Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

multiBic 2 mmol/l potassium solution for haemodialysis/haemofiltration

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

multiBic 2 mmol/l potassium is provided in a two-compartment bag with 4750 ml of an alkaline hydrogen carbonate solution in one compartment and 250 ml of an acidic electrolyte, glucose solution in the other compartment.

BEFORE MIXING:
1000 ml solution contain:

Acidic electrolyte, glucose solution (small compartment)

Potassium chloride	2.982 g
Calcium chloride dihydrate	4.410 g
Magnesium chloride hexahydrate	2.033 g
Glucose monohydrate	22.00 g
(Glucose)	(20.00 g)
K^+	40 mmol/l
Ca^{2+}	30 mmol/l
Mg^{2+}	10 mmol/l
Cl^-	122 mmol/l
Glucose	111 mmol/l

Alkaline hydrogen carbonate solution (large compartment)

Sodium chloride	6.453 g
Sodium hydrogen carbonate	3.104 g
Na^+	147 mmol/l
Cl^-	110 mmol/l
HCO_3^-	37 mmol/l

AFTER MIXING:
1000 ml of the ready-to-use solution contain:

Potassium chloride	0.1491 g
Sodium chloride	6.136 g
Sodium hydrogen carbonate	2.940 g
Calcium chloride dihydrate	0.2205 g
Magnesium chloride hexahydrate	0.1017 g
Glucose monohydrate	1.100 g
(Glucose)	(1.000 g)
K^+	2.0 mmol/l
Na^+	140 mmol/l
Ca^{2+}	1.5 mmol/l
Mg^{2+}	0.50 mmol/l
Cl^-	111 mmol/l
HCO_3^-	35 mmol/l
Glucose	5.55 mmol/l

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for haemodialysis/haemofiltration.

The ready-to-use solution is clear and colourless.

Theoretical osmolarity:
296 mOsm/l

pH ≈ 7.4

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

multiBic 2 mmol/l potassium is indicated for intravenous use as substitution solution in haemofiltration and haemodiafiltration, and as dialysis solution in haemodialysis and haemodiafiltration.

For use in patients

- with acute kidney injury requiring continuous renal replacement therapy: continuous haemodialysis, haemofiltration or haemodiafiltration treatments.
- with chronic kidney disease in whom a transient treatment is indicated, e.g. during the stay on an intensive care unit.
- when continuous renal replacement therapy is indicated as part of the treatment of an intoxication with water soluble, filterable/dialyzable toxins.

multiBic 2 mmol/l potassium is indicated in adults.

4.2 Posology and method of administration

Continuous renal replacement therapy including the prescription of this medicinal product should be performed under the direction of a physician with experience in these treatments.

Posology
In acute kidney injury, a continuous treatment with a dose of 2000 ml/h multiBic 2 mmol/l potassium is appropriate in adults with a body weight of 70 kg to remove metabolic waste products depending on the metabolic status of the patient. The dose should be adapted to the body size of the patient.

In patients with chronic kidney disease, unless clinically indicated otherwise, the dose of multiBic 2 mmol/l potassium should be at least one third of the body weight per session with three sessions applied per week. Increasing the volume applied per week or distributing this weekly volume to more than 3 treatments per week can be required.

The dose and the duration of haemodialysis, haemofiltration or haemodiafiltration necessary in treatment of acute states of intoxication depends on the toxin and its concentration and the severity of clinical symptoms and has to be clinically decided on the individual patient's condition.

A maximum dose of 75 litre per day is recommended.

Paediatric population
The safety and efficacy of multiBic 2 mmol/l potassium in children have not yet been established (see sections 4.4 and 5.1).

Method of administration
For intravenous use and haemodialysis.
For instructions on use of the product, see section 6.6.

4.3 Contraindications

Solution related contraindications:
multiBic 2 mmol/l potassium:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Hypokalaemia
- Metabolic alkalosis

Contraindications for use of the technical procedure itself:

- Inadequate blood flow from vascular access.
- If there is a high risk of haemorrhage on account of systemic anticoagulation.

