CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ionolyte, solution for infusion
Fresenius Kabi Nederland B.V., Belgium

sodium acetate trihydrate
sodium chloride
potassium chloride
magnesium hexahydrate

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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/1364/001/DC
Registration number in the Netherlands: RVG 102596

11 May 2010

Pharmacotherapeutic group:	solutions affecting the electrolyte balance, electrolytes
ATC code:	B05BB01
Route of administration:	intravenous
Therapeutic indication:	predominantly extracellular dehydration, regardless of cause; hypovolemia regardless of cause; mild metabolic acidosis.
Prescription status:	prescription only
Date of authorisation in NL:	30 October 2009
Concerned Member States:	Decentralised procedure with BE, CZ, DK, ES, FR, HU, NO, PL, PT, SE, SK
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 member states have granted a marketing authorisation for Ionolyte, solution for infusion from Fresenius Kabi Nederland B.V. The date of authorisation was on 30 October 2009 in the Netherlands.

The product is indicated for:

- predominantly extracellular dehydration, regardless of cause (vomiting, diarrhea, fistulas, etc.).
- hypovolemia regardless of cause (hemorrhagic shock, burns, peri-operative water and electrolyte loss).
- mild metabolic acidosis.

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

Ionolyte solution for infusion is an isotonic solution of electrolytes. The constituents of Ionolyte solution for infusion and their concentrations are designed to match those of plasma. The product is used for correction of disturbances in the serum electrolyte balance and in the acid-base balance. Electrolytes are given to achieve or to maintain normal osmotic conditions in the extracellular as well as the intracellular compartment. Acetate is metabolised into bicarbonate in hepatic and extrahepatic tissues (e.g. muscles and peripheral tissues) and produces a mild alkalising effect. Due to the amount of metabolisable anions, Ionolyte solution for infusion is suitable for patients with a tendency to acidosis.
The pharmacology of intravenously infused solutions with similar composition is known from long-standing use in clinical and emergency medicine.
The pharmacodynamic properties of this solution are those of its components (water, sodium, potassium, magnesium, acetate, and chloride). The main effect of Ionolyte solution for infusion is the expansion of the extracellular compartment including both the interstitial and intravascular fluids.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC, well-established use. This application concerns a bibliographical application based on well-established medicinal use of sodium acetate trihydrate, sodium chloride, potassium chloride, and magnesium hexahydrate in solutions 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.

No paediatric development programme has been submitted.

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 substances are sodium acetate trihydrate, sodium chloride, potassium chloride and magnesium chloride hexahydrate. All active substances are established and described in the European Pharmacopoeia (Ph.Eur.*). Different manufacturers are use for the active salts.

Manufacturing process
The manufacturing process of the inorganic salts and the organic sodium acetate trihydrate has been adequately described.

Quality control of drug substance
The specifications of the inorganic salts and of sodium acetate are in accordance with the respective Ph.Eur. monographs and take into account the additional requirements for parenteral dosage forms specified in these monographs. Limit for total viable aerobic count and endotoxins are included in the specifications of all active substances. Batch analytical data demonstrating compliance with the drug substance specification have been provided for all active substances.

Stability of drug substance
Stability data have been provided for all active substances. A re-test period of 24 months has been granted for all active substances.

** 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
Ionolyte contains:

	500 ml	1000 ml
Sodium acetate trihydrate	2.32 g	4.63 g
Sodium chloride	3.01 g	6.02 g
Potassium chloride	0.15 g	0.30 g
Magnesium chloride hexahydrate	0.15 g	0.30 g

Electrolytes:

Na^+	137.0 mmol/l
K^+	4.0 mmol/l
Mg^{++}	1.5 mmol/l
Cl^-	110.0 mmol/l
CH_3COO^-	34.0 mmol/l

Theoretical osmolarity:	286.5 mosm/l
Titrable acidity:	< 2.5 mmol NaOH/l
pH:	6.9 – 7.9

The product is a clear and colourless solution.

The solution for infusion is packed in polyolefin bags (Free*flex*®) with overwrap, or LDPE bottles (KabiPac®). Both 500 and 1000 ml bags and bottles are available.

The excipients are: sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections.

Pharmaceutical development

The development of the product was adequately described, the choice of excipients is justified and their functions explained. The objective of the development for the finished product was to provide a solution in a balanced carrier matrix with a composition that resembles the principal ionic constituents of normal plasma. As the finished product is presented as ready-to-use solutions for intravenous infusion, consisting of well-known active substances and excipients with well-established physicochemical properties and compatibility, no selection and optimisation of the manufacturing process of the bulk solution was necessary.

