FRESENIUS MEDICAL CARE ISRAEL P.B. LTD.

פרזניוס מדיקל קר ישראל פי.בי. בע"מ

דצמבר 2020

רופא/ה רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא ועלון לצרכן של

**Multibic Potassium – Free**
**Multibic 2 mmol/l Potassium**
**Multibic 3 mmol/l Potassium**
**Multibic 4 mmol/l Potassium**

חומר פעיל:

| | MULTIBIC potassium-free | MULTIBIC 2 mmol/l potassium | MULTIBIC 3 mmol/l potassium | MULTIBIC 4 mmol/l potassium |
|---|---|---|---|---|
| Potassium chloride | - | 0.1491 g | 0.2237 g | 0.2982 g |
| Sodium chloride | 6.136 g | 6.136 g | 6.136 g | 6.136 g |
| Sodium hydrogen carbonate | 2.940 g | 2.940 g | 2.940 g | 2.940 g |
| Calcium chloride dihydrate | 0.2205 g | 0.2205 g | 0.2205 g | 0.2205 g |
| Magnesium chloride hexahydrate | 0.1017 g | 0.1017 g | 0.1017 g | 0.1017 g |
| Glucose monohydrate (Glucose) | 1.100 g (1.000 g) | 1.100 g (1.000 g) | 1.100 g (1.000 g) | 1.100 g (1.000 g) |

**להלן עדכונים בעלון לרופא** (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן בצהוב משמעותו החמרה):

## 1. NAME OF THE MEDICINAL PRODUCT

**MULTIBIC potassium-free ~~Solution for Haemofiltration~~**
**MULTIBIC 2 mmol/l potassium ~~Solution for Haemofiltration~~**
**MULTIBIC 3 mmol/l potassium ~~Solution for Haemofiltration~~**
**MULTIBIC 4 mmol/l potassium ~~Solution for Haemofiltration~~**

Note: this document presents the SmPCs for all four MULTIBIC ~~multiBic~~ strengths (potassium-free/2/3/4 mmol/l potassium) in one document, clearly indicating with grey-shaded titles the strength to which alternative text elements refer.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MULTIBIC potassium-free/2/3/4 mmol/l potassium is provided in a two-compartment bag with ~~4.75 l~~ 4750 ml of an alkaline hydrogen carbonate solution in one compartment and ~~0.25~~ 1250 ml of an acidic electrolyte, glucose solution in the other compartment.

BEFORE MIXING:

~~each~~ 1000 ml solution contain~~s~~:

Acidic electrolyte, glucose solution (small compartment)

| | MULTIBIC potassium-free | MULTIBIC 2 mmol/l potassium | MULTIBIC 3 mmol/l potassium | MULTIBIC 4 mmol/l potassium | ~~Unit~~ |
|---|---|---|---|---|---|
| Potassium chloride | ~~0~~ - | 2.982 g | 4.473 g | 5.964 g | ~~g~~ |
| Calcium chloride dihydrate | 4.410 g | 4.410 g | 4.410 g | 4.410 g | ~~g~~ |
| Magnesium chloride hexahydrate | 2.033 g | 2.033 g | 2.033 g | 2.033 g | ~~g~~ |
| | | | | | |
| Glucose ~~anhydrous as Glucose~~ monohydrate | 2~~0~~.00 g ~~22.00~~ | ~~20~~22.00 g ~~22.00~~ | ~~20~~22.00 g ~~22.00~~ | 2~~0~~.00 g ~~22.00~~ | ~~g~~ |
| (Glucose) | (20.00 g) | (20.00 g) | (20.00 g) | (20.00 g) | |
| | | | | | |
| $K^{+}$ | 0 mmol/l | 40 mmol/l | 60 mmol/l | 80 mmol/l | ~~mmol~~ |
| $Ca^{2+}$ | 30 mmol/l | 30 mmol/l | 30 mmol/l | 30 mmol/l | ~~mmol~~ |
| $Mg^{2+}$ | 10 mmol/l | 10 mmol/l | 10 mmol/l | 10 mmol/l | ~~mmol~~ |
| $Cl^{-}$ | 82 mmol/l | 122 mmol/l | 142 mmol/l | 162 mmol/l | ~~mmol~~ |
| Glucose | 111 mmol/l | 111 mmol/l | 111 mmol/l | 111 mmol/l | ~~mmol~~ |

