CENTER FOR DRUG EVALUATION AND RESEARCH

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21-703

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	PrismaSol
(Proposed) Trade Name	PrismaSol™ solutions
Therapeutic Class	Infusate
Applicant	Renal therapeutics
Priority Designation	S
Formulation	Solution
Dosing Regimen	N/A
Indication	Infuse solution for continuous renal replacement therapy [redacted] for Hemodialysis and Hemodiafiltration
Intended Population	Acute renal failure

CLINICAL REVIEW

Clinical Review Section

Table of Contents

1 EXECUTIVE SUMMARY 4

1.1 RECOMMENDATION ON REGULATORY ACTION 4
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS 6
1.2.1 Risk Management Activity 6
1.2.2 Required Phase 4 Commitments 6
1.2.3 Other Phase 4 Requests 6
1.3 SUMMARY OF CLINICAL FINDINGS 6
1.3.1 Brief Overview of Clinical Program: 6
1.3.2 Efficacy 6
1.3.3 Safety 7
1.3.4 Dosing Regimen and Administration 7
1.3.5 Drug-Drug Interactions 7
1.3.6 Special Populations 7

2 INTRODUCTION AND BACKGROUND 8

2.1 PRODUCT INFORMATION 8
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 10
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 10
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 11
2.5 PRESUBMISSION REGULATORY ACTIVITY: 11
2.6 OTHER RELEVANT BACKGROUND INFORMATION 11

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 11

3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE): 11
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 11

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 11

4.1 SOURCES OF CLINICAL DATA 11
4.2 TABLES OF CLINICAL STUDIES 11
4.3 REVIEW STRATEGY 11
4.4 DATA QUALITY AND INTEGRITY 11
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 11
4.6 FINANCIAL DISCLOSURES: 11

5 CLINICAL PHARMACOLOGY 12

6 INTEGRATED REVIEW OF EFFICACY 12

6.1 INDICATION 12
6.1.1 Methods 12
6.1.2 General Discussion of endpoints 12
6.1.3 Study Design 12
6.1.4 Efficacy Findings 12
6.1.5 Efficacy Conclusions 23

CLINICAL REVIEW

Clinical Review Section

7 INTEGRATED REVIEW OF SAFETY 23

8 ADDITIONAL CLINICAL ISSUES 24

8.1 DOSING REGIMEN AND ADMINISTRATION 24
8.2 DRUG-DRUG INTERACTIONS 24
8.3 SPECIAL POPULATIONS 25
8.4 PEDIATRICS 25
8.5 ADVISORY COMMITTEE MEETING 25
8.6 LITERATURE REVIEW 25
8.7 POSTMARKETING RISK MANAGEMENT PLAN 25
8.8 OTHER RELEVANT MATERIALS 25

9 OVERALL ASSESSMENT 25

9.1 CONCLUSIONS 25
9.2 RECOMMENDATION ON REGULATORY ACTION 26
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS 27
9.4 LABELING REVIEW 27
9.5 COMMENTS TO APPLICANT 27

10 APPENDICES 28

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS 28
10.2 PRE-NDA MEETING MINUTES 37

Abbreviations

ACHDF	acute continuous hemodiafiltration
ARF	acute renal failure
C-ARF	acute renal failure in children
CAVH	continuous arterio-venous hemofiltration
CAVHD	continuous arterio-venous hemodialysis
CAVHDF	continuous arterio-venous hemodiafiltration
CONC	Concentration
CRRT	continuous renal replacement therapy
CVVH	continuous veno-venous hemofiltration
CVVHD	continuous veno-venous hemodialysis
CVVHDF	continuous veno-venous hemodiafiltration
ESRD	end stage renal disease
FDA	US Food & Drug Administration
H	Hour
HD	Hemodialysis
HDF	Hemodiafiltration
HF	Hemofiltration
ICU	intensive care unit
IHD	intermittent hemodialysis
IT	intermittent treatment
IV	Intravenous
L	Liter
mEq	Milliequivalent
mL	Milliliter
mmol	Millimole
MODS	multiple organ dysfunction syndrome
NA	not available
PTH	parathyroid hormone
RRT	renal replacement therapy
TT	Treatment

CLINICAL REVIEW

Clinical Review Section

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

1. It is recommended that PrismaSol be approved for the indication as a replacement solution in continuous renal replacement therapy (CRRT) to treat the patients with acute renal failure.

Based on the results of published clinical studies, the medical reviewer concludes that there is sufficient documentation in these articles to adequately evaluate the safety and efficacy of the PrismaSol formulations in the indicated ARF patient population when used as replacement solutions in CRRT. Within the physiological osmolarity, these solutions contain a buffer and electrolytes in concentration aiming for physiological levels and taking into account preexisting deficits or excesses. Even though not all of the formulations have been tested in every condition and age group, **the range of concentrations of electrolytes and dextrose proposed in this application is covered by the cited reports as shown in the following table.** Although formulations 2, 6, and 9 from PrismaSol are calcium-free solutions which have not been used regularly, calcium-free dialysates have been commonly used to treat the dialysis patients with hypercalcemia. In addition, 10% $CaCl_2$ can be added to the solution if necessary during CRRT. Therefore, these formulations are acceptable. There were no specific clinical studies conducted by the sponsor on this product. Support for efficacy and safety has been based on the clinical reports from published literature.