Manufacturing process

The drug substances are dissolved in water for injection and, if necessary, the pH is adjusted. The solution is passed through a pre-filter and a sterile filter. The container closure system is prepared and the solution filled into the solution bags. The finally assembled systems are terminally sterilised by steam. The manufacturing process is considered to be a standard procedure in all aspects, except for the sterilisation process of the product in LDPE containers (KabiPac®). The LDPE containers are terminally sterilised by autoclaving at a lower than usual temperature, as the material of the container cannot withstand a temperature of 121°C. The validation report for the sterilisation procedure for both container sizes has been included. The MAH committed to clarify the points/requests regarding the validation of the sterilisation method of LDPE containers.
The products in the Freeflex® bags are terminally sterilised by autoclaving at >121°C, which is considered a standard sterilisation procedure. Validation focused on the steam sterilisation process as well as on validation of physicochemical properties. This is considered to be sufficient.

Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, pH value, identity and content of sodium, magnesium, chloride, acetate, and potassium, particulate matter (visible and subvisible particles), extractable volume, sterility, endotoxins, and loss of weight. The release and shelf life requirements are not identical. Weight loss is only included in the shelf life specification, identity testing of the active substances is only included in the release specification, and the assay for active substances allows ± 5% from nominal value whereas the release specification is tighter (+ 0% / - 5%).
The analytical methods performed at both manufacturing sites have been adequately described and validated. Batch analytical data from the proposed production sites were provided for three commercial-scale batches demonstrating compliance with the release specifications. For the product packed in LDPE containers, the MAH committed to provide production-scale validation data for the first production batches. For the product packed in Freeflex bags, the MAH committed to provide batch analyses results for three full-scale production batches.

Container closure systems

Kabipack bottles

Polyethylene containers are unit dose containers manufactured by the blow-fill-seal technology of medical grade polyethylene. The only component that is in contact with the drug product is the polyethylene container (LDPE).
The polyethylene (LDPE) employed in the manufacture of the primary packaging complies with Ph.Eur. monograph 3.1.4 *Polyethylene without additives for containers for parenteral preparations and for*

ophthalmic preparations. The material also complies with Directive 2002/42/EC. The polyethylene containers comply with Ph.Eur. monograph 3.2.2.1 *Plastic containers for aqueous solutions for parenteral infusion*.
Certificates of analysis of the primary packaging material have been provided and the material also complies with the relevant Ph.Eur. monograph, Ph.Eur. 3.1.3 *Polyolefines* and Directive 2002/72/EC. Sufficient information has been provided.

Freeflex infusion bag
The freeflex bag is a polyolefine bag system for parenteral solutions containing no PVC material. The bag system is already approved for various infusion solutions like electrolytes, glucose and colloids.
Each component is described in detail in the provided in-house monographs.
Based on the results from chemical, biological, physical and technical investigations the freeflex bag produced with all components is proven to be suitable and safe for storage of parenteral solutions. Certificates of analysis of the primary packaging material have been provided.

Microbiological attributes
The drug product is sterilised in the final container. The integrity of the container is tested with a microbiological integrity test. In addition, the impermeability to micro-organisms of freeflex bags was tested during the development.

Stability of drug product
Kabipack bottles
Stability data on the product has been provided for one batch of the 1000 mL volume and for two batches of the 500 mL volume. The batches were packed in the packaging material as used for commercial supply. The conditions used in the stability studies are according to the ICH stability guideline for aqueous solutions in semi permeable containers. With the exception of an increase in weight loss and its influence on assay and extractable volume, no trends have been observed in any of the tested parameters at both storage conditions. On the basis of the provided 12 months stability data, a shelf life of 24 months could be granted. The product should not be frozen, and should be used immediately after opening.

Freeflex bags
Stability data on the product have been provided for one batch of a volume of 1000 mL and for two batches of a volume of 500 mL. The batches were packed in the packaging material as used for commercial supply. The conditions used in the stability studies are according to the ICH stability guideline for aqueous solutions in semi permeable containers. With the exception of an increase in weight loss and its influence on assay and extractable volume, no trends have been observed in any of the tested parameters at both storage conditions. On the basis of the provided 12 months stability data, a shelf life of 24 months could be granted. The product should not be frozen. The product should not be refrigerated or frozen, and should be used immediately after opening.

