CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Natriumchloride Fresenius Kabi 100 mg/ml (10%), concentrate for solution for infusion Fresenius Kabi Nederland B.V., Belgium

sodium chloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 103379

19 November 2012

Pharmacotherapeutic group:	blood substitutes and perfusion solutions, electrolyte solutions
ATC code:	B05XA03
Route of administration:	intravenous
Therapeutic indication:	correction of severe hyponatremia when administration of limited amounts of water through slow intravenous infusion is recommended; administration of sodium as an additive to limited-volume parenteral nutrition supplements
Prescription status:	prescription only
Date of authorisation in NL:	5 August 2010
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Natriumchloride Fresenius Kabi 100 mg/ml (10%), concentrate for solution for infusion from Fresenius Kabi Nederland B.V. The date of authorisation was on 5 August 2010 in the Netherlands.

The product is recommended for:

- Correction of severe hyponatremia when administration of limited amounts of water through slow intravenous infusion is recommended.
- Administration of sodium as an additive to limited-volume parenteral nutrition supplements.

A comprehensive description of the indications and posology is given in the SPC.

Natriumchloride Fresenius Kabi 100 mg/ml (10%) is a hypertonic solution with osmolarity of 3422.31 mOsm/l. The pharmacodynamics properties of the solution are those of sodium and chloride ions, responsible for the fluid and electrolyte balance. The sodium ion circulates through the cell membrane by a variety of mechanisms, such as the sodium pump (NA+, K+-ATP-ase). Sodium plays an important role in the neurotransmission and electrophysiology of the heart and kidney functions.

This national procedure concerns a well-established use application for sodium chloride 10% concentrate for solution for infusion. In the Netherlands this particular formulation has never been licensed. However, it is already more than 20 years in use for the sought indication and in humans exclusively in the clinical setting.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC.

This application concerns a bibliographical application based on well-established medicinal use of Natriumchloride 100 mg/ml (10%), concentrate for solution for infusion. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ''Medicinal use'' does not exclusively mean ''use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No new pre-clinical and clinical studies were conducted, which is acceptable for this well-established use application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, which is acceptable for a well-established use application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is sodium chloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is highly soluble in water. Since the active substance is an inorganic salt only limited data is required.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
A narrative of the manufacturing process for all 3 suppliers of sodium chloride has been provided. The submitted information is regarded to be sufficient given the inorganic nature of the drug substance. Results of various batches, in compliance with the specification of Ph.Eur., demonstrate that the process is under control.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for microbiological quality and the packaging material. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 2 batches from each manufacturer.

Stability of drug substance
Three batches have been analysed after 24 months of storage. All results comply with the specifications.
The active substance is stable for 2 years, without specific storage condition, and is based on the fact that the drug substance is inorganic and not susceptible to change.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Natriumchloride Fresenius Kabi 100 mg/ml (10%) is a clear, colourless and odourless solution with pH 4.5 – 7.0 and osmolarity of 3422.31 mOsm/l.
The electrolyte profile of 1 ml sodium chloride 10% corresponds to sodium 1.71 mmol and chloride 1.71 mmol.

The concentrate for solution for infusion is packed in 10 ml or 20 ml polypropylene containers.

The only excipient used is water for injections.

Pharmaceutical development

The development of the product has been described, the choice of excipient is justified and its function explained. No overages are applied. NaCl 10% is consequently terminally sterilized in an autoclave with a validated process. Bacterial endotoxin levels and sterility are measured as part of the drug product release. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug substance is dissolved in water for injection, the solution is filtered prior to filling. The ampoules are manufactured by means of a blow-fill-seal technique. The obtained ampoules are steam sterilised. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. No further validation data as part of the registration file is required.

Control of excipients
The excipient water for injections complies with the Ph.Eur. This specification is acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, sodium chloride concentration, pH, extractable volume, particulate matter, endotoxins and sterility. The release and end of shelf-life limits are identical and are considered to be acceptable. Analytical testing is performed in accordance with the Ph.Eur. or USP. The alternative test for aluminum is an in-house procedure which has been adequately described and validated.
Batch analytical data from the proposed production site have been provided on 3 commercial-scale batches of both volumes, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 5 commercial-scale batches stored for 36 months at 25°C/60%RH (1 batch), 6 months at 40°C/60%RH (1 batch), 36 months at 25°C/40%RH (4 batches), and 6 months at 40°C/<25%RH (3 batches). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging. The proposed shelf-life of 3 years, without specific storage condition, is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

Sodium chloride solution has been available the European market for over 20 years. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment
An environmental risk assessment is considered not necessary since sodium chloride is a natural compound which is widespread in the environment.