Summary of Compositions of Bicarbonate Replacement solutions Used in CRRT from Published Literature

Components	Bicarbonate Replacement Solution
Sodium	138-142 mEq/L
Potassium	0-4.5 mEq/L
Chloride	95-115 mEq/L
Magnesium	1-2.5 mEq/L
Calcium*	0-8mEq/L
Bicarbonate	30-40 mEq/L
Lactate	0-3 mEq/L
Dextrose	0-100mg/dL
Osmolality	284-310 mOsm/L
pH	N/A

*: Calcium will be added in calcium-free solutions if necessary

Composition of PrismaSol solutions:

	HCO_3^- mEq/L	Lactate mEq/L	Ca^{2+} mEq/L	Mg^{2+} mEq/L	K^+ mEq/L	Na^+ mEq/L	Cl^- mEq/L	Dextrose mg/dL
# 1 (PrismaSol BK0/3.5)	32	3.0	3.5	1.0	0	140	109.5	0
# 2 (PrismaSol BGK2/0)	32	3.0	0	1.0	2.0	140	108.0	100
# 3 (PrismaSol BGK2/3.5)	32	3.0	3.5	1.0	2.0	140	111.5	100
# 4 (PrismaSol BGK4/3.5)	—	—	—	—	—	—	—	—
# 5 (PrismaSol BGK4/2.5)	32	3.0	2.5	1.5	4.0	140	113.0	100
# 6 (PrismaSol BGK4/0)	32	3.0	0	1.5	4.0	140	110.5	100
# 7 (PrismaSol BK4/2.5)	—	—	—	—	—	—	—	—
# 8 (PrismaSol BGK0/2.5)	32	3.0	2.5	1.5	0	140	109.0	100
# 9 (PrismaSol BK0/0)	32	3.0	0	1.5	0	140	106.5	0

Summary of Compositions of All types of Replacement Solutions used in CRRT from Published Literature*

	Study 1		Study 2		Study 3		Study 4			Study 5
	CVVH		CVVH		CVVH		CVVH			CAVH
Na (mmol/L)	135	140	142	140	140	140	142	140	140	140
K (mmol/L)	2	2	0	0	3.7	3.7	0	0	0	0
Mg (mmol/L)	0.75	0.5	0.75	0.5	0.8	0.5	0.75	1.0	0.5	0.5
Ca (mmol/L)	1.875	1.5	2.0	1.75	1.6	1.75	2.0	2.0	1.5	1.75
C l(mmol/L)	109	111	103	110	100	109.5	103	111	109	110
HCO_3 (mmol/L)	0	35	0	34.5	0	32	0	0	35	31.4
Lactate (mmol/L)	33.75	0	44.5	3	46	3	44.5	0	0	2.9
Acetate (mmol/L)	0	0	0	0	0	0	0	35	0	0
Glucose (mmol/L)	8.3	5.6	5.6	5.6	10.8	0	0	0	0	0
Anion (meql/L)	143	146	147.5	147.5	146	145	147.5	146	144	144.3
Cation (meq/L)	142	146	145.5	144.5	147	148.2	145.5	146	144	144.5
Osmolality (mOsm)	293	298	299	297	304	293	293	292	288	289

	Study 6		Study 7	Study 8		Study 9		Study 14	Study 15
	HF		HF	HDF		CVVHDF	CVVH	CRRT	CVVHD
Na (mmol/L)	142	142	140	138	139	150	140	145	140
K (mmol/L)	0	0	1.5	2.0	2.0	0	1.0	4.5	2
Mg (mmol/L)	0.75	0.5	1.5	1.0	1.0	1.25	0.8	0.53	1
Ca (mmol/L)	2.0	1.75	4.0	3.5	3.5	0.55	1.5	1.84	0[a]
Cl (mmol/L)	111	110	113	110	106	112.5	100	115	95
HCO_3 (mmol/L)	0	40	40	0	36	37.5	0	35	40
Lactate (mmol/L)	45	3	0	0	0	0	46	3.16	0
Acetate (meq/L)	0	0	4	35	4	0	0	0	0
Glucose (mmol/L)	0	5.6	0	0	0	0	0	0	5.6
Anion (mEq/L)	156	153	157	145	146	140	146	153.16	135
Cation (mEq/L)	147.5	147.5	152.5	149	150	153.6	145.6	154	144
Osmolality (mOsm)	304	306	310	294	296	293.6	292	307	284

*: Solution buffers including bicarbonate, acetate, and lactate. a: $CaCl_2$ was added separately.

Outstanding issues with regard to these solutions include the following:

- PrismaSol solutions as replacement solutions in CRRT contained 9 formulations. The selection of the different formulations from PrismaSol solution and the monitoring of the balance of body fluids, electrolytes and acid-base situations in patients are the key factors for CRRT for safety concerns. Therefore, indications of each formulation of PrismaSol solutions in CRRT should be labeled in detail to avoid the misuse of the solution and cause the imbalance of body volume and acid-base, and disturbance of plasma electrolytes.
- Application of citrate as an anticoagulant in patients with hemorrhagic trends and treated with CRRT is common. After the long-term use of this anticoagulant agent, the plasma concentration of bicarbonate will significantly increase due to the conversion of metabolized citrate to bicarbonate, and the concentrations of sodium or calcium may also change significantly. Therefore, the formulations of the PrismaSol solutions may need to be adjusted in that situation. This information should be added to the labeling.
- PrismaSol solutions do not contain phosphate and phosphate supplementation is generally required at some stage during CRRT. Therefore, customized solutions may be necessary in patients with some electrolyte imbalances. This information should also be added into the labeling.

1.2 Recommendation on Post-marketing Actions:
N/A

1.2.1 Risk Management Activity:
N/A

1.2.2 Required Phase 4 Commitments
There are no required phase 4 commitments associated with this review or submission.

1.2.3 Other Phase 4 Requests:
N/A

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program:
No specific clinical program was conducted by the sponsor. All clinical data were cited from published literature. The sponsor provided a total of 34 papers in this application to support the product. These papers included 10 about hemofiltration, 6 about hemodiafiltration, 13 about hemodialysis, 3 about CRRT in children and 2 about continuous veno-venous hemofiltration (CVVH) or continuous veno-venous hemodialysis (CVVHD) for intoxication. In addition, the reviewer has also performed PubMed search using the words of " dialysate, replacement solutions, CRRT, hemofiltration, or hemodiafiltration" to compare the solutions that were used in these published studies with the PrismaSol solutions.