4.4 Special warnings and precautions for use

Use only after mixing of the two solutions.

multiBic 2 mmol/l potassium should be warmed prior to use with appropriate equipment to approximately body temperature and must not be used under any circumstances below room temperature.

The warming of the ready-to-use solutionto approximately body temperature must be carefully controlled verifying that the ready-to-use solutionis clear and without particles.
During application of the ready-to-use solution, white calcium carbonate precipitation has been observed in the tubing lines in rare cases, particularly close to the pump unit and the heating unit warming the ready-to-use solution.
Precipitations particularly can occur if the temperature of the ready-to-use solution at the inlet of the pump unit is already higher than 30°C.
Therefore, the ready-to-use solutionin the tubing lines must be closely visually inspected every 30 min during continuous renal replacement therapy in order to ensure, that the solution in the tubing system is clear and free from precipitate. Precipitations may occur also with substantial delay after start of treatment.
If precipitate is observed, the ready-to-use solution and the tubing lines used for continuous renal replacement therapy must be replaced immediately and the patient carefully monitored.

The serum potassium concentration must be checked regularly before and during continuous renal replacement therapy. The potassium status of the patient and its trend during the treatment must be considered:
In case of hypokalaemia supplementation of potassium and / or changing to a solution for haemodialysis/haemofiltration with higher potassium concentration may be required.
In case of hyperkalaemia an increase in the applied dose and / or change to a solution for haemodialysis/haemofiltration with a lower potassium concentration may be indicated as well as usual measures of intensive care medicine.

The serum sodium concentration must be checked regularly before and during use of this solution for haemodialysis/haemofiltrationto control risks related to hypo/hypernatraemia. The solution for haemodialysis/haemofiltration may be diluted with an adequate amount of water for injections or concentrated sodium chloride solution may be added if required. The speed of desired normalisation must then be carefully planned to avoid adverse reactions due to rapid changes in serum sodium concentration.

In addition, the following parameters must be monitored before and during continuous renal replacement therapy: Serum calcium, serum magnesium, serum phosphate, serum glucose, acid-base status, levels of urea and creatinine, body weight and fluid balance (for the early recognition of hyper- and dehydration).

Clinically important substances may be removed with the haemodialysis, haemofiltration and haemodiafiltration treatment and are not supplemented with this medicinal product. This removal of important nutrients must be compensated by adequate nutrition, nutritional supplements, or an adapted parenteral nutrition.

Paediatric population
There is no clinical experience on the use of this product in children. This medicinal product is not recommended for use in children until further data become available (see sections 4.2 and 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The correct dose of multiBic 2 mmol/l potassium and strict monitoring of clinical chemistry parameters and vital signs will avoid risks related to interactions with other medicinal products.

The following interactions are conceivable:

- Toxic effects of digitalis may be masked by hyperkalaemia, hypermagnesaemia and hypocalcaemia. The correction of these electrolytes by continuous renal replacement therapy may precipitate signs and symptoms of digitalis toxicity, e.g. cardiac arrhythmia.
- Electrolyte substitutions, parenteral nutrition and other infusions usually given in intensive care medicine interact with the serum composition and the fluid status of the patient. This must be considered during application of continuous renal replacement therapy.

- Continuous renal replacement therapy may reduce the blood concentration of drugs, especially of drugs with a low protein binding capacity, with a small distribution volume, with a molecular weight below the cut-off of the haemofilter and of medicinal products adsorbed to the haemofilter. An appropriate revision of the dose of such medicinal products may be required.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of multiBic 2 mmol/l potassium in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
multiBic 2 mmol/l potassium should not be used during pregnancy unless the clinical condition of the woman requires continuous renal replacement therapy.

Breastfeeding
There is insufficient information on the excretion of multiBic 2 mmol/l potassium active substances/metabolites in human milk. Breastfeeding is not recommended during treatment with multiBic 2 mmol/l potassium.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse reactions may result from the treatment mode itself or may be induced by this medicinal product:
Gastrointestinal disorders - nausea, vomiting
Vascular disorders - hypertension, hypotension
Musculoskeletal and connective tissue disorders - muscle cramps

The following adverse reaction can be anticipated for the treatment mode:
Metabolism and nutrition disorders - hyper- or hypohydration, electrolyte disturbances (e.g., hypokalaemia), hypophosphataemia, hyperglycaemia, and metabolic alkalosis.

