MINISTERIO
DE SANIDAD
Y POLÍTICA SOCIAL

agencia española de
medicamentos y
productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

Parque Empresarial Las Mercedes
Edificio 8
C/Campezo 1,
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

B. BRAUN VET CARE HYPERTONIC NaCl SOLUTION (7.5 g/100 ml)

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0149/001/MR
Name, strength and pharmaceutical form	B. Braun Vet Care hypertonic NaCl solution (7.5 g/100 ml) Solution for infusion for horses, cattle, sheep, goats, pigs, dogs and cats (AT, BE, DE, FR, IE, IT, NL, UK) Hipertónico Salino 7.5 g/100 ml Braun Uso Veterinario (ES)
Applicant	B. Braun Vet Care GmbH Am Aesculap-Platz 78532 Tuttlingen Germany
Active substance(s)	Sodium chloride
ATC Vet code	QB05BB
Target species	Cattle, horses, sheep, goats, pigs, dogs and cats.
Indication for use	Indications for all target animal species: As adjunctive therapy in the treatment of emergency situations, like haemorrhagic, endotoxic, septic or hypovolaemic shock, when a rapid increase in the plasma circulation volume is required in order to restore or maintain vital organ functions.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 13.a of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 29/07/2009
Date product first authorised in the Reference Member State (MRP only)	29/09/2000
Concerned Member States for original procedure	AT, BE, DE, FR, IE, IT, NL and UK

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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.

II. QUALITY ASPECTS

A. Composition

The product contains sodium chloride (7.5 g/100 ml) as the active substance and water for injections as the excipient.

The container/closure system is a low density polyethylene bottle of 500 ml. The bottle is blown, filled and sealed in a continuous integrated working cycle. The bottle and a polyethylene cap incorporated to the closed bottle are sealed together. The cap contains a latex free membrane to ensure a tight closure when an infusion kit is connected or drugs are added. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

The product 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 product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The flow chart of the manufacturing process has been included.

The manufacturing process consists in weighing out and preparation of a bulk solution, filtration through a pre-filter (0.2 - 4.5 µm) and then through a main-filter (0.22 µm), filling on an automatic bottle-pack machine, sterilization in an autoclave to achieve a F_0 ≥ 8 minutes at a nominal temperature of >111.5ºC and final packaging in cartons.

Process validation data on 3 production batches of the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is sodium chloride, an established active substance described in the current edition of the European Pharmacopoeia monograph 0193.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Water for injections complies with Ph. Eur. monograph 0169. Certificates of analysis are included.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control tests on intermediate products

Not applicable.

F. 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 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.

G. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (3 years) when stored under the approved conditions (protect from direct sunlight).

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL) (*for pharmaceuticals only)*

As this is an application according to Article 13a – well established veterinary use – appropiate scientific literature about safety and residues tests was provided.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that infusion of a hypertonic saline solution leads to an osmotic expansion of the plasma and a shift increase of the volume of the plasma from the interstitial fluid.

This solution, after administering into the body, produces an increase in plasma crystalloid osmotic pressure, and then the water flows from the interstitial compartment to the vascular and the salt to the interstitial fluid, so that the extracellular fluid is hypertonic. As a result, the water passes from cell to the extracellular fluid, thus increasing the volume of it, decreasing the intracellular fluid. Then the crystalloid concentration and the osmotic pressure or osmolality of all body fluids are increased.

The kidneys excrete excess sodium and chloride, particularly by reducing the secretion of aldosterone, resulting in the elimination of hypertonic urine. Hypertonia of the extracellular fluid stimulates osmoreceptores with increased secretion of antidiuretic hormone, which reduces the diuresis.

Hypertonia of the intracellular fluid causes thirst, so the animal will drink until the normal osmotic pressure or osmolality of the body is restored.

Toxicological Studies

The applicant has provided bibliographical data which show that the NaCl contained in this product is physiologically occurring in the organism. Sodium chloride is broadly employed and known to be generally of low toxicity.
Therefore, statements about the toxicity of this substance may also be derived from its chemical nature and the clinical experience and systematic toxicity data are rarely available in the relevant literature.

The safety of the veterinary medicinal product has not been established during pregnancy and lactation so it will be only administered after risk/benefit evaluation by the responsible veterinarian.

At the recommended posology it is not expected that NaCl causes any kind of genotoxicity and carcinogenicity.

User Safety

The applicant has provided a user safety assessment which shows that the risk for the professional user is acceptable when the product is used in accordance with label recommendations.

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

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation
(Delete for non food producing species and for immunologicals)

Residue Studies

No residue depletion studies were conducted because sodium and chloride are essential nutrients and physiologically occurring in the animal's body, primarily in the extracellular space. Therefore, the amount of sodium and chloride in the body following therapeutic treatment of food-producing animals with this product, would be indistinguishable from those naturally occurring in the animal.

MRLs

NaCl is listed in Annex II of Council Regulation 470/2009 for all food-producing species.

Withdrawal Periods

Based on the data provided above, a withdrawal period of:
Meat and offal: zero days
Milk: zero hours,
in cattle, horses, sheep, goats and pigs was justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies (pharmaceuticals only)

Pharmacology

The applicant provided bibliographical information to show that the goal of fluid therapy in shock states is to rapidly expand circulating blood volume to improve perfusion and oxygen delivery. Hypertonic saline can rapidly expand circulating volume by redistributing extravascular fluids into the vascular space.

Tolerance in the Target Species of Animals

Hypernatraemia and hyperchloraemia may occur after i.v. administration of hypertonic NaCl solutions. Administration of i.v. solutions can cause fluid or solute overload, congestive heart failure, overhydration, congested states or acute pulmonary oedema, especially in patients with cardiovascular disease, in patients with renal insufficiency and in patients receiving corticosteroids or corticotropin or drugs that may give rise to sodium retention. The risk of dilutional states is inversely proportional to the electrolyte concentration. The risk of solute overload causing congested states with peripheral and pulmonary oedema is directly proportional to the electrolyte concentration. Further, too rapid application can lead to hypertension, cardiac arrhythmias, haemolysis, haemoglobinuria, bronchoconstriction and hyperventilation. Additionally, increased diuresis may occur, which leads to hypertonic urine.

Overdose

Hypernatraemia may occur after inappropriate i.v. use of HS. Further, complications such as hypokalaemia, cardiovascular shock, central nervous system (CNS) disorders, extensive haemolysis, cortical necrosis of the kidneys, and severe local tissue necrosis (if administered extravasculary) can occur. Excess **chloride** in the body may cause a loss of bicarbonate and thus exert an acidifying effect. Because of these interactions with the bicarbonate buffer system and influences on the homeostasis of other electrolytes metabolic acidosis is a possible adverse effect of hyperchloraemia.

Local Tolerance

Searches of published literature in relevant databases revealed the following results with topical application of the concentrated salt: NaCl was found to cause mild skin irritations in rabbits at a dose of 50-500 mg over 24 h.
Moderate irritations were observed by administering a dose of 100 mg for 24 h in a rabbits eye. Perivascular injection should be avoided, as hypertonic NaCl induces tissue necrosis.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Laboratory Trials

The applicant provided bibliographical data regarding the therapeutic indications in the different target species. The contributed bibliography is considered sufficient.

Field Trials

The applicant provided bibliographical data regarding the therapeutic indications in the different target species. The contributed bibliography is considered sufficient.

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.

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 veterinary Heads of 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.

None