for complementary treatment of parturient paresis in addition to Ca/Mg therapy and for prevention of ketosis development in cattle; for adjunctive therapy suffering from muscular exhaustion in horses.
Target species: horse, cattle, dog.
A comprehensive description of the indications and posology is given in the SPC.

Butasal-100 is a product which is based on the reference product Catosal solution for injection, 100 mg/ml + 50.0 µg/ml, authorised in Czech Republic by company Bayer s.r.o. This formulation has been used in Europe since 1994. The application is considered as hybrid according to the Article 13(3) of of Directive 2001/82/EC, as amended.

Pharmacovigilance

The pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as solution for injection containing 100 mg/ml + 0,05 mg/ml of Butafosfan and Cyanocobalamin as active substances and Benzyl alcohol as preservative. Other ingredients are sodium citrate, citric acid and water for injections, commonly used in the parenteral formulations.
Butasal-100 solution for injection is red solution packaged in 100 ml amber glass vial, closed with bromobutyl rubber stoppers and secured with an aluminium cap or flip-off cap with polypropylene cover.

II.2 Drug Substance

Butasal-100 contains three active substances: Butafosfan and Cyanocobalamin.
Butaphosphan is not listed in any pharmacopoeia (IP, BP, USP and Ph. Eur.). An ASMF

in CTD-format has been provided for the butaphosphan:
Cyanocobalamin is included in European Pharmacopoeia, monograph 0547, in force.
The Cyanocobalamin manufacturer holds a valid Ph. Eur. CEP issued by EDQM.
The packaging materials and re-test periods of the substances are in line with the conditions of the current ASMF and CEP.

II.3 Veterinary Medicinal Product

The product is manufactured by Interchemie Werken De Adelaar Eesti AS.
The finished product is manufactured by sterile filtration in a combination with aseptic processing.
Validation of the manufacturing process has been performed with three maximum scale batches.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented and are considered acceptable.
Batch analysis has been performed on three commercial batches. The batch analysis results show that the finished product meets the proposed specifications.
The conditions used in the stability studies are according to the VICH stability guideline. 24 months stability data under long-term/intermediate and 6 months data under accelerated conditions are presented on three production scale batches. Shelf-life of 24 months for the finished product is claimed and is acceptable. The accepted storage conditions are: "Do not store above 25 °C. Keep the vial in the outer carton in order to protect from light." Shelf-life after first opening of the immediate packaging is 28 days.

III. SAFETY AND RESIDUE ASPECTS

III.1 User Safety

As Butasal-100 has been demonstrated to be bioequivalent with Catosal, the potential impact of the active substances in respect of user safety will be the same for both the generic (hybrid) and reference product.
The generic product Butasal-100 and the reference product Catosal contain different excipients. The excipients in Butasal-100 (benzyl alcohol, sodium citrate, citric acid and water for injections) are well established and have an extensive history of use in parenteral preparations. Therefore additional sentences were added by the applicant under the section "Special precautions to be taken by the person administering the veterinary medicinal product to animals" and are adequate to ensure safety to users of the product:
"Benzyl alcohol may cause hypersensitivity (allergic reactions). People with known hypersensitivity to benzyl alcohol should avoid contact with the product."
"The product can cause skin, eye or mucous membranes irritation. Dermal, mucous membranes and ocular exposure should therefore be avoided. In case of accidental dermal, mucous membranes or ocular exposure rinse the skin and/or the eye with water."
"Do not eat, drink or smoke while handling this product."
"Wash hands after use of the veterinary medicinal product."

III.2 Ecotoxicity/environmental risk assessment (ERA)

The Applicant has referred to the decision tree in the Guideline on Environmental impact assessment for veterinary medicinal products Phase I (EMEA/CVMP/ERA/418282/2005-rev.1)
The environmental risk assessment can be stopped at phase I for all target species.
Based on data provided, it is accepted that the use of this product is unlikely to represent an unacceptable risk to the environment when used according to the instructions stated in the SPC.

III.3 Residue documentation

MRLs
The active substances are listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 and no MRL is required for any of the food producing species.

Withdrawal Periods
Given the MRL status of each of the substances ('no MRL required'), a zero day withdrawal period can be accepted for meat and offal and zero hours withdrawal period for milk can be accepted for horses and cattle.