The exact frequency of such events is not known (cannot be estimated from the available data).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance.
Website: www.hpra.ie

4.9 Overdose

After use of recommended doses no reports of emergency situations have arisen; moreover, the administration of this medicinal product can be discontinued at any time. If fluid balance is not accurately calculated and monitored, hyperhydration or dehydration may occur, with the resultant associated circulatory reactions. These may be manifest through changes in blood pressure, central venous pressure, heart rate, and pulmonary arterial pressure. In cases of hyperhydration congestive cardiac failure and/or pulmonary congestion may be induced.

In cases of hyperhydration, net fluid removal should be increased on the device used for continuous renal replacement therapy. In cases of marked dehydration, net fluid removal by the device used for continuous renal replacement therapy should be decreased or discontinued; alternatively, fluid resuscitation can be applied to restore the hydration status.

If too large volume is applied, this may result in disturbances of electrolyte concentrations and the acid-base-balance, e. g. an overdose of bicarbonate may occur if an inappropriate large volume of the solution for haemodialysis/haemofiltration is infused / administered. This could possibly lead to metabolic alkalosis, decrease of ionized calcium, or tetany.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Haemofiltrates, ATC code: B05Z B

Mechanism of action
Basic principles of haemodialysis, haemofiltration and haemodiafiltration:

During haemofiltration water and solutes such as uremic toxins, electrolytes, and bicarbonate are removed from the blood by ultrafiltration. The ultrafiltrate is replaced by a solution for haemofiltration, with a balanced electrolyte and buffer composition.

During haemodialysis, water and solutes such as uremic toxins, electrolytes, bicarbonate and other small molecules are exchanged between the patient's blood and the solution for haemodialysis by diffusion. The direction and the magnitude of the diffusion process depend on the relevant concentration gradients between the blood and the solution for haemodialysis.

In haemodiafiltration, the underlying principles of haemofiltration and haemodialysis are combined.

This medicinal product is a bicarbonate-buffered solution for intravenous administration or for use as haemodialysis solution for the balancing of water and electrolyte removal during continuous renal replacement therapies which are applied, e.g. in the treatment of acute kidney injury.
The electrolytes Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^-, and bicarbonate are essential for the maintenance and correction of fluids and electrolyte homeostasis (blood volume, osmotic equilibrium, acid-base balance).

Paediatric population
There is no clinical experience on the use of this product in children. This medicinal product is not recommended for use in children until further data become available (see sections 4.2 and 4.4).

5.2 Pharmacokinetic properties

This medicinal productmust only be administered intravenouslyor used as haemodialysis solution.

Distribution/Biotransformation/Elimination
The distribution of electrolytes and bicarbonate is regulated in accordance with requirements and the metabolic status and residual renal function. The active substances of this medicinal productare not metabolised except for glucose. The elimination of water and electrolytes depends on cellular requirements, the metabolic status, the residual renal function, and on other routes of fluid losses (e.g., gut, lung, and skin).

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Small compartment:
Water for injections
Hydrochloric acid 25 %

Large compartment:
Water for injections
Carbon dioxide
Sodium dihydrogen phosphate dihydrate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

Storage conditions after mixing of the two compartments (ready-to-use solution):
Chemical and physical in-use stability of the ready-to-use solution has been demonstrated for 48 hours at 30 °C. It is not recommended to store the ready-to-use solution longer than 48 h including duration of treatment or at a temperature higher than 30 °C prior to the inlet of the pump unit.
From a microbiological point of view, once connected to the haemodialysis,haemofiltration or haemodiafiltration circuit, and as hydrogen carbonate is present, the product shall be used immediately.

6.4 Special precautions for storage

Do not store below +4 °C.

6.5 Nature and contents of container

Double chamber bag with 4750 ml (alkaline hydrogen carbonate solution) + 250 ml (acidic electrolyte, glucose solution) = 5000 ml (ready-to-use solution).

The foil used for the bag is made of polyethylene-terephthalate, SiOx, polyamide, and polyolefine.