Alkaline hydrogen carbonate solution (large compartment)

| | MULTIBIC potassium-free | MULTIBIC 2 mmol/l potassium | MULTIBIC 3 mmol/l potassium | MULTIBIC 4 mmol/l potassium | ~~Unit~~ |
|---|---|---|---|---|---|
| Sodium chloride | 6.453 g | 6.453 g | 6.453 g | 6.453 g | ~~g~~ |
| Sodium hydrogen carbonate | 3.104 g | 3.104 g | 3.104 g | 3.104 g | ~~g~~ |
| $Na^{+}$ | 147~~.37~~ mmol/l | 147~~.37~~ mmol/l | 147~~.37~~ mmol/l | 147~~.37~~ mmol/l | ~~mmol~~ |
| $Cl^{-}$ | 110~~.42~~ mmol/l | 110~~.42~~ mmol/l | 110~~.42~~ mmol/l | 110~~.42~~ mmol/l | ~~mmol~~ |
| $HCO_3^{-}$ | 3~~76.95~~ mmol/l | 3~~76.95~~ mmol/l | 3~~76.95~~ mmol/l | 3~~76.95~~ mmol/l | ~~mmol~~ |

AFTER MIXING:
1000 ml of the ready-to-use solution ~~MULTIBIC potassium-free/2/3/4 mmol/l~~ contain: ~~potassium contains:~~

| | MULTIBIC potassium-free | MULTIBIC 2 mmol/l potassium | MULTIBIC 3 mmol/l potassium | MULTIBIC 4 mmol/l potassium | ~~Unit~~ |
|---|---|---|---|---|---|
| Potassium chloride | ~~-0~~ | 0.1491 g | 0.2237 g | 0.2982 g | ~~g~~ |
| Sodium chloride | 6.136 g | 6.136 g | 6.136 g | 6.136 g | ~~g~~ |
| Sodium hydrogen carbonate | 2.940 g | 2.940 g | 2.940 g | 2.940 g | ~~g~~ |
| Calcium chloride dihydrate | 0.2205 g | 0.2205 g | 0.2205 g | 0.2205 g | ~~g~~ |
| Magnesium chloride hexahydrate | 0.1017 g | 0.1017 g | 0.1017 g | 0.1017 g | ~~g~~ |
| Glucose ~~anhydrous as Glucose~~ monohydrate | 1.~~000~~100 g ~~1.100~~ | 1.~~000~~100 g ~~1.100~~ | 1.~~1~~000 g ~~1.100~~ | 1.~~000~~100 g ~~1.100~~ | ~~g~~ |
| (Glucose) | (1.000 g) | (1.000 g) | (1.000 g) | (1.000 g) | |
| | | | | | |
| $Na^+$ | 140 mmol/l | 140 mmol/l | 140 mmol/l | 140 mmol/l | ~~mmol~~ |
| $K^+$ ~~+~~ | 0 mmol/l | 2.0 mmol/l | 3.0 mmol/l | 4.0 mmol/l | ~~mmol~~ |
| $Ca^{2+}$ | 1.5 mmol/l | 1.5 mmol/l | 1.5 mmol/l | 1.5 mmol/l | ~~mmol~~ |
| $Mg^{2+}$ | 0.50 mmol/l | 0.50 mmol/l | 0.50 mmol/l | 0.50 mmol/l | ~~mmol~~ |
| $Cl^-$ | 109 mmol/l | 111 mmol/l | 112 mmol/l | 113 mmol/l | ~~mmol~~ |
| $HCO_3^-$ ~~-~~ | 35 mmol/l | 35 mmol/l | 35 mmol/l | 35 mmol/l | ~~mmol~~ |
| Glucose | 5.55 mmol/l | 5.55 mmol/l | 5.55 mmol/l | 5.55 mmol/l | ~~mmol~~ |

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.

[…]

pH ≈ 7.4~~2~~

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic ~~Indication~~indication

MULTIBIC potassium-free/2/3/4 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 potassium-free/2/3/4 mmol/l potassium is indicated in adults.

~~with acute renal failure requiring continuous haemofiltration.~~

**4.2 Posology and ~~Method~~ method of ~~Administration~~administration**

Continuous ~~Haemofiltration in patients with acute~~ renal replacement therapy~~failure~~ including the prescription of this medicinal product ~~substitution solutions~~ should be performed under the direction of a physician with experience in these~~is~~ treatments.