1.3.2 Efficacy:
Based on the clinical reports from the published data, the nine formulations of PrismaSol solution appear to be acceptable for CRRT. In pediatric patients, PrismaSol solutions appear to

match the requirements in the CRRT treatment. However, more studies may be needed based on the limited publications and available data. Details were provided in section 6.

1.3.3 Safety:
No specific safety studies with the solutions were reported. Based on the clinical studies published from literature, the compositions of PrismaSol solution were formulated from normal physiological electrolytes, buffers, dextrose, and water. No significantly solution-related safety issues were reported. Details were provided in section 7.

1.3.4 Dosing Regimen and Administration:
The proposed dosing depends on the mode of therapy, solute formulation, flow rates and length of therapy and depends on the clinical condition of the patient as well as the patient's fluid, electrolyte, acid-base and glucose balance. However, indication for each formulation of the nine formulations of PrismaSol should be labeled. For example, patients with hyperkalemia should not be treated with PrismaSol solutions # 4,5, 6, or 7 at the beginning. Patients with hypocalcemia should not be treated with solutions # 2, 6, or 9.

1.3.5 Drug-Drug Interactions:
As with the use of other replacement and dialysis solutions, plasma concentrations of filterable/dialyzable drugs may be influenced by CRRT. The blood concentrations of certain drugs may need to be monitored and appropriate therapy implemented to correct for removal during treatment. In patients with cardiovascular disease, especially those using cardiac glycoside medications, plasma levels of calcium, potassium and magnesium must be carefully monitored. If citrate is used as the anticoagulation agent, the formulations of PrismaSol solution may need to be adjusted.

1.3.6 Special Populations
Gender Differences:
Males and females were enrolled in some of the studies (for examples, section 6.1.4.1, studies 2, 3, 4, 6, 7, 8). There was no reported subgroup analysis by gender.

Elderly:
The published studies included elderly patients. However, no geriatric subgroup analysis or formal specific geriatric population studies were reported.

Ethnic/Racial Studies:
There was no subgroup analysis by race.

Pediatric studies:
In pediatric patients, PrismaSol solutions appear to match the requirements in the CRRT treatment. Based on the similar plasma levels of electrolytes between the children and adults, the PrismaSol should be effective and safe in pediatric use.

Use in pregnancy:
There are no data available concerning use in pregnancy.

2. INTRODUCTION AND BACKGROUND

Continuous renal replacement therapy (CRRT) is used to complement or supplant intermittent hemodialysis (IHD) in critically ill patients with acute renal failure. This method involves the application of lower solute clearances and ultrafiltration rates for substantial periods of every day. CRRT provides better stability due to lower ultrafiltration rates and better steady-state control of azotemia even in severely catabolic patients. The CRRT techniques are described in the following table.

Modality*	Blood pump	Dialysate (D) Infusate (I)	Urea clearance (ml/min)	Middle molecular clearance
Slow continuous ultrafiltration (SCUF)	Yes/No	No	1-3	+
Continuous arteriovenous hemofiltration (CAVH)	No	I	7-10	++
Continuous venous hemofiltration (CVVH)	Yes	I	15-17	+++
Continuous arteriovenous hemodialysis (CAVHD)	No	D	17-21	-
Continuous venovenous hemodialysis (CVVHD)	Yes	D	17-21	-
Continuous arteriovenous hemodiafiltration (CAVHDF)	No	I+D	25-26	+++
Continuous venovenous hemodiafiltration (CVVHDF)	Yes	I+D	25-26	+++

*: Johnson R, et al. Comprehensive clinical nephrology, 2nd edition, 2003. *

2.1 Product Information

2.1.1. Drug Name:

PrismalSol solutions

2.1.2. Chemical Structure:

PrismaSol solutions included nine different solutions as shown in the following tables and are packaged in a two compartment bag. The small compartment A has a volume of 250ml and contains the electrolyte solution. The large compartment B has a volume of 4750ml, and contains the buffer solutions as shown in the following figure. The final reconstituted solution (5000ml) is obtained after breaking the red frangible pin between compartment A and B and mixing both solutions.

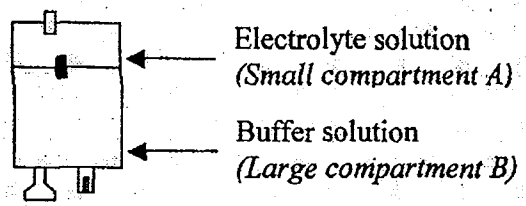


Fig. 1 Schematic drawing of a two-compartment bag

The compositions of each PrismaSol solution were summarized in the following tables including both before and after reconstitution.