II.3 Clinical aspects

Introduction
Sodium chloride (NaCl) 10% solution for injection is sterile and pyrogen free and is suitable for intravenous administration. The active pharmaceutical ingredient is NaCl, a salt (with a molecular weight of 58.44.D. A NaCl 10% solution contains 100 g/l sodium chloride.

In the Netherlands this particular formulation has never been licensed. However, it is already more than 20 years in use for the same purpose and in humans exclusively in the clinical setting.

The efficacy of standard solutions for intravenous administration (like 10% NaCl solution) has been well documented over many years of widespread clinical use. NaCl 10% solution is indispensable for the adequate treatment of symptomatic hyponatremia to protect the patient against life threatening cerebral oedema. It has been in use much longer than 10 years with a high frequency in first aid facilities and the ICU-setting (Upadhyay 2006,Crop 2007,Hawkins 2003). Safety and efficacy are documented extensively in the relevant literature and textbooks. The benefits are indisputable. Furthermore the product submitted has the same active ingredient in the same concentration as the product described and used for the same indication in the bibliographic dossiers. The following references are used to depict the general, well established practice: Kasper DL et al.eds. Harrison's Principles of Internal Medicine, 16th edition,2005, Burton D Rose, Clinical Physiology of Acid-Base and Electrolyte disorders, fifth edition 2001, de Jong, Koomans and Weening, Klinische Nefrologie, 4e druk 2005, Di Bartola ,2006, Rose BD, Up To Date, last literature review 17.1:jan.1,2009.

The safety profile is also well documented. Essential is that the treating physician is following the international guidelines to avoid the irreversible damage of osmotic demyelination

Clinical efficacy

Correction of hyponatremia

Hyponatremia is the most common electrolyte disorder, with a marked increase among hospitalized and nursing home patients. A 1985 prospective study of inpatients in a US acute care hospital found an overall incidence of approximately 1% and a prevalence of approximately 2.5%. On the surgical ward, approximately 4.4% of postoperative patients developed hyponatremia within 1 week of surgery. Hyponatremia has also been observed in approximately 30% of patients treated in the intensive care unit (Upadhyay et al. 2006). Hyponatremia has been observed in 30% of patients hospitalized in an acute care setting in Rotterdam and in 42.6% of patients in a large acute care hospital in Singapore (Crop et al. 2007, Hawkins 2003). Treatment of hyponatremia depends largely on its onset, etiology and symptomatology. Initial evaluation of patients with hyponatremia involves identification of the onset of the condition (acute or chronic), presence of symptoms and assessment of volume status (Biswas & Davies 2007, Reynolds & Seckl 2005). NaCl 10% solution for injection can be used to correct serious hyponatremia when the administration of limited amounts of water as a slow intravenous solution is indicated. In patients with severe life-threatening symptoms of SIADH, it may be necessary to administer hypertonic sodium chloride solution at a rate that increases the serum sodium concentration by 1-2 mmol/h, in addition to restricting fluid intake, until the serum sodium concentration exceeds 125 mmol. Loop diuretics such as furosemide interfere with the kidney's ability to produce concentrated urine. Consequently these agents can be combined with hypertonic saline for the treatment of life-threatening hyponatremia (Hardman et al. 2001).

Sodium supplementation

NaCl 10% solution for injection can be added to limited-volume parenteral nutrition as needed.

Dosage and method of administration

The dose administered depends on age, gender, weight and clinical condition of the patient. It is of vital importance to obtain data on the patient's sodium and water requirements. The finished product should never be injected directly without prior dilution.

Since the osmolarity in the cells is the same as that in the extracellular fluid, the effect of plasma sodium concentration is distributed through the total body water. Depending on weight and gender the TBW and total body effective solute can be calculated (and also the assumed total body sodium deficit).Further calculations will give information about the expected rise in plasma sodium and extracellular volume (ECF) if a defined amount of sodium has been brought into the circulation. Then a decision has to be made about the rate of infusion in order not to exceed a maximal rise in plasma sodium of 12 mmol/l/24 hrs.