Posology
In acute kidney injury, a continuous treatment with a dose of 2000 ~~renal failure treatment is carried out for a limited period and is discontinued when renal function is fully restored.~~
~~MULTIBIC potassium-free/2/3/4 mmol/l potassium is exclusively indicated for intravenous use.~~
~~Infuse the ready-to-use solution into the extracorporeal circulation by means of a metering pump.~~
~~As blood serum is filtered off in haemofiltration the filtered volume, minus the necessary ultrafiltration fluid, must be substituted in the form of haemofiltration solution.~~
~~The filtration rate is prescribed by the attending physician depending on the clinical status and the body weight of the patient. Unless otherwise prescribed a total filtration rate of 800 to 1400~~ ml/h MULTIBIC potassium-free/2/3/4 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 potassium-free/2/3/4 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 potassium-free/2/3/4 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.
~~A maximum filtration rate of 75 l per day is recommended.~~
~~There is no clinical experience on the use and dosing of this product in children.~~ For instructions on use of the product, see section 6.6.

**4.3 Contraindications**

Solution related ~~dependent~~ contraindications:

**MULTIBIC potassium-free/2/3 mmol/l potassium:**
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

~~• Hypokalaemia~~
- Hypokalaemia
~~•~~ - Metabolic alkalosis

**MULTIBIC 4 mmol/l potassium:**
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
~~•~~ - Hyperkalaemia
~~•~~ - Metabolic alkalosis

~~Haemofiltration dependent c~~Contraindications for use of ~~due to~~ the technical procedure itself:

- ~~Renal failure with increased hypercatabolism in cases where uraemic symptoms can no longer be relieved by haemofiltration.~~
- Inadequate blood flow from vascular access.
- If there is a high risk of haemorrhage on account of systemic anticoagulation.

### 4.4 Special ~~w~~Warnings and ~~p~~Precautions for ~~u~~Use

Use only after mixing of the two solutions.

MULTIBIC potassium-free/2/3/4 mmol/l potassium
~~The haemofiltration solution~~ should be warmed prior to use ~~infusion~~ with appropriate equipment to approximately body temperature and must not be used ~~infused~~ under any circumstances below room temperature.

The warming of ~~this~~ the ready-to-use solution to approximately body temperature must be carefully controlled verifying that the ready-to-use solution is clear and without particles.
During application of the ready-to-use solution~~multiBic in CRRT~~, 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~~multiBic~~.
Precipitations particularly can occur if the temperature of the ready-to-use ~~multiBic~~ solution at the inlet of the pump unit is already higher than ~~25~~30°C.
Therefore, the ready-to-use ~~multiBic~~ solution in the tubing lines must~~should~~ be closely visually inspected every 30 min during continuous renal replacement therapy~~CRRT~~ 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 ~~multiBic~~ solution and the~~CRRT~~ 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~~haemofiltration~~. The potassium status of the patient and its trend during the treatment ~~haemofiltration~~ 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.
~~If hypokalaemia is present or tends to develop, supplementation of potassium and / or changing to a substitution solution with higher potassium concentration may be required.~~
~~MULTIBIC potassium-free:~~
~~If~~ In case of hyperkalaemia ~~tends to develop,~~ an increase in the applied dose and / or change to a solution for haemodialysis/haemofiltration with a lower potassium concentration ~~filtration rate~~ 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/haemofiltration to 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.

~~**MULTIBIC 2/3/4 mmol/l potassium:**~~

~~If hyperkalaemia tends to develop, an increase in the filtration rate and / or changing to a substitution solution with a lower potassium concentration may be indicated as well as usual measures of intensive care medicine.~~
In addition, the following parameters must~~should~~ be monitored before and during continuous renal replacement therapy~~haemofiltration~~:
Serum ~~sodium, 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).~~Prior to use the solution bag must be carefully inspected as described in detail in Section 6.6 "Special precautions for disposal and other handling".~~

~~Do not use before mixing the two solutions.~~

## 4.5 Interaction with o~~O~~ther m~~M~~edicinal p~~P~~roducts and o~~O~~ther f~~F~~orms of i~~I~~nteraction

No interaction studies have been performed.

The correct dose of MULTIBIC potassium-free/2/3/4 mmol/l potassium ~~dosing of substitutions solutions~~ and strict monitoring of clinical chemistry parameters and vital signs will avoid risks related to interactions with other medicinal products~~drugs~~.