BEFORE RECONSTITUTION
1,000 mL of electrolyte solution (small compartment A) contains:

	PrismaSol BK 0/3.5 # 1	PrismaSol BGK 2/0 # 2	PrismaSol BGK 2/3.5 # 3	PrismaSol BGK 4/3.5 # 4	PrismaSol BGK 4/2.5 # 5	PrismaSol BGK 4/0 # 6	PrismaSol BK 4/2.5 # 7	PrismaSol BGK 0/2.5 # 8	PrismaSol BK 0/0 # 9
Calcium chloride, 2 H_2O	5.15 g/L	0 g/L	5.15 g/L	—	3.68 g/L	0 g/L	—	3.68 g/L	0 g/L
Magnesium chloride, 6 H_2O	2.03 g/L	2.03 g/L	2.03 g/L	—	3.05 g/L	3.05 g/L	—	3.05 g/L	3.05 g/L
Dextrose anhydrous	0 g/L	20.0 g/L	20.0 g/L	—	20.0 g/L	20.0 g/L	—	20.0 g/L	0 g/L
Lactic acid	5.40 g/L	5.40 g/L	5.40 g/L	—	5.40 g/L	5.40 g/L	—	5.40 g/L	5.40 g/L

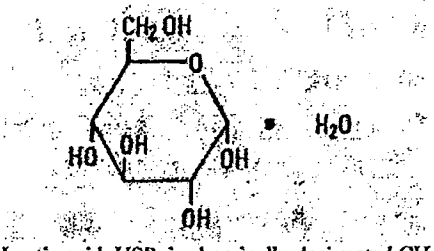
1,000 mL of buffer solution (large compartment B) contains:

	PrismaSol BK 0/3.5 # 1	PrismaSol BGK 2/0 # 2	PrismaSol BGK 2/3.5 # 3	PrismaSol BGK 4/3.5 # 4	PrismaSol BGK 4/2.5 # 5	PrismaSol BGK 4/0 # 6	PrismaSol BK 4/2.5 # 7	PrismaSol BGK 0/2.5 # 8	PrismaSol BK 0/0 # 9
Sodium chloride	6.46 g/L	6.46 g/L	6.46 g/L	—	6.46 g/L	6.46 g/L	—	6.46 g/L	6.46 g/L
Sodium bicarbonate	3.09 g/L	3.09 g/L	3.09 g/L	—	3.09 g/L	3.09 g/L	—	3.09 g/L	3.09 g/L
Potassium chloride	0 g/L	0.157 g/L	0.157 g/L	—	0.314 g/L	0.314 g/L	—	0 g/L	0 g/L

AFTER RECONSTITUTION of compartments A and B
1,000 mL of the reconstituted solution contains:

in mEq/L except where noted	PrismaSol BK 0/3.5 # 1	PrismaSol BGK 2/0 # 2	PrismaSol BGK 2/3.5 # 3	PrismaSol BGK 4/3.5 # 4	PrismaSol BGK 4/2.5 # 5	PrismaSol BGK 4/0 # 6	PrismaSol BK 4/2.5 # 7	PrismaSol BGK 0/2.5 # 8	PrismaSol BK 0/0 # 9
Calcium Ca^{++}	3.5	0	3.5	—	2.5	0	—	2.5	0
Magnesium Mg^{++}	1.0	1.0	1.0	—	1.5	1.5	—	1.5	1.5
Sodium Na^{+}	140	140	140	—	140	140	—	140	140
Chloride Cl^{-}	109.5	108.0	111.5	—	113.0	110.5	—	109.0	106.5
Lactate	3.0	3.0	3.0	—	3.0	3.0	—	3.0	3.0
Bicarbonate HCO_3^{-}	32	32	32	—	32	32	—	32	32
Potassium K^{+}	0	2.0	2.0	—	4.0	4.0	—	0	0
Dextrose	0	100 mg/dL	100 mg/dL	—	100 mg/dL	100 mg/dL	—	100 mg/dL	0
Theoretical Osmolarity	287 mOsm/L	291 mOsm/L	296 mOsm/L	—	300 mOsm/L	296 mOsm/L	—	292 mOsm/L	282 mOsm/L

Calcium chloride, USP, is chemically designated calcium chloride dihydrate ($CaCl_2$, 2 H_2O).
Magnesium chloride, USP, is chemically designated magnesium chloride hexahydrate ($MgCl_2$, 6 H_2O).
Dextrose, USP, is chemically designated D-Glucose anhydrous ($C_6H_{12}O_6$) or D-Glucose monohydrate ($C_6H_{12}O_6$, H_2O).



Lactic acid, USP, is chemically designated $CH_3CH(OH)COOH$.
Sodium chloride, USP, is chemically designated NaCl.
Potassium chloride, USP, is chemically designated KCl.
Sodium bicarbonate, USP, is chemically designated $NaHCO_3$.

2.1.3. Proposed Trade Name:
PrismaSol™ solutions

2.1.4. Proposed Indication:

According to proposed labeling, PrismaSol solution is used in continuous renal replacement therapies (CRRT) either as replacement solution in hemofiltration (HF) and hemodiafiltration (HDF) [redacted]

2.1.5. Drug Class:
PrismaSol solution is a pharmacologically inactive solution with normal physiological buffer and electrolytes and is used as replacement solution to replace water and electrolytes removed during HF and HDF. [redacted]

2.1.6. Dose/Regimens:
Doses will be based on the mode of therapy, solute formulation, flow rates and length of therapy as well as the patient's fluid, electrolyte, acid-base and glucose balance. According to the sponsor, the commonly used flow rates for [redacted] replacement fluid in hemofiltration, hemodiafiltration and hemodialysis are 500-2500ml/hour in adult and adolescents, and 15-35ml/kg/hour in children. PrismaSol can be used as an in intravenous replacement solution in HF and HDF [redacted] When used as a replacement solution, PrismaSol solution can be administered into an extra-corporeal circuit before (pre-dilution) and/or after hemofilter or hemodiafilter (post-dilution).

2.1.7. Age Groups:
In pediatric patients, PrismaSol solutions appear to match the requirements in the CRRT treatment. Based on the similar plasma levels of electrolytes between the children and adults, the PrismaSol should be effective and safe in pediatric use. In Geriatric group, Safety and effectiveness in geriatric patients have been reported in some studies on the general population. The ages of patients in these studies were up to 80s. However, no geriatric subgroup analysis or formal specific geriatric population studies were reported.