The international guidelines give assistance in the calculating of the dosage and rate of infusion in an individual situation. The correct use of the guidelines gives protection against the most important risks of fast correction of hyponatremia. The dose recommendation in the SPC is in agreement with international guidelines.

Safety and adverse effects

General references: AHFS 2008, DiBartola 2006, Martindale 2005, Munson et al. 1995.

Undesirable effects are not expected when the solution is administered according to the recommendations.

Osmotic demyelination

Too rapid correction of severe hyponatremia (plasma sodium usually less than 110 to 115 mmol/l) can lead to the development of a neurologic disorder called osmotic demyelination syndrome (ODS) characterised by bulbar palsy, paralysis of all limbs, coma and death. Therefore hypertonic sodium chloride solutions should only be administered to patients with life-threatening symptoms. ODS does not usually occur in patients with acute-onset severe hyponatremia if the rate of correction does not exceed 24 mmol over 48 hours (Sterns 1986).

Hypokalemia may predispose patients to develop ODS following correction of hyponatremia.

In neurologically stable patients with severe hyponatremia it may be beneficial to correct hypokalemia prior to correction of hyponatremia. This may reduce the incidence of ODS (Heng 2007, Lohr 1994).

Electrolyte disturbances

If by infusion of hypertonic sodium solution hypernatremia is achieved, a rapid decrease in brain volume may cause rupture of cerebral vessels and focal haemorrhage. If hypernatremia develops slowly the brain has time to adapt to the hypertonic state by production of osmotic active intracellular solutes that prevent dehydration of the brain.

Salt and fluid overload is especially a danger in patients with severe renal insufficiency; the kidney cannot cope with the sodium overload and possibly also the fluid overload.

Effects on the administration site

Hyperosmotic solutions may cause local pain, thrombophlebitis and tissue necrosis if extravasation occurs. So unhampered access to the circulation is important.

The MAH gives a correct description of the most important complications of the use of 10% NaCl solution. These are adequately described in the SPC.

Precautions and contraindications

The management of hyponatremia is very complex and should only be attempted by experienced physicians. Solutions containing sodium ions should be used with great care in patients with congestive heart failure, liver cirrhosis, severe renal insufficiency, and in clinical states in which there exists oedema with sodium retention. The intravenous administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary oedema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the solutions. The risk of solute overload causing congested states with peripheral and pulmonary oedema is directly proportional to the electrolyte concentrations of the solution. In patients with diminished renal function, administration may result in sodium retention. Caution must be exercised in the administration of parenteral fluids, especially those containing sodium ions, to patients receiving corticosteroids or corticotrophin.

The i.v. use of hypertonic 10% NaCL solution has to be restricted to experienced physicians. The MAH gives a correct description of the precautions and contraindications that have to be taken into account by these physicians. These are adequately described in the SPC.

Use in pregnancy and lactation

No adverse effects are expected when this product is administered during pregnancy or lactation. This regards all solutions containing no other active ingredients than sodium chloride.

This statement is correct if the pregnancy is not complicated by pre-eclampsia or eclampsia. In these situations the physician has to consider the balance between the different threats for the patient. These are adequately described in the SPC.

Interactions

Combined use with drugs that are associated with retention of sodium and water may lead to oedema and hypertension. The renal toxicity of amphotericine B can be associated with sodium depletion. Replacement of the sodium improves the renal function.
There is an important interplay between Lithium and Sodium. Ingestion of marked amounts of sodium can prevent adequate Lithium levels and a shortage of sodium may increase Lithium levels and Lithium toxicity (Stockley 2008).
Patients taking lithium containing medication for treatment of manic episodes of bipolar illness should be monitored for lithium levels since large sodium intake may decrease lithium serum levels. All relevant interactions are summarized in the SPC.
There are no direct interactions in combined use with drugs known from the literature but the interplay between lithium and sodium deserves to be mentioned in the SPC. This is adequately described in the SPC.