Conclusion
Since the application was submitted in accordance with Article 13(3) of Directive 2001/82/EC as amended, for a generic (hybrid) veterinary product, the same withdrawal periods as approved for the reference product were established.

IV. CLINICAL ASPECTS

As this application is submitted in accordance with Article 13(3) of Directive 2001/82/EC as amended, for a generic (hybrid) veterinary medicinal product, information on the clinical efficacy is not required.

IV.A Pre-Clinical Aspects

Pharmacodynamics
No data were submitted under this section. Applicant cited the pharmacodynamic data for the reference product.

Pharmacokinetics
No data were submitted under this section. Applicant cited the pharmacokinetic data for the reference product.

IV.B Clinical Aspects

Since this application is submitted in accordance with Article 13(3) of Directive 2001/82/EC as amended, for a generic (hybrid) veterinary medicinal product, information on the clinical efficacy is not required. The efficacy claims for the generic product are equivalent to those of the reference product.

Conclusion

The applicant has proved the bioequivalence with the reference product according to the guideline EMEA/CVMP/016/00-Rev.2. It is accepted that no additional documentation on pre-clinical and clinical data is required.

Based on data provided, it is accepted that the use of this product is unlikely to represent an unacceptable risk to the animals when used according to the precautions stated in the SPC. The efficacy of the product is demonstrated for the reference product and consequently applies for generic product Butasal-100, and therefore the benefit/risk ratio is evaluated as positive.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

VI. PROCEDURAL STEPS TAKEN AND SCIENTIFIC INFORMATION AFTER THE END OF THE MR PROCEDURE EE/V/0106/001/MR

Application reference	Scope	Date of opinion/acceptance	Product Information affected
NP: 19559	Submission of a group of variations to the term of one marketing authorisation (national procedure). All proposed changes have been agreed on during the MR procedure - EE/V/0106/001/MR.	06.05.2021	Yes: SPC, PL, LAB
EE/V/0106/001/IA/001/G	Notification about change in the responsible person for Pharmacovigilance (QPPV).	21.01.2021	No
ID_2698	C.1 Change(s) in the name or address or contact details of a qualified person for pharmacovigilance (QPPV)	30.09.2022	No
ID_7714	C.10.a) Administrative information concerning the holder's representative (RO)	28.04.2023	National RO
ID_7952	C.6 Introduction of a summary of the PSMF or changes to the summary of the PSMF not already covered elsewhere in this Annex	05.06.2023	No
ID_9206	C.9 Editorial changes to SPC, package leaflet or labelling if inclusion in an upcoming procedure is not possible (FI)	24.07.2023	National FI
ID_10498	C.10.a) Administrative information concerning the holder's representative (BE, NL)	13.10.2023	National BE, NL
ID_11192	B.44 Submission of a new or updated Ph. Eur. CEP from an already approved manufacturer for a non-sterile active substance; starting material, reagent or intermediate used in the manufacturing process of the active substance; or excipient B.47.b) Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.3.d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) of an active substance, a starting material or an intermediate or reagent used in the manufacturing process of the active substance	17.11.2023	No

ID_12776	C.1 Change(s) in the name or address or contact details of a qualified person for pharmacovigilance (QPPV), C.6 Introduction of a summary of the PSMF or changes to the summary of the PSMF not already covered elsewhere in this Annex	28.02.2024	No
EE/V/0106/A/002/G	2 x F.II.b.3. a Minor change in the manufacturing process F.II.e.1.b. 2 Sterile medicinal products and biological/ immunological medicinal products	15.05.2024	Yes: SPC, PL, LAB
ID_17886	B.21 - Replacement or addition of a secondary packaging site of a finished product B.39 - Change in any part of the primary packaging material not in contact with the finished product formulation	03.01.2025	No
EE/V/0106/A/004/G	Harmonisation of the generic/hybrid product according to article 71(1) after SPC harmonisation of the reference product One-off alignment of the product information with version 9.0 of the QRD templates	10.02.2025	Yes: SPC, PL, LAB
EE/V/0106/A/003/G	F.I.f.1 Substantial changes in the updated version of the ASMF or the active substance part of the dossier. F.I.d.1.c Change in the re-test period/storage period of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier. Extension or introduction of a re-test period/storage period supported by real time data. F.I.b.2.b Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate.	14.02.2025	No