2.2 Currently Available Treatment for Indications:
This can be the first marketed replacement solution for CRRT in US. In the US, up to now, only customized solutions compounded by the hospitals or Lactate Ringer's solutions are used as replacement solutions in CRRT. CRRT replacement solutions for hemofiltration and hemodiafiltration with formulations similar to those of PrismaSol replacement solutions have been in use worldwide for many years. PrismaSate solutions, another product from the sponsor, were approved by the FDA as a medical device (510(k) K013448) in January of 2002. PrismaSate has the same exact packaging, same range of composition, and the same manufacturing site as PrismaSol. Additionally, similar solutions are produced and used in Europe since several years, with the same packaging, range of composition, and indication for use as PrismaSol. So far, there were no safety concerns reported.

2.3 Availability of Proposed Active Ingredient in the United States:
PrismaSol solution is not currently marketed in this country.

2.4 Important Issues With Pharmacologically Related Products:
As with the use of other replacement and dialysis solutions, blood concentrations of filterable/dialyzable drug may be influenced by CRRT.

2.5 Pre-submission Regulatory Activity:
During the pre-NDA meeting held on December 9, 2003, the division has agreed that this application would be submitted under section 505 (b) (2) of the Federal Food, Drug, and cosmetic Act. These nine formulations are considered as dosages of the same drug, as the differences in composition are not significant and the use of each formulation is equivalent. (Please appendix 10.3 pre-NDA meeting minutes)

2.6 Other Relevant Background Information:
N/A

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1. CMC (and Product Microbiology, if Applicable):
The CMC and product microbiology reviews have no significant findings related to approval. Please see their reviews for further details.
3.2. Animal Pharmacology/Toxicology:
The drug substances of the PrismaSol solutions are normal constituents of the physiological plasma in human and they do not exert any real pharmacological action. In addition, considering the available clinical experience with similar solutions, the non-clinical studies of pharmacology and toxicology were not required.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1. Sources of Clinical Data

Clinical studies were not conducted with this specific product.

4.2. Tables of Clinical Studies

N/A

4.3. Review Strategy
Data were from published literatures provided by sponsor and reviewer self.

4.4. Data Quality and Integrity
N/A

4.5. Compliance with Good Clinical Practices
Not submitted

4.6. Financial Disclosures:
Not submitted

5. CLINICAL PHARMACOLOGY:
N/A

6. INTEGRATED REVIEW OF EFFICACY

6.1. Indication
The PrismaSol line of products consists of nine different pre-packaged sterile solutions and was proposed as replacement solutions for CRRT.

6.1.1 Methods
The main data source for this review was based on the published data provided by sponsor and the literatures from the published scientific Journals.

6.1.2 General Discussion of Endpoints:
The therapeutic goal of replacement solutions is to compensate for fluid loss and to restore or normalize the acid-base and electrolyte balance in the blood of patients suffering of acute renal failure (ARF) during HF and HDF therapies. The compositions of replacement solutions are made to correspond to normal electrolyte and dextrose plasma composition as closely as possible.

6.1.3 Study Design:
Data were collected from published journals from Medline database using keywords such as hemofiltration, hemodiafiltration, hemodialysis and solutions. Original investigations or case-collections only were selected if they addressed the question of solution composition and investigated bicarbonate as a buffer. Duplicate publications of the same study were ruled out. A total of 34 papers are provided from the sponsor in this application including 10 about hemofiltration, 6 about hemodiafiltration, 13 about hemodialysis, 3 about CRRT in children and 2 about continuous veno-venous hemofiltration (CVVH) or continuous veno-venous hemodialysis (CVVHD) for intoxication. In addition, the reviewer also performed a PubMed literature search for the application of replacement solutions in CRRT.

6.1.4 Efficacy Findings:
In CRRT, buffered electrolyte solutions are required for parenteral replacement of volume lost during HD, HF and HDF. The current replacement solutions used in the US for HF or HDF in CRRT consist of either Lactated Ringer's solution, peritoneal dialysis solution (used off-label), or custom solution formulated and prepared in hospital pharmacies. Lactated Ringer's solution can cause accumulation of lactates when exposes to patients with liver failure or circulatory shock and lacks some electrolytes or dextrose. Peritoneal dialysis solution can cause much higher dextrose solution than the physiological values. To bypass these drawbacks, pharmacy compounding of custom replacement solutions has increased significantly but also has some risks like mis-formulation, microbiological contaminations, etc.

In evaluation of the clinical efficacy of PrismaSol solutions as the replacement in CRRT, 34 reported studies from published literature that cumulate 1553 patients were summarized to determine the appropriate concentrations of bicarbonate as a buffer and different electrolytes in the replacement solutions as shown in the following table.

Number of patients

Procedure	Number of patients	Number of patients with bicarbonate buffer
HF	1046	458
HDF	250	89
HD	257	227
Total	1553	774

6.1.4.1. Justification of the use of bicarbonate as a buffer
In the buffer selection, different treatment procedures including CAVH, CVVH, CVVHD, CVVHDF, HF, HDF, and HD were studied based on the published literatures. It appears that bicarbonate is the first choice for replacement solutions than the lactate and acetate. Bicarbonate-containing solutions provide benefit to the patient, especially when liver function is compromised, when there is circulatory failure or when a large volume of replacement fluid is used during CRRT. The appropriate concentrations of bicarbonate were in the range of 30 to 40 mmol/Lwith or without 3mmol/L lactate. The following nine applicable studies were summarized to justified the use of bicarbonate as a buffer for replacement solutions in CRRT.