Overdose
General reference: Dart 2004.
Considering the composition of NaCl 10%, solution for injection overdosing could lead to hypernatremia. Excess sodium chloride within the body may produce the following general gastrointestinal effects: nausea, vomiting, diarrhoea and cramps. Salivation and lacrimination are reduced, whilst thirst and swelling are increased. Possible other symptoms include hypotension, tachycardia, renal failure, peripheral and pulmonary oedema and respiratory arrest. Symptoms of the CNS include headache, dizziness, irritability, restlessness, weakness, muscle twitching or rigidity, convulsions, coma and death.
These statements are correct. The ODS syndrome is the most important threat by overdosing. This is adequately described in the SPC.

Overall conclusion
NaCl 10% solution for injection contains sodium chloride and provides by venous use a source of electrolytes (sodium). NaCl 10% solution for injection is indicated for the treatment of hyponatremia and can be used for sodium supplementation, added to limited-volume parenteral nutrition. The claimed therapeutic indications are consistent with the spectrum of activity reported in standard references and published literature, and also with the currently well established clinical use of the product.
The data related to the clinical properties of the active pharmaceutical ingredient are collected from and based upon a careful and extensive literature search. There is a vast volume of published literature on the pharmacokinetics and pharmacodynamics of the active principles. Sterile, pyrogen free standard infusion solutions, when administered correctly and in volumes adapted to the age, weight and clinical condition of the patient will rarely, if ever, cause adverse effects. However, hypernatremia and hypervolemia may occur after inappropriate intravenous administration. In order to avoid infection at the site of injection, parenteral administration should be done under optimum conditions of hygiene. A careful administration technique should be employed to avoid venous thrombosis or phlebitis and extravasation. The management of hyponatremia is very complex and should only be attempted by experienced physicians. Appropriate warnings and contraindications have been included in the product documentation. In conclusion, the data presented concerning the use of NaCl 10% solution for injection have been adequately summarised in the SPC. The information presented confirms the suitability and efficacy of these products when used as recommended.

Risk management plan
The safety profile of sodium chloride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national is adequate and has been adapted in accordance with the MEB's comments.

Readability test

The package leaflet has not been evaluated via a user consultation study. A post-approval commitment was made to submit the results of a readability test before placing the product on the market. This commitment has been fulfilled.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Natriumchloride Fresenius Kabi 100 mg/ml (10%), concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a well-established medicinal product. Based on the submitted dossier and further literature, Natriumchloride Fresenius Kabi 100 mg/ml (10%) can be considered effective in correction of severe hyponatremia and for administration as an additive to limited-volume parenteral nutrition supplements.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling include adequate information and are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered well-established medicinal use sufficiently demonstrated, and has therefore granted a marketing authorisation. Natriumchloride Fresenius Kabi 100 mg/ml (10%), concentrate for solution for infusion was authorised in the Netherlands on 5 August 2010.

The following post-approval commitment has been made during the procedure:

Product information

- The MAH committed to submit the results of a readability test before placing the product on the market. This commitment has been fulfilled. For a brief discussion of the results, refer to Annex I to this PAR (page 14).

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Transfer of the marketing authorisation. Change in the name and/or address of the marketing authorisation holder.	--	IB/G	22-9-2010	19-10-2010	Approval	N
Submission of a readability test.	--	Post-approval commitment	27-3-2012	6-9-2012	Approval	Y, Annex I

Literature references

1. AHFS 2008 Drug Information. ASHP Bethesda.

2. Aurell M. [Salt, renal function and high blood pressure--reflections on a current issue], Lakartidningen 2002 Nov 21;99(47):4736-40.

3. Biswas M, Davies JS. Hyponatraemia in clinical practice. Postgrad Med J. 2007, Jun;83(980):373-8.

4. Crop MJ, Hoorn EJ, Lindemans J, Zietse R. Hypokalaemia and subsequent hyperkalaemia in hospitalized patients. Nephrol Dial Transplant. 2007 Dec;22(12):3471-7.

5. Dart RC. Medical Toxicology, 3rd ed. Lippincott Williams & Wilkins, Philadelphia PA. 2004.

6. Daugirdas JT. Pathophysiology of dialysis hypotension: an update. Am J Kidney Dis 2001 Oct;38(4 Suppl 4):S11-7.

7. DiBartola SP. Fluid, electrolyte, and acid-base disorders in small animal practice. Saunders Elsevier 2006.

8. Faubel S, Topf J. The fluid electrolyte and acid-base companion. Alert and Oriented Publishing Co. San Diego CA. 1999.