Each bag is equipped with a HF-connector, a Luer-lock-connector and an injection port, and is covered by a protective foil.

Pack size:
2 bags of 5000 ml

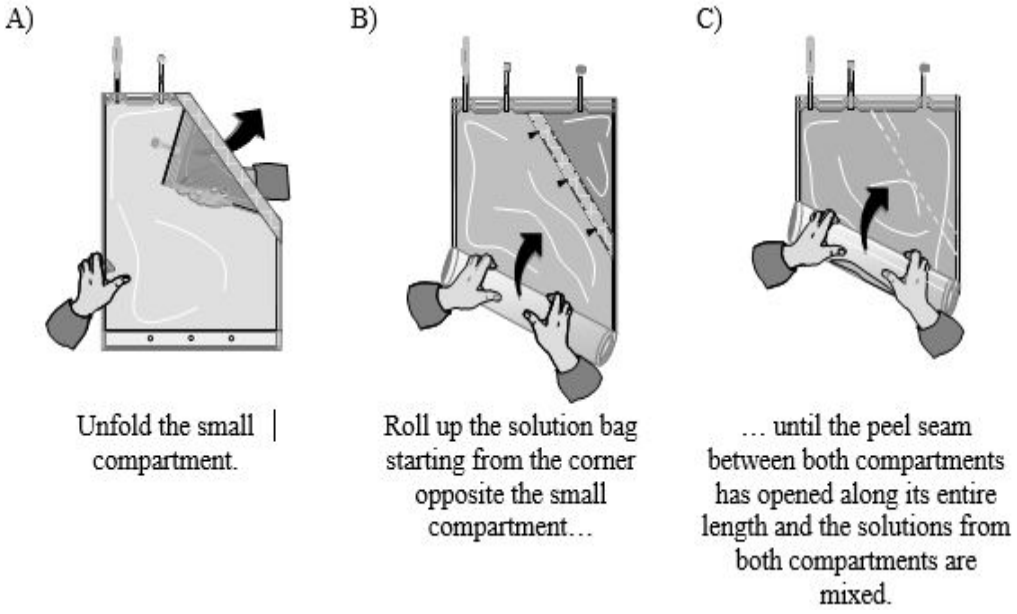
6.6 Special precautions for disposal and other handling

Do not use unless the ready-to-use solution is clear and colourless and the bag and connectors are undamaged.
For single use only. Any unused solution must be discarded.
Must be used by means of metering pumps.

The solution for haemodialysis/haemofiltration should be administered in three steps:

1. Removal of the protective foil and careful inspection of the bag
The protective foil should only be removed immediately before administration.
Plastic containers may occasionally be damaged during transport from the manufacturer to the clinic or within the clinic itself. This can lead to contamination and microbiological or fungal growth in the solutions. Therefore, careful visual inspection of the bag and the solutions before mixing is necessary. Particular attention should be paid to even the slightest damage to the closure, the welded seam and the corners of the bag in view of a possible contamination.

2. Mixing of the two compartments
The two-compartment-bag - the bicarbonate and the electrolytes including glucose compartments - are mixed immediately before use to obtain a ready-for-use solution.



After mixing both compartments, it must be checked, that the peel seam is completely open, that the mixed solution is clear and colourless and that the bag is not leaking.

3. Application of the ready-to-use solution

The ready-to-use solution must be used immediately, but within a maximum of 48 hours after mixing.
Any admixture to the ready-to-use solution must only be done after the ready-to-use solution has been thoroughly mixed. After such an admixture, the ready-to-use solution should again be thoroughly mixed prior to use.

Admixtures of sodium chloride solution (concentration between 3% and 30% sodium chloride; up to 250 mmol sodium chloride per 5 litre multiBic solution) and water for injection (up to 1250 ml per 5 litre multiBic solution) are compatible with this medicinal product.

If not otherwise prescribed, the ready-to-use solution should be warmed immediately before use to 36.5°C – 38.0°C. The exact temperature must be selected depending on clinical requirements and the technical equipment used.

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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61352 Bad Homburg v.d.H.
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8 MARKETING AUTHORISATION NUMBER

PA1350/009/002

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