Study 1. Effect of bicarbonate- and lactated buffered replacement fluids on cardiovascular out come in CVVH patients. (Kidney Int 2000; 58: 1751-1757). This open, randomized, multi-center study was performed in 117 patients to investigate the effect of bicarbonate replacement fluid and lactate replacement fluid on cardiovascular outcome in patients requiring CVVH following acute renal failure. The results indicated that the administration of bicarbonate replacement fluids was superior in normalizing acidosis of patients without the risk of alkalosis and reduces the frequency of hypotensive cases in critically ill patients with acute renal failure, particularly those with previous cardiovascular disease or heart failure. **The bicarbonate concentration in this study was 35mEq/L.** Data were summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)		Assessment criteria	Results efficacy	Adverse events
Kidney International 2000; vol 58: 1761-1767	Effect of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients. Barenbrock M, Hausberg M, Matzkies F, De La Motte S, Schaefer RM.	Open Randomized multicenter study	117 patients divided in 2 groups. *CVVH with RF-Bic:* 61 patients mean age= 59 ±15 yrs *CVVH with RF-Lac:* 56 patients mean age= 64 ±10 yrs Death : • 20 (33%) patients in the RF-Bic and 24 (43%) in the RF-Lac died during the study (p=NS) • In cardiac failure patient group, 7 (29%) in the RF-Bic and 12 (57%) in the RF-Lac died (p=0.058)	- patients with acute renal failure, treated at a medical ICU - age between 18 and 80 yrs - development of acute oliguric or anuric renal failure, acute azotemia, or acute deterioration of renal function associated with volume overload refractory to diuretic therapy. - no chronic renal failure (serum creatinine >3mg) - no serum lactate >5 mmol/L, - no blood pH <7.3 - no malignant disease - no pregnancy or lactation.	5-day CVVH (continuous veno-venous hemofiltration) treatment or until either renal function was restored or the patient was withdrawn from the study.	Bicarbonate-replacement fluid (RF-Bic): • Without K^+ Na^+: 140 mmol/L Ca^{2+}: 1.5 mmol/L Mg^{2+}: 0.5 mmol/L Cl: 109 mmol/L HCO_3^-: 35 mmol/L Lactate: - Dextrose: 5.6 mmol/L • With K^+ Na^+: 140 mmol/L K^+: 2 mmol/L Ca^{2+}: 1.5 mmol/L Mg^{2+}: 0.5 mmol/L Cl: 111 mmol/L HCO_3^-: 35 mmol/L Lactate: - Dextrose: 5.6 mmol/L	Lactate replacement fluid (RF-Lac): • Without K^+ Na^+: 135 mmol/L Ca^{2+}: 1.88 mmol/L Mg^{2+}: 0.75 mmol/L Cl: 106.5 mmol/L HCO_3^-: - Lactate: 33.75 mmol/L Dextrose: 7.5 mmol/L • With K^+ Na^+: 135 mmol/L K^+: 2 mmol/L Ca^{2+}: 1.875 mmol/L Mg^{2+}: 0.75 mmol/L Cl: 106.5 mmol/L HCO_3^-: - Lactate: 33.75 mmol/L Dextrose: 8.3 mmol/L	- clinical status, diuresis per 24h, frequency of hypotensive episodes, (SBP< 70mmHg), daily fluid balance, infusion site and anticoagulation. - blood count, serum creatinine, serum urea, ALT, AST, gamma GT, total protein, fibrinogen levels - respiratory rate, central venous pressure, electrolytes, dextrose, lactate and activated clotting time. - blood flow, ultrafiltration, heart rate, blood pressure, blood gas analysis. - adverse events	Hemofiltration regimen was comparable between both study groups. Serum bicarbonate levels : in RF-Lac treated patients < in RF-Bic treated patients (p<0.01). Blood lactate levels: in RF-Bic treated patients < in RF-Lac treated patients (p<0.05).	Number of hypotensive episodes: in RF-Bic treated patients < in RF-Lac treated patients (p<0.05). CV events : 15% RF-Bic patients and 38% RF-Lac patients developed cardiovascular events (p<0.01). A multiple regression analysis showed that it was dependent on replacement fluid and previous cardiovascular disease, and not on age or BP.

Study 2. CVVH in acute renal failure: is a bicarbonate- or lactate buffered substitution better? (Contrib Nephrol BaselKarger 1995; vol 116: 38-47). This is a prospective, randomized, crossover study to investigate the influence of a lactate-buffered and a bicarbonate-buffered replacement solution on acid-base status, electrolytes and metabolic change in 20 critically ill patients with acute renal failure undergoing CVVH. **The lactate solution contained 44.5mEq/L lactate and the bicarbonate solution contained 34.5mEq/L bicarbonate and 3mEq/L lactate.** Results speculated that bicarbonate buffered solution may be helpful in patients with hyperlactatemia or altered lactate metabolism. Data were summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)		Assessment criteria	Results efficacy	Adverse events
Contrib Nephrol Basel Karger 1995; vol 116:36-47	Continuous veno-venous hemofiltration in acute renal failure: is a bicarbonate- or lactate-buffered substitution better ? Klerdorf H, Laue C, Heintz B, Riehl J, Metzler H, Sieberth HG.	Prospective Randomized Crossover study	From a total of 32 patients, 12 were eliminated because they did not complete the 6 day CVVH period (1 : patients died, and 1 stopped for major bleeding). 20 patients were included in the analysis: 11 male, 9 women mean age= 61.5 years (range: 35 - 81)	- patients with acute oliguric (<400mL) or anuric renal failure - additional respiratory failure (mechanical ventilation, positive end-expiratory pressure >10 cm H_2O and/or fraction of inspired FIO_2 >0.4). - no hepatic failure - no pre-existing renal failure (creatinine ≥200µmol/L), lactemia (lactate ≥ 3.5 mmol/L) or known diabetes mellitus.	6-day CVVH (continuous veno-venous hemofiltration) treatment: - 4 days with the bicarbonate-buffered substitution followed by - 4 days with the lactate-buffered substitution alternatively, in reverse order.	Bicarbonate-buffered substitution: Na^+: 140 mmol/L Cl: 110 mmol/L HCO_3^-: 34.5 mmol/L Lactate: 3 mmol/L Ca^{2+}: 1.75 mmol/L Mg^{2+}: 0.5 mmol/L Dextrose: 5.6 mmol/L	Lactate-buffered substitution: Na^+: 142 mmol/L Cl: 103 mmol/L HCO_3^-: - Lactate: 44.5 mmol/L Ca^{2+}: 2.0 mmol/L Mg^{2+}: 0.75 mmol/L Dextrose: 5.6 mmol/L	- acid base status - serum electrolytes control - metabolic parameters	No difference in daily hemofiltrate and net ultrafiltration rate between 2 groups. No difference in mean arterial blood pressure No difference between two groups in phosphate, potassium, chloride or sodium. Some minor differences appear for calcium, magnesium and chloride. No difference in pH or base excess between the groups or within the groups. Comparing the lactate values before CVVH treatment in both groups, there was a slight decrease in lactate, the decrease being most marked during bicarbonate substitution.	*Due to the technique:* None reported *Due to the replacement fluid:* None reported

