Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Sterofundin ISO B. Braun Vet Care
Infusionslösung für Rinder, Pferde, Schafe, Ziegen, Schweine, Hunde und Katzen

Date: 31 March 2025

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0193/001/DC
Name, strength and pharmaceutical form	Sterofundin ISO B. Braun Vet Care Solution for Infusion for cattle, horse, sheep, goat, pig, dog and cat
Applicant	B. Braun Melsungen AG Carl-Braun-Str. 1 34212 Melsungen Germany
Active substance(s)	Sodium chloride Potassium chloride Magnesium chloride hexahydrate Calcium chloride dihydrate Sodium acetate trihydrate L-Malic acid (E296)
ATC Vetcode	QB05BB01
Target species	Cattle, Horses, Sheep, Goats, Pigs, Dogs, Cats
Indication for use	Dog and cat: Correction of hypotonic and isotonic dehydration, for fluid and electrolyte replacement under the conditions of undisturbed acid-base balance or mild acidosis. Cattle, horse, sheep, goat and pig: Correction of hypotonic and isotonic dehydration and for fluid and electrolyte replacement under the conditions of undisturbed acid-base balance. All target species: Short term intravascular volume replacement.

MODULE 2

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).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	3rd July 2019
Concerned Member States for original procedure	AT, ES and PT
Concerned Member States for subsequent recognition procedure	BE, DK, FR, IE, IT, NL, PL, RO and SE

*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

I. 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.
The efficacy of the VMP was demonstrated according to the claims made in the SPC.
It has been shown that the VMP can be safely used in the target species. Adequate information on adverse effects and warnings to ensure efficacious and safe use are provided 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 overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The VMP contains 6.80 mg/l sodium chloride, 0.30 mg/l potassium chloride, 0.20 mg/l magnesium chloride hexahydrate, 0.37 mg/l calcium chloride dihydrate, 3.27 mg/l sodium acetate trihydrate and 0.67 mg/l L-Malic acid as active substances. Sodium hydroxide for pH-adjustment and water for injections are used as excipients.

The container/closure system consists of low density polyethylene bottles with a high density polyethylene closure cap. In between an elastomeric latex free disk is placed. Bottles of 250, 500 and 1000 ml capacity are applied. The pack sizes are 10 x 250 ml, 10 x 500 ml and 10 x 1000ml.

The choice of the formulation and the absence of preservatives are justified.

The VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

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

The VMP is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substances are sodium chloride, potassium chloride, magnesium chloride hexahydrate, calcium chloride dihydrate, sodium acetate trihydrate and L-Malic acid. The active substances are established substances described in the European Pharmacopoeia or in the German Pharmacopoeia respectively in case of L-Malic acid. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substances specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with this specifications have been provided.

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on intermediate products

No intermediates are generated in the manufacturing process.

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 sites have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the VMP throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Toxicological Studies

The application is made according to Article 13a of Directive 2001/82/EC. Hence, the applicant did not provide data of pre-clinical tests for safety assessment. Instead, the applicant has provided relevant bibliographical data, including publically available scientific literature and research articles as well as excerpts from textbooks and online databases to substantiate the single dose, repeated dose, and reproductive toxicity as well as possible mutagenicity and carcinogenicity of the active ingredients of Sterofundin ISO B. Braun Vet Care.
Generally, the availability of toxicological data of the Sterofundin ISO B. Braun Vet Care constituents throughout public literature is rather low. Thus, for some toxicological endpoints relevant data could not be provided for every constituent. However, considering the nature of the constituents of Sterofundin ISO B. Braun Vet Care and the long and safe history of use of similar products in human and veterinary medicine, the form and extent of the safety assessment of Sterofundin ISO B. Braun Vet Care are acceptable. No NOAELs or other points of departure were derived for the constituents of Sterofundin ISO B. Braun Vet Care, due to their essential functions and natural occurrence in animal and human organisms.

Sterofundin ISO B. Braun Vet Care contains sodium, potassium, magnesium, calcium, and chloride at concentrations of physiological blood levels and is an isosmotic solution for infusion. Due to its intended use for correction of hypotonic and isotonic dehydration, it can be assumed that physiological blood levels of sodium, potassium, magnesium, calcium and chloride will most likely not be exceeded under treatment with Sterofundin ISO B. Braun Vet Care according to the SPC. Following potential transient excess, physiological blood levels would be restored rapidly and be maintained due to distribution and renal excretion, provided regular kidney, endocrine, and circulatory functions. Malate and acetate are distributed and metabolised rapidly and extensively following infusion, leading to the rapid formation of carbon dioxide and bicarbonate. Sterofundin ISO B. Braun Vet Care is intended to achieve or maintain physiological conditions after loss of extracellular fluids and will only be used as long as parenteral application of fluid and electrolytes is required in individual animals.