The MAH committed to place the first three commercial batches of both packages on long term stability studies throughout the proposed shelf life of 24 months, and at least two batches under accelerated conditions for 6 months.
Also, a commitment was made to include at least one batch of drug product in infusion bags per year in the long term stability program.

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

For the treatment of electrolyte and fluid depletion, the use of isotonic electrolyte solutions for intravenous infusion is well-established. In Ionolyte, solution for infusion no new drug substances are involved.

Preclinical data have been superseded by clinical experience, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
According to the NfG on the environmental risk assessment of medicinal products for human use, an environmental risk assessment is not required for these compounds (EMEA/CHMP/SWP/4447/00). Electrolytes are unlikely to result in a significant risk to the environment.

II.3 Clinical aspects

For this well-established use application, the MAH provided an overview on the clinical efficacy and safety of Ionolyte, solution for infusion. The product is similar to several other products already available on the European market. Of these products, the MAH refers to Volulyte®, which is identical concerning the proportions/concentrations of electrolytes (Volulyte® also contains hydroxyethyl starch), Plasma-lyte A® and Jonostreril®.

Clinical efficacy
The claimed indications are envisaged to be reasonable based upon the type of product and the similarities to products already marketed in the EU.

Critical review of clinical efficacy data, including a description of the search strategy relevant to the claimed indications, was provided. In addition, the MAH provided evidence supporting the appropriateness of the proposed posology and use in the paediatric population.

Clinical efficacy data
A review has been made of a series of databases to obtain a full update to the literature on the different clinical efficacy and safety studies of this active drug substance. The databases consulted in search of pharmacological and toxicological data are:

- Medline (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi)
- TOXLINE Special (http://toxnet.nlm.nih.gov/)
- DART Special (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC.htm)
- HSDB (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.htm)
- IRIS (http://www.epa.gov/iris/)
- GENETOX (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX.htm)
- CCRIS (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS.htm)
- TRI (http://www.epa.gov/tri/)
- CHEMIDplus (http://chem.sis.nlm.nih.gov/chemidplus/setupenv.html)
- CAS (http://www.cas.org/)
- RTECS (http://www.ccohs.ca/products/databases/rtecs.html).

Epidemiological studies were not found in the literature search.
Since the components of this medicinal product have been used for many decades, comprehensive information exists on their biochemistry, pharmacology, toxicology and clinical use. It is therefore reasonable that the MAH provided evidence for the indications, efficacy, and safety of this medicinal product by referring to published literature describing the use of similar products (Ringer lactate, diverse isotonic solutions, etc.).

In their overview the MAH provided an appropriate critical assessment of the efficacy of Ionolyte, infusion for solution. The references provided by the MAH in support of the current application are sufficient to demonstrate efficacy in the sought indications.

Paediatric use
The dose and rate of administration depends on age, body weight, clinical and biological conditions of the patient and the concomitant therapy. The proposed posology is based on experience with similar

electrolyte solutions. For the posology instructions please refer to the literature sources Altemeyer and Kraus (1990), Thomas & Carcillo (1998) and Upadhyay *et al.* (2005).
Although no clinical studies have been performed with Ionolyte solution for infusion, relevant experience with Voluven and other electrolyte solutions do not indicate specific risks when this product is used in children (see above mentioned literature).

In order to demonstrate the advise regimen in children the MAH referred to specific literature. The available literature strongly suggests that isotonic solutions are preferable in children. The efficacy and safety of comparable isotonic solutions in children from 2 years on was demonstrated.

Clinical Safety
Clinical studies investigating the use of similar electrolyte solutions do not indicate specific risks in patients with impaired renal function and ischaemic stroke. Safety of administration in special patient groups is based on experience with similar electrolyte solutions (Jonosteril, Plasma-Lyte A, Sodium chloride 0.9%).
Similar electrolyte solutions (Jonosteril, Plasma-Lyte A, Ringer Lactate and Ringer Acetate) are not contraindicated in patients with impaired liver function according to the corresponding SPCs. Acetate is the only metabolizable component of Ionolyte, solution for infusion and can be metabolized in many other tissues apart from the liver, in contrast to lactate (e.g. contained in Ringer Lactate). It is not to be expected that accumulation of acetate occurs. Therefore the product can be used in patients with liver imparement.
The fluid management in the various special patient groups is different from patient group to patient group and depends on the methods chosen by the physician. In general crystalloid solutions – such as Ionolyte, are preferred over colloid containing solutions in critically ill patients with renal impairment.