Study 3. The acid-base effects of continuous HF with lactate or bicarbonate buffered replacement fluids (Int J Artif Organs 2003; 26: 477-483). This is a prospective, randomized, double crossover study to investigate the influence of a lactate-buffered and a bicarbonate-buffered replacement solution on acid-base balance in 8 patients with acute renal failure under

going CVVH. **The lactate solution contained 46mEq/L lactate and the bicarbonate solution contained 32mEq/L bicarbonate and 3mEq/L lactate.** Results suggested that bicarbonate buffered replacement solution was recommended in patients with pre-treatment hyperlactatemia or liver dysfunction (difficult conversion of lactate to bicarbonate in liver dysfunction condition). Data were summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)		Assessment criteria	Results efficacy	Adverse events
Int J Artif Organs 2003; 26: 477-483.	The acid-base effects of continuous hemofiltration with lactate or bicarbonate buffered replacement fluids. Tan HK, Uchino S, Bellomo R.	Prospective Randomized Double crossover study	8 patients were included in the analysis: 4 men, 4 women mean age= 55.8 years (range: 39 - 72)	- established acute renal failure (anuria for >24hrs, a plasma urea level >25 mmol/L, and need for CVVH)	24-hour period of lactate-buffered CVVH or bicarbonate buffered CVVH with cross over and with the same procedure repeated the following day.	Bicarbonate-buffered substitution: Na^+: 140 mmol/L Cl: 109.5 mmol/L HCO_3^-: 32 mmol/L Lactate: 3 mmol/L Ca^{2+}: 1.75 mmol/L Mg^{2+}: 0.5 mmol/L KCl is added to a final concentration of 3.7mmol/L to prevent hypokalemia.	Lactate-buffered substitution: Na^+: 140 mmol/L K^+: 1 mmol/L Cl: 100 mmol/L Lactate: 46 mmol/L Ca^{2+}: 1.6 mmol/L Mg^{2+}: 0.8 mmol/L Dextrose: 10.8 mmol/L KCl is added to a final concentration of 3.7mmol/L to prevent hypokalemia.	- arterial blood gases - UF gases (pH, carbon dioxide tension, oxygen tension, calculated standard bicarbonate and standard base excess) - lactate concentrations.	Within 60min of treatment, lactate CVVH led to: - a significantly higher lactate concentration (3.9 vs. 2.5 mmol/L, p=0.0011) - a significantly lower base excess (2.3 vs. 4.1 mEq/L, p=0.0019) - a significantly lower bicarbonate concentration (26.7 vs. 28.3 mmol/L, p=0.0036). - unchanged $PaCO_2$. These differences persisted during the study period. The UF of patients receiving lactate CVVH contained significantly more lactate and less bicarbonate than bicarbonate CVVH resulting in a mean buffer-base balance of +20.3mEq/hr compared to +2.5mEq/hr for treatment B (p<0.0001).	Not specified.

Study 4. The use of different buffers during continuous HF in critically ill patients with acute renal failure. (Intensive Care Med 1999; 25: 1244-1251). This prospective, randomized, study was performed in 41 patients to compare acid-base balance, lactate concentration, hemodynamic and O_2 transport variables during HF with **replacement fluid containing lactate (44.5mEq/L) or bicarbonate (40mEq/L + lactate 3mEq/L).** Results indicated that in the bicarbonate- and lactate-based buffer solutions were superior to acetate-based replacement fluid for the correction of acidosis. Detailed information was summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)		Assessment criteria	Results efficacy	Adverse events
Intensive Care Med 1999; 25: 1244-1251	The use of different buffers during continuous hemofiltration in critically ill patients with acute renal failure Hoenig P, Ivens K, Thümler O, Morgera S, Heintzen M, Passtick-Deetjen J, Willers R, Strauer BE, Grabensee B.	Prospective Cohort study	132 patients were enrolled in the study:. group 1: lactate: 52 patients (34 men, 18 women) mean age= 60.2 ± 15.2 years group 2: acetate: 32 patients (25 men, 7 women) mean age= 61.5 ± 15.3 years group 3: bicarbonate: 48 patients (30 men, 18 women): mean age= 57.5 ± 14.4 years	ARF diagnosed, based on one of the following criteria: - fluid overload owning to inadequate urine production, despite administration of diuretic agents and maintenance of adequate blood pressure - serum creatinine rising to above 265mol/L - serum potassium >5mmol/L due to anuria.	CVVH (continuous veno-venous hemofiltration) treatment until death or discharge from ICU. Mean CVVH duration was 9.8±8.1 days.	Bicarbonate-buffered substitution: Na^+: 140 mmol/L Cl: 109 mmol/L HCO_3^-: 35 mmol/L Ca^{2+}: 1. 6 mmol/L Mg^{2+}: 0.5 mmol/L	Lactate-buffered substitution: Na^+: 142 mmol/L Cl: 103 mmol/L Lactate: 44.5 mmol/L Ca^{2+}: 2.0 mmol/L Mg^{2+}: 0.75 mmol/L Acetate-buffered substitution: Na^+: 140 mmol/L Cl: 111 mmol/L Acetate: 5 mmol/L Ca^{2+}: 2.0 mmol/L Mg^{2+}: 1.0 mmol/L	- creatinine, - blood urea oxygen (BUN), - electrolytes - arterial blood gas analysis - cardiovascular hemodynamics in a subset of patients	Lactate- and bicarbonate-based HF led to significantly higher serum bicarbonate and arterial pH values as compared to the acetate-based HF. Serum bicarbonate values at 48h after initiation of CVVH: Lactate group: 25.7±3.8 mmol/L (p<0.001) Acetate group: 20.6±3.1 mmol/L Bicarbonate group: 23.3±3.9 mmol/L (p<0.001).	Mortality was 65%. Cardiovascular hemodynamics were superior in patients treated with Lactate- and bicarbonate as compared to those treated with acetate-based HF.