9. Geigy Scientific Tables. Part 1, Units of Measurement, Body Fluids, Composition of the Body, Nutrition. Lentner C ed. 8th edition. Ciba-Geigy Ltd, Basle Switzerland 1981.

10. Goh KP. Management of hyponatremia. Am Fam Physician. 2004 May 15;69(10):2387-94.

11. Hardman, JG, Limbird LE, Goodman AG (eds.). Goodman and Gillman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001.

12. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. Clin Chim Acta. 2003 Nov;337(1-2):169-72.

13. Heng AE, Vacher P, Aublet-Cuvelier B, Garcier JM, Sapin V, Deteix P, Souweine B. Centropontine myelinolysis after correction of hyponatremia: role of associated hypokalemia. Clin Nephrol. 2007 Jun;67(6):345-51.

14.deJong PE,Koomans HA, Weening JJ. Klinische Nefrologie, 4e druk 2005.

15. Kasper DL et al. eds. Harrison’s Principles of Internal Medicine. 16th edition. McGraw- Hill, New York 2005.

16. Lohr JW. Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia. Am J Med. 1994 May;96(5):408-13.

17 Luque Ramirez M, Bajo Martinez A, Bernal Morell E, Manzano Espinosa L. [Severe hiponatremia associated with the use of fluoxetine in the elderly] Rev Clin Esp 2002 Apr;202(4):246.

18. Martindale, The Complete Drug Reference 34th Edition, Ed. K. Parfitt. The Pharmaceutical Press, (London), 2005.

19. Munson PL, Mueller RA, Breese GR. Principles of pharmacology, basic concepts & clinical applications. Chapman & Hall NY 1995.

20. Patel GP, Kasiar JB. Syndrome of inappropriate antidiuretic hormone-induced hyponatremia associated with amiodarone. Pharmacotherapy. 2002 May;22(5):649-51.

21. Raphael K, Tokeshi J. Hyponatremia associated with sertraline and fluoxetine: a case report. Hawaii Med J 2002 Mar;61(3):46-7.

22 Reynolds RM, Seckl JR. Hyponatraemia for the clinical endocrinologist. Clin Endocrinol (Oxf). 2005 Oct;63(4):366-74.

23. Romerio SC, Radanowicz V, Schlienger RG. [SIADH with epileptic seizures and coma in fluoxetine therapy] Schweiz Rundsch Med Prax 2000 Mar 2;89(10):404-10.

24.Rose BD, Up to Date,last literature review 17-1: jan 1, 2009.

25. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med. 1986 Jun 12;314(24):1535-42.

26. Stockleys's Drug Interactions, 8th ed.. Pharmaceutical Press 2008.

27. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006 Jul;119(7 Suppl 1):S30-5.

Annex I - Post-approval commitment: results of a readability test on the package leaflet

The readability testing of the Natriumchloride Fresenius Kabi 100 mg/ml (10%), concentrate for solution for infusion package leaflet was performed in two test rounds with ten participants each.
The questionnaire used for these interviews, representing the content of the package leaflet, consisted of 14 questions. These questions tested the ability of the respondents to understand and find the information given in the leaflet.
At the beginning of the interview the respondents' first impressions and general remarks were noted by the interviewer. Comments made whilst answering the questions and observations of the respondents' behaviour were also taken into account when assessing whether the contents of the leaflet were understood properly.
The results were evaluated according to the predefined success criteria of the current guideline (at least 16 out of 20 respondents (80%) should be able to answer each question correctly). Also the guidance from FAGG was taken into consideration during the readability test.
The results obtained in this readability test fulfil the requirements of the EU Readability Guideline and suggest that most potential users (patients) are able to trace, comprehend and apply the information in the resulting leaflet. Therefore, it can be stated that the leaflet of Natriumchloride Fresenius Kabi 100 mg/ml (10%) is in compliance with Directive 2001/83/EC (1) as amended by Directive 2004/27/EC (2) and the EU Readability Guideline (3).