The discussion of the clinical safety of Ionolyte is considered to be adequate. Information provided by the MAH is consistent with, for example, information given in the SPC of Ringer lactate Fresenius, a solution for infusion intended for similar indications.

Risk management plan
The active substances are considered well-known. In view of the existing knowledge and experience with the active substances, the available data and the known risk benefit profile it is accepted that the MAH will perform the standard pharmacovigilance activities as described in volume 9 of *The rules governing medicinal products in the European Union*. No product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. An additional Risk Management Plan and Risk Minimisation Plan are not required at the moment.

Product information

SPC
The content of the SPC approved during the decentralised procedure was partially harmonised with the SPC of Ringer lactate (FR/H/208/01). Hypercalcaemia was not included in the contraindications, and severe renal insufficiency was maintained as a contraindication.
Section 4.8 *Undesirable effects* was also not fully harmonised with the SPC of Ringer lactate (FR/H/208/01), as the undesirable effects mentioned in the SPC of Ionolyte are undesirable effects generally known to occur after intravenous administration of electrolyte solutions, for instance for similar electrolyte solutions of the same pharmaceutical class (e.g. Ringer Acetate, Jonosteril). It is considered appropriate to include these undesirable effects.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test was performed in English, and consisted of a pilot test with to participants, followed by two rounds with 10 participants each. Male and female representative subjects over the age of 18-74 years were chosen as target population. The inclusion/exclusion criteria are acceptable. The leaflet was tested by interviewing each subject, noting not only the time to find the information but other physical factors (e.g. asking questions , turns over the leaflet and/ or scans the leaflet without direction, reading sections more than once, hesitation to report location or explaining in their own words).
A questionnaire with fourteen questions was used. The questionnaire focused on the identified safety key issues associated with treatment with Ionolyte infusion. Eleven questions addressed the content of the package leaflet. The other three questions were posed to obtain the subjects opinion about content and lay-out.
The criteria for a valid round (at least 90% of the interviewees are able to find the information, of whom 90% can show that they understand it), were predefined before the start of the test rounds. This is considered acceptable.
Following the pilot round, no modifications to the PIL were considered necessary.
In the first round of testing on 10 participants 90% of the interviewees were able to find the information requested and gave and correct answer. In the second round, again the 90% criterium was met. Regarding the lay-out, the heading and bold printing were positively commented on by the participants. The most unfavourable comments were obtained for the leaflet size. In order to be in line with the SPC, no information could be omitted. Therefore the MAH made no amendments.
The readability test has been sufficiently performed and shows that the PIL meets the required readability standards.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The member states, on the basis of the data submitted, considered that Ionolyte, solution for infusion demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.
The chemical-pharmaceutical documentation in relation to the proposed product is of sufficient high quality in view of the present European regulatory requirements.

Provided that the post-approval commitment is fulfilled (see below), the systems and services are in place to ensure compliance with the pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with similar products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Ionolyte, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 3 September 2009. Ionolyte, solution for infusion was authorised in the Netherlands on 30 October 2009.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from 3 September 2009 to 3 September 2012.

The date for the first renewal will be: 3 September 2014.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to provide production-scale validation data for the first production batches of drug product in LDPE containers.
- The MAH committed to provide batch analysis results for three full-scale production batches of drug product in Freeflex infusion bags.
- The MAH committed to clarify the points/requests regarding the validation of the sterilisation method of LDPE containers.
- The MAH committed to place the first three commercial batches of both packages on long term stability studies throughout the proposed shelf life of 24 months, and at least two batches under accelerated conditions for 6 months.
- The MAH committed to include at least one batch of drug product in infusion bags per year in the long term stability program.

Pharmacovigilance system

- The MAH committed to submit a complete and updated version of the Pharmacovigilance System, prior to marketing the product.

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

References

Altemeyer, K.-H. and Kraus, G.B. (1990). Die perioperative Infusionstherapie im Kindesalter. Anaesthesist 39: 135-143.

Thomas, N.J. and Carcillo, J. A. (1998). Hypovolemic Shock in Pediatric Patients. New Horizons Vol. 6, No. 2: 120-129.

Upadhyay, M., Singhi, S., Murlidharan, J., Kaur, N. and Majumdar, S. (2005). Randomized Evaluation of Fluid Resuscitation with Crystalloid (saline) and Colloid (polymer from degraded Gelatin in saline) in Pediatric Septic Shock. Indian Pediatrics Vol. 42: 223-231.

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