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.~~when prescribing haemofiltration treatment.~~
- Continuous renal replacement therapy ~~Haemofiltration treatment~~ 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 ~~drugs~~ adsorbed to the haemofilter. An appropriate revision of the dose of such medicinal products ~~drugs~~ may be required.

- ~~Toxic effects of digitalis may be masked by hyperkalaemia, hypermagnesaemia and hypocalcaemia. The correction of these electrolytes by haemofiltration may precipitate signs and symptoms of digitalis toxicity, e.g. cardiac arrhythmia.~~

### 4.6 Fertility, Pregnancy and Lactation

Pregnancy
There are no or limited amount of data from the use of MULTIBIC potassium-free/2/3/4 mmol/l potassium in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
MULTIBIC potassium-free/2/3/4 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 potassium-free/2/3/4 mmol/l potassium active substances/metabolites in human milk.
Breastfeeding is not recommended during treatment with MULTIBIC potassium-free/2/3/4 mmol/l potassium.

Fertility

No data available.

~~At present no clinical experience is available. The bicarbonate-buffered substitution solution must only be used after assessment of the potential risks and benefits for the mother and child.~~

### 4.7 Effects on ~~a~~Ability to ~~d~~Drive and ~~u~~Use ~~m~~Machines

Not relevant.

### 4.8 Undesirable ~~e~~Effects

Adverse reactions~~, such as nausea, vomiting, muscle cramps, hypotension and hypertension,~~ may result from the treatment mode itself or may be induced by this medicinal product:~~the substitution solution.~~
Gastrointestinal disorders - nausea, vomiting
Vascular disorders - hypertension, hypotension
Musculoskeletal and connective tissue disorders - muscle cramps
~~In general, the tolerability of bicarbonate buffered haemofiltration solution is good. However,~~
~~the~~ The following adverse reaction ~~potential side effects of the treatment~~ can be anticipated for the treatment mode:
Metabolism and nutrition disorders- h~~H~~yper- 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 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

**4.9 Overdose**

After use of recommended doses no reports of emergency situations have arisen; moreover, the administration of this medicinal product ~~the solution~~ 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 ~~ultrafiltration~~ should be increased on~~, and~~ the device used for continuous renal replacement therapy~~rate and volume of substitution solution infused reduced~~. In cases of marked dehydration, net fluid removal by the device used for continuous renal replacement therapy ~~, ultrafiltration~~ should be decreased or discontinued~~;~~ alternatively, fluid resuscitation can be applied to restore the hydration status~~and the volume of substitution solution infused increased as appropriate~~.

If too large volume is applied, this ~~Over treatment~~ 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~~substitution~~ 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 p~~P~~roperties**

Pharmacotherapeutic group:
~~Group: Solution for h~~Haemofiltrates~~,ion~~
ATC code**:** B05Z B
~~- Haemofiltrates~~
Mechanism of action
Basic principles of haemodialysis, ~~Haemofiltration~~haemofiltration and haemodiafiltration:

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

~~The ready-to-use haemofiltration solution~~ 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 ~~substitution~~ 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 ~~renal failure of any origin by continuous haemofiltration~~.

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 ~~p~~Properties

This medicinal product~~The ready-to-use haemofiltration solution~~ must only be administered intravenously or 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 product ~~the substitution solution~~ are not ~~metabolized~~ 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 ~~S~~safety ~~D~~data

There are no preclinical data of relevance to the prescriber.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of ~~E~~excipients

~~In s~~small compartment ~~A~~:
Water for injections
Hydrochloric acid 25%

~~In l~~large compartment ~~B~~:
Water for injections
Carbon dioxide
Sodium dihydrogen phosphate dihydrate

### 6.2 Incompatibilities

TIn the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. If an addition to the substitution solution is done, it should be done only after evaluating the compatibility with the substitution solution and only after the two compartments of the substitution solution have been thoroughly mixed.except those mentioned in section 6.6.

### 6.3 Shelf Life

The expiry date of the product is indicated on the packaging materials.

Storage conditions after mixing of the two compartments (ready-to-use solution):
Shelf life
of the medicinal product packaged for sale 12 months
Shelf life after opening of the container: -
Shelf life after mixing: 48 hours
Chemical and physical in-use stability of the ready-to-use solution has been demonstrated for 48 hours at 2530°C. It is not recommended to store the ready-to-Other in use solution storage times and conditions prior to use (longer than 48 hours including the duration of the treatment or at a temperature, higher than 2530°C prior to the inlet of the pump unit) are the responsibility of the user.

