College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Addimag 160/84 solution for infusion for cattle
Addimag 240/126 solution for infusion for cattle

PRODUCT SUMMARY

EU procedure number	NL/V/0352/001-002
Name, strength and pharmaceutical form	Addimag 160/84 solution for infusion for cattle Addimag 240/126 solution for infusion for cattle
Applicant	Alfasan Nederland B.V. Kuipersweg 9 3449 JA Woerden The Netherlands
Active substance(s)	Calcium gluconate monohydrate and Magnesium chloride hexahydrate
ATC vetcode	QA12AX
Target species	Cattle
Indication for use	For the treatment of clinical hypomagnesaemia (grass tetany) accompanied by deficiency of calcium and for the treatment of clinical hypocalcaemia (milk fever) complicated by deficiency of magnesium.

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*	Addimag 160/84: Generic application made in accordance with Article 13(1) of Directive 2001/82/EC Addimag 240/126: Hybrid application made in accordance with Article 13(3) of Directive 2001/82/EC
Reference product (RP)	Glucamagnesium oplossing voor infusie voor runderen
Marketing authorisation holder	Bridgefarma BV
MS where the RP is or has been authorised	
Marketing authorisation number	REG NL 3567
Date of authorisation	16 January 1992
Date of completion of the original decentralised procedure	22 December 2021
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, HR, IE, IS, IT, LT, LU, LV, NO, PL, PT, RO, SE, SI, SK, UK(NI).
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Withdrawn CMS during original decentralised procedure	-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

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the reactions observed are indicated in the SPC.

The VMP is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the VMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

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

A. Product description

The VMP concerns a solution for infusion for cattle containing either 160+84 mg/ml or 240+126 mg of calcium gluconate monohydrate + magnesium chloride hexahydrate as active substances.

The VMP contains boric acid, glucose monohydrate and water for injection as excipient.

The solution for infusion is packed in 500 ml or 750 ml clear polypropylene bottles fitted with bromobutyl stoppers and secured with aluminium caps.

The product represents an established pharmaceutical form and their development is adequately described in accordance with the relevant European guidelines.

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The VMP is manufactured according to a standard manufacturing process using conventional manufacturing techniques.

Process validation reports for each strength have been included. The manufacturing process itself is completely validated. The process validation data show that the formulation and manufacturing process of the VMP is fully under control to produce a product that meets the pre-set specifications and that no trends are present.

C. Production and control of starting materials

The active substances calcium gluconate monohydrate and magnesium chloride hexahydrate are established active substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

Each active substance specification is considered adequate to control the quality of the respective material.

Batch analytical data demonstrating compliance with this specification have been provided.

The excipients are in conformity with the requirements of their Ph. Eur. monographs.

The polypropylene bottles and bromobutyl stoppers are in conformity with the Ph. Eur. requirements.

There are no substances within the scope of the TSE guideline present or used in the manufacture of this VMP.

D. Control tests carried out on isolated intermediates during the manufacturing process

Not applicable.

E. Control tests on the finished product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification and their limits have been justified and are considered appropriate to adequately control the quality of the VMP.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability tests

The Certificates of Suitability for Calcium gluconate monohydrate and Magnesium chloride hexahydrate confirm the retest period of 60 months respectively 36 months of these active substance without specific storage conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines demonstrating the stability of the VMP throughout the claimed shelf life of 36 months respectively 24 months for Calcium gluconate/Magnesium chloride solution for infusion 160/84 mg/ml and 240/126 mg/ml when stored under the approved conditions..

G. Other information

Not applicable.

3. SAFETY DOCUMENTATION (safety and residues tests)

Addimag 160/84: As this is a generic application made in accordance with Article 13(1) of Directive 2001/82/EC and essential similarity to a reference VMP has been demonstrated, results of safety tests are not required.

Addimag 240/126: As this is a hybrid application made in accordance with Article 13(3) of Directive 2001/82/EC and essential similarity to a reference VMP has been demonstrated, results of safety tests are not required.

The safety aspects of these VMPs are identical to the reference VMP.

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

Pharmacological studies

The applicant has provided bibliographical data which show that:

- Calcium is an essential element that is required for normal nerve and musculoskeletal function, cell membrane and capillary permeability and activation of enzymatic reactions. Only free ionised calcium in the blood is biologically active.

  Approximately 99% of total body calcium is found in bone and teeth. The remaining 1% is found mainly in the extra-cellular fluid. Calcium is eliminated mainly through the faeces with small amounts eliminated in the urine

- Magnesium is a cofactor in a number of enzyme systems and plays a role in muscular excitement and neurochemical transmission. In the heart magnesium leads to delayed conduction. Magnesium stimulates the secretion of parathyroid hormone and therefore regulates serum calcium levels.

  In adult animals, around 60% of magnesium is found in bone where it is relatively difficult to mobilize. It is excreted by the kidneys at a rate proportional to the serum concentration and glomerular filtration

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that no ‘special precautions to be taken by the person administering the veterinary medicinal product to animals’ are necessary.

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 the residue levels in edible tissues are expected to be the same as that of the reference product.

Maximum Residue Limits

Calcium gluconate and Magnesium chloride 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**	**Therapeutic Classification**
Calcium gluconate	Not Applicable	All food producing species	No MRL required	Not Applicable	No entry	No entry
Magnesium chloride	Not Applicable	All food producing species	No MRL required	Not Applicable	No entry	No entry

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for meat in cattle and zero hours for milk are justified.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

Addimag 160/84: As this is a generic application made in accordance with Article 13(1) of Directive 2001/82/EC and essential similarity to a reference VMP has been demonstrated, results of safety tests are not required.

Addimag 240/126: As this is a hybrid application made in accordance with Article 13(3) of Directive 2001/82/EC and essential similarity to a reference VMP has been demonstrated, results of safety tests 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