The toxic effects of the individual constituents of Sterofundin ISO B. Braun Vet Care described in the provided literature are due to excess and hyperosmolarity and do not reflect the intended dosage and duration of application nor the concentrations of the constituents in Sterofundin ISO B. Braun Vet Care. No toxic effects for target animals and users are to be expected from the use, when Sterofundin ISO B. Braun Vet Care is applied according to the SPC.

User Safety

The applicant has provided a user risk assessment, which is essentially in compliance with the relevant guidelines and which demonstrates that no relevant risks arise from the use of Sterofundin ISO B. Braun Vet Care, when used according to the product literature.

Consequently, no additional risk management communications were introduced to the product literature

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 active substances are natural substances, the use of which will not alter the concentration or distribution of the substance in the environment.

In conclusion, there are no concerns about the safety of Sterofundin ISO B. Braun Vet Care originating from the provided toxicological literature, when it is applied according to the SPC. The introduction of additional risk management phrases in the product literature to assure user safety of Sterofundin ISO B. Braun Vet Care is not required. The VMP does not pose a risk to the environment, when used according to the SPC.

III.B Residues documentation

Residue Studies

The application is made according to Article 13a of Directive 2001/82/EC. Thus, this application refers to published scientific literature.

MRLs

The active substances contained in Sterofundin ISO are listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 with the following entries:

Pharmacologically active substance	Marker Residue	Animal Species	MRL	Target Tissues	Other Provisions Art 14(7) of Reg. (EC) No 470/2009
Sodium chloride	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY
Calcium chloride	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY
Magnesium chloride	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY
Malic acid	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY
Substances with E number	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	Only substances approved in foodstuffs for human consumption with the exception of preservatives listed in Part C of annex III to the council Directive 95/2 EC

Potassium chloride and sodium acetate as substances with E numbers (E508 and E262, respectively) are covered via the entry in the last line.
Furthermore, the VMP contains water for injection, which is considered as not falling within the scope of Regulation (EC) No. 470/2009 (EMA/CVMP/519714/2009–Rev.38). Sodium hydroxide is used for pH adjustment only. The substance is approved in foodstuffs for human consumption (E524) and is covered by the entry in the last line in the table above.

Withdrawal Periods

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

Cattle, horses, sheep, goats, pigs:
Meat and offal: Zero days.

Cattle, horses, sheep, goats:
Milk: Zero hours.

IV. CLINICAL ASSESSMENT (EFFICACY)

Sterofundin ISO B. Braun Vet Care (here after named Sterofundin ISO) is a solution for infusion for cattle, horses, sheep, goats, pigs, dogs, and cats containing sodium chloride, potassium chloride, magnesium chloride hexahydrate, calcium chloride dihydrate, sodium acetate trihydrate, and L-malic acid. The VMP is intended for correction of hypotonic and isotonic dehydration, for fluid and electrolyte replacement, and for fluid substitution under the condition of undisturbed acid-base balance or mild acidosis. The veterinary medicinal product may also be used in conditions requiring a short term intravascular volume replacement.

Since the components of this solution have been used for many decades in veterinary and human medicines respectively, and similar products are marketed in several European countries, their pre-clinical properties and clinical use are reported comprehensibly by published scientific literature and review articles.

IV.A Pre-Clinical Studies
Pharmacology

The applicant has provided bibliographical data to demonstrate pharmacodynamic effects of the ingredients of Sterofundin ISO B. Braun Vet Care.

The amounts of the electrolytes Na^+, K^+, Ca^{2+}, and Mg^{2+} in Sterofundin ISO correspond to physiological concentrations in the target species and are necessary to maintain or correct fluid and electrolyte homeostasis.

Additionally, Sterofundin ISO contains a balanced combination of the anions chloride, malate, and acetate intended to counteract metabolic acidosis. Malate and acetate are bicarbonate precursors and are used as alkalinizing agents.

Since the concentration of chloride ions in Sterofundin ISO is higher than the physiological plasma concentrations in cows, horses, pigs, sheep, and goats, this VMP is only indicated under the conditions of undisturbed acid-base balance in these animal species.

Tolerance in the Target Species of Animals

The tolerance of Sterofundin ISO in the target species was demonstrated based on comprehensive literature data mainly consisting of excerpts from textbooks and overview articles addressing fluid therapy in humans and animals.