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. Other in-use storage times and conditions are the responsibility of the user.

### 6.4 Special pPrecautions for sStorage

Do not store below +4°C.

Do not refrigerate or freeze

### 6.5 Nature and cContents of cContainer

Double chamber bag: with 4750 ml
4.75 l (alkaline hydrogen carbonate solution) + 250 ml 0.25 l (acidic electrolyte, glucose solution) = 5000 ml 5.0 l (ready-to-use solution).

The foilfilm used for the bag is made of polyethylene polyethylene terephthalate, which is coated with SiOx as a gas barrier, polyamide, and a polypropylene synthetic elastomer blend.
Overwrapping:
The double chamber bag is wrapped into a film made of a
polyolefine synthetic
elastomer and/or plastomer blend.

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
~~(carton)~~

**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 ~~haemofiltration~~ solution ~~should~~ for haemodialysis/haemofiltration should be administered in three ~~the following~~ steps:

1. Removal of the protective foil ~~overwrapping~~ and careful inspection of the ~~haemofiltration~~ bag

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

~~The solution should only be used if clear and colourless and if the container and connectors are undamaged and intact.~~

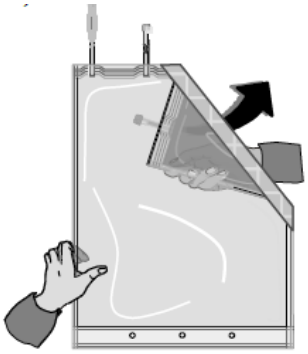
~~In case of doubt, the treating physician should decide about the use of the haemofiltration solution.~~

~~4.~~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

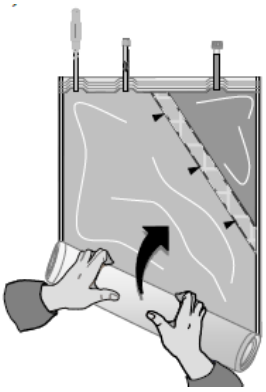
~~solution~~ ready-for-use solution.~~. The mixed solution is clear and colourless.~~

A)



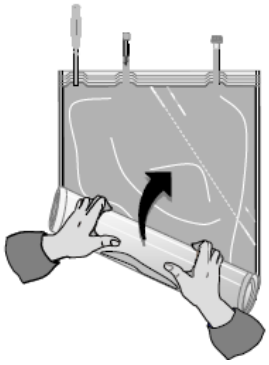
Unfold the small compartment.

B)



Roll up the solution bag starting from the corner opposite the small compartment ...

C)



…until the peel seam between both compartments has opened along its entire length and the solutions from both compartments are mixed.

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 container is not leaking.

3. Application of the r~~R~~eady-to-use solution

The ready-to-use solution must~~should~~ be used immediately, but within a maximum of 48 hours after mixing.

Any admixture ~~addition~~ to the ready-to-use~~substitution~~ solution must~~should~~ only be done after the ready-to-use ~~substitution~~ solution has been thoroughly mixed. ~~(see also 6.2).~~
After such an admixture ~~addition~~, the ready-to-use ~~substitution~~ solution should again be thoroughly mixed prior to ~~the start of the infusion~~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 ~~substitution~~ solution should be warmed immediately before ~~-~~ use ~~infusion~~ 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. ~~The haemofiltration solution is for single use.~~

~~Partially used and damaged containers should be discarded.~~

## 7. ~~7.~~ MANUFACTURER

Fresenius Medical Care Deutschland GmbH
Else-Kroner-Strasse 1, 61352 Bad Homburg v.d.H
~~61346 Bad Homburg v.d.H~~
Germany

## 8. MARKETING AUTHORISATION NUMBER

Multibic Potassium- Free 136-15-31270-00
Multibic 2 mmol/l Potassium 136-17-31272-00
Multibic 3 mmol/l Potassium 136-16-31271-00
Multibic 4 mmol/l Potassium 136-18-31273-00

## ~~8.~~9. REGISTRATION HOLDER:

Fresenius Medical Care Israel P.B.~~NEPHROMED~~ -LTD.
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בברכה
חגי וגנר
רוקח ממונה

FRESENIUS MEDICAL CARE
ISRAEL P.B. LTD.

פרזניוס מדיקל קר
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