College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

**DECENTRALISED PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## Calcibel 240/60/60 mg/ml solution for infusion for horses, cattle, sheep, goats and pigs

**Created: December 2019**

# MODULE 1

## PRODUCT SUMMARY

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|---|---|
| EU Procedure number | NL/V/0197/001/DC |
| Name, strength and pharmaceutical form | Calcibel 240/60/60 mg/ml solution for infusion for horses, cattle, sheep, goats and pigs |
| Applicant | Bela-Pharm GmbH & Co. KG<br>Lohner Straße 19<br>49377 Vechta<br>Germany |
| Active substance(s) | Calcium gluconate, Magnesium chloride hexahydrate , Boric acid |
| ATC Vetcode | QA12AX (calcium , combination with other pharmaceuticals) |
| Target species | Horse, cattle, sheep, goat, pig |
| Indication for use | Acute hypocalcaemic conditions |

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| Calcibel 240/60/60 mg/ml solution for infusion for horses, cattle, sheep, goats and pigs | NL/V/0197/001/DC |
| Bela-Pharm GmbH & Co. KG | DCP |
| | Publicly available assessment report |

# MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

# MODULE 3

## PUBLIC ASSESSMENT REPORT

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| Legal basis of original application | Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended. |
| Date of completion of the original decentralised procedure | 27 January 2016 |
| Date product first authorised in the Reference Member State (MRP only) | N/A |
| Concerned Member States for original procedure | AT, CY, CZ, DK, EL, ES, FI, HR, HU, IE, PL, PT, RO, SE, SI, SK, UK |

## I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product 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 product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

Calcibel 240/60/60 mg/ml is a hybrid of the reference product C-B Gluconat 24% plus 6% Infusionslösung zur langsamen intravenösung zur langsamen intravenösen Anwendug für Pferde, Rinder, Schafe, Ziegen, Schweine, registered in Germany since 2 April 2004 (marketing authorisation number: 6933364.00.00) of MAH Bela Pharm GmbH & Co. KG.

## II. QUALITY ASPECTS

### *A. Qualitative and quantitative particulars*

The application concerns Calcibel 240/60/60 mg/ml solution for infusion for horse, cattle, sheep, goat and pig, containing 240 mg/ml of calcium cluconate for injection, 60 mg/ml of magnesium chloride hexahydrate and 60 mg/ml of boric acid.

The product contains only water for injection as excipient.

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

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

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## *B. Method of Preparation of the Product*

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

A process validation report has been included. The manufacturing process itself is completely validated. The process validation data show that the formulation and manufacturing process of the product Calcibel 240/60/60 mg/ml solution for infusion is fully under control to produce a product that meets the pre-set specifications and that no trends are present.

Validation data regarding the holding times after filling and before and before final sterilisation should be provided.

The tests performed during production are described. Adequate in-process specifications are provided. IPC sampling details ae provided.

## *C. Control of Starting Materials*

The active substances calcium cluconate for injection, magnesium chloride hexahydrate and boric acid 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.

Water for Injection is in conformity with the requirements of their Ph.Eur. monographs.

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

## *D. Control on intermediate products*

Not applicable.

## *E. Control Tests on the Finished Product*

The finished product specification controls the relevant parameters for the pharmaceutical form. The specification is considered appropriate to adequately control the quality of the product.

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*

The Certificates of Suitability for magnesium chloride hexahydrate and boric acid confirm the retest period of 36 months of these active substance without specific storage conditions.

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Additional stability results for calcium gluconate monohydrate demonstrate a retest period of 60 months without specific storage conditions

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout the claimed shelf life of 36 months with the storage restriction *"Do not refrigerate or freeze. Protect from frost."*

### *G. Other Information*

None.

## III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a hybrid application according to Article 13(3), and Calcibel 240/60/60 mg/ml is a hybridof the reference product C-B Gluconat 24% plus 6%, results of pharmacological and toxicological tests are not required.

### *User Safety*

The applicant has provided a user safety assessment in compliance with the relevant guideline. The user risk warmings of the reference product C-B Gluconat 24% plus 6% are retained for the hybrid product Calcibel 240/60/60 mg/ml. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

### *Environmental Risk Assessment*

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines. The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment.

### *III.B Residues documentation*

### *Residue Studies*

No residue depletion studies were conducted because Calcibel 240/60/60 mg/ml is a hybrid of the reference product C-B Gluconat 24% plus 6%. In addition literature data was presented by the applicant.

### *MRLs*

Calcium gluconate, magnesium chloride and boric acid are included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

| **Active substance** | **Animal Species** | **MRL (µg/kg)** | **Target Tissues** |
|---|---|---|---|
| Calcium gluconate | All food producing species | No MRL required | Not applicable |
| Magnesium chloride | All food producing species | No MRL required | Not applicable |
| Boric acid and borates | All food producing species | No MRL required | Not applicable |

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### *Withdrawal Periods*

Based on the data provided above, a withdrawal period of 0 days for meat in cattle, sheep, goat, horse, pig and 0 days for milk in cattle, sheep, goat, horse are justified.

## IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a hybrid application according to Article 13(3), and Calcibel 240/60/60 mg/ml is an autogeneric of the reference product C-B Gluconat 24% plus 6%, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

### *IV.A Pre-Clinical Studies*

### *Tolerance in the Target Species of Animals*

Post marketing information has been provided which shows that adverse events were only reported in the bovine species and the incidence of adverse reactions was calculated to be 0.0009%.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

### *IV.B Clinical Studies*

Since this is a hybrid application no data were presented.

## V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product 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 product for humans and the environment is acceptable.

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# MODULE 4

## POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicines Agencies website (www.HMA.eu ).

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 product.

| **Summary of change (Application number)** | **Section updated** | **Approval date** |
|---|---|---|
| Update CEP from an already approved manufacturer (NL/V/0197/001/IA/001) | N/A | 18 October 2017 |
| 2x (grouped variation) Update CEP from an already approved manufacturer (NL/V/0197/IA/002/G) | N/A | 14 March 2019 |
| Renewal – NL/V/0197/001/R/001 | N/A | 27 January 2021 |