Since Sterofundin ISO is an isotonic crystalloid solution for infusion and the amounts of cations correspond to the physiological ranges in the target species, adverse reactions can primarily be expected if very large volumes and/or too rapid infusion rates are applied. Appropriate information on infusion regimen is provided in the SPC and other product literature to avoid overdosing.

Similarly, the safety of the combination of chloride, malate and acetate to counteract metabolic acidosis in the target species was confirmed based on a comprehensive literature. However, the concentration of chloride ions in Sterofundin ISO is higher than the physiological plasma concentrations in cattle, horses, pigs, sheep, and goats. Therefore, the VMP should not be used in animals with mild acidosis, but only under the conditions of undisturbed acid-base balance in these target species.

Adverse reactions are reported mainly in humans after application Sterofundin ISO for use in humans including hypersensitivity related to intravenous administration of magnesium salts and effects on heart. Moreover, overdose or too rapid infusion rates can cause pulmonary oedema, hyperkalemia, hypercalcemia, hypermagnesemia, acidification of the blood, and metabolic alkalosis. These adverse reactions are to be exptected in the target species in the same way and are adequately addressed in the SPC and other product literature.

The local tolerance of Sterofundin ISO has been demonstrated based on bibliographical data on studies in rabbits. Data demonstrate that incidence of phlebitis depends on certain factors, such as pH, osmolarity and titration acidity of the solution administered. According to the product literature, Sterofundin ISO has a low pH of 5.1 – 5.9, a relatively low theoretical osmolarity of 309 mOsm/l and a low titratable acidity of < 6 mmol/L. Venous phlebitis, local pain or reactions, venous irritation, thrombosis or extravasation cannot be ruled out after use and are therefore adequately addressed in the product literature.

IV.B Clinical Studies

A comprehensive set of scientific published references was provided dealing with fluid therapy in general, and specifically with the use of parenteral crystalloid solutions for infusion in cats, dogs, horses, and calves. For the species pigs, adult cattle, goats and sheep only limited data are available.

Sufficient justification was provided that crystalloid solutions for infusions with a similar composition as Sterofundin ISO (e.g. lactated Ringer's solution, Plasma Lyte A or ELO-Mel isoton) are widely used since many years in veterinary medicine for the same indications as indicated for Sterofundin ISO in all target species.

Based on published references, it can be concluded that minor differences in the composition of Sterofundin ISO, i.e. electrolyte (chloride, magnesium) and metabolisable anion concentrations (malate and acetate instead of lactate), compared with other solutions for infusion for fluid therapy frequently used in the veterinary medicine (for example lactated Ringer’s solution), do not affect safety and efficacy of Sterofundin ISO. Therefore, study results obtained with other solutions for infusion can be extrapolated to Sterofundin ISO.

Consequently, the use of crystalloid solutions for infusion, including Sterofundin ISO, can be considered as well-established standard infusion therapy.

The entire data set derived from scientific literature provides sufficient evidence that Sterofundin ISO can be used effectively for the correction of hypotonic and isotonic

dehydration, fluid and electrolyte replacement under the conditions of undisturbed acid-base balance or mild acidosis in dogs and cats, and in cattle, horses, sheep, goats and pigs under the conditions of undisturbed acid-base balance.

There is no documented evidence of an unacceptable risk associated with the use of crystalloid solutions for infusion similar to Sterofundin ISO in these species. Consequently, based on the entire data set the clinical use of Sterofundin ISO as indicated in the label is accepted.

The product literature comprises adequate statements and warnings ensuring the effective and safe use of Sterofundin ISO in all target species.

The dosage regimen of Sterofundin ISO referred to in the SPC is based on scientific references.

In general, treatment of an animal depends on its initial clinical condition and should be established individually. A precise knowledge about the following parameters is essential to ensure a correct treatment of the different indications in all target species:

- Current volume deficit
- Fluid maintenance requirements
- Continuous fluid losses due to persistence of the treating disease.

Administration should take place under the supervision of the veterinarian.

Accordingly, a comprehensive advice including general principles related to fluid intake, calculation of fluid volume for rehydration and maintenance requirements for adult animals and neonates, and advice related to infusion rates are provided in the SPC and other product literature. In addition, adequate target species-specific advices and age-dependent recommendations are included.

In conclusion, the current recommendations in the product literature allow an effective and safe use of Sterofundin ISO to treat the following indications in the target species:

"Dog and cat: Correction of hypotonic and isotonic dehydration, for fluid and electrolyte replacement under the conditions of undisturbed acid-base balance or mild acidosis.
Cattle, horse, sheep, goat and pig: Correction of hypotonic and isotonic dehydration and for fluid and electrolyte replacement under the conditions of undisturbed acid-base balance.
All target species: Short term intravascular volume replacement."

V. 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.

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 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.