Study 5. Bicarbonate-buffered instead of lactate-buffered substitution fluid for CAVH in intensive care. (Anasth. Intensivther. Notfallmed 1990; 25: 164-167). This is a non-randomized study to determine the impact of bicarbonate replacement solution in 7 intensive care patients with acute renal failure undergoing CAVH. Results suggested that bicarbonate-buffered substitution solution is recommended for CAVH. **The bicarbonate concentration was 31.4mEq/L with lactate of 2.9mEq/L.** Data were summarized in the following table (see below):

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)	Assessment criteria	Results efficacy	Adverse events
Anasth. Intensivther. Notfallmed 1990; 25: 164-167	Bikarbonat-statt Lakatgepufferter Substitutionslösung zur Kontinuierlichen Hämofiltration im Intensivbereich. (Bicarbonate-buffered instead of Lactate-buffered substitution fluid for continuous haemofiltration in Intensive Care) Olbricht CJ, Huxmann-Nägeli D, Bischoff H	Prospective study	7 patients. Mean age= 52.7 years (range: 38 - 66)	- patients under mechanical ventilation suffering from post-operative acute renal failure treated exclusively with CAVH (continuous arterio-venous hemofiltration) for 6 days.	6 days.	One plastic bag (4.5 L) containing basic solution and one glass bottle (160mL) containing 8.4% sodium bicarbonate solution (1000 mmol/L). Prior to use the 160mL bicarbonate is led into the basic solution via the transfusion sets and the solution is mixed for 5 minutes. *Final substitution solution:* HCO_3^- : 31.4 mmol/L Na^+ : 140.1 mmol/L Ca^{2+} :1.75 mmol/L Mg^{2+} : 0.50 mmol/L Cl^- : 110.24 mmol/L Lactate : 2.9 mmol/L *The substitution* was carried out with the final reconstituted solution into the venous line of the system.	- in vitro analyses cations concentrations - in vivo analyses: laboratory parameters are measured at 4- to 24-hour intervals: Ca^{2+}, Mg^{2+}, K^+, Na^+, Cl^-, phosphate, creatinine, urea, blood gas analysis and lactate	In vivo results: The laboratory parameters were not significantly altered during the course of the 6 days CAVH with bicarbonate –buffered substitution fluid.	*Due to the technique:* None reported *Due to the replacement fluid:* None reported.

Study 6. Which bicarbonate concentration is adequate to lactate-buffered substitution fluids in maintenance HF. (Clinical Nephrology 1994; vol 42 (4): 257-262). This is prospective, crossover and non-randomized clinical study to investigate the metabolic and hemodynamic effects of a lactate- and a bicarbonate-buffered HF substitution fluid in 11 patients with end stage renal disease undergoing intermittent HF. The results suggested that bicarbonate is recommended in the condition of lactate intolerance, liver failure or hyperlactatemia. **The bicarbonate concentration was 31.4-39.7mEq/L with lactate of 2.9-3mEq/L.** Data were summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)		Assessment criteria	Results efficacy	Adverse events
Clinical Nephrology 1994; vol 42 (4): 257-262.	Which bicarbonate concentration is adequate to lactate-buffered substitution fluids in maintenance hemofiltration ? Böhm R, Gladziwa U, Classen W, Richl J, Mann H, Sieberth HG.	Prospective Crossover study	*Part A of the study:* 11 patients: 7 men, 4 women mean age= 61.6 yrs (range: 51 - 76) *Part B of the study:* 6 patients	- patients with end stage renal disease undergoing intermittent hemofiltration [mean duration of hemofiltration= 35 months (range:1-98)]	*Part A of the study:* 9 week cross over trial: - 3wks with lactate-buffered solution, - followed by 3wks of bicarbonate-buffered solution (type I), - ended by 3wks with lactate-buffered solution. 3 times hemofiltration per week with a total of filtration duration ranging from 165 to 330 min. *Part B of the study:* 3 weeks of bicarbonate-buffered solution (type II), at the same intervals with a filtration duration of 150-315 min.	*Part A of the study:* Type I Bicarbonate-buffered substitution: Na^+: 140.1 mmol/L Cl: 110.2 mmol/L HCO_3^-: 31.4 mmol/L Lactate: 3 mmol/L Ca^{2+}: 1.75 mmol/L Mg^{2+}: 0.50 mmol/L Dextrose: 1 g/L *Part B of the study:* Type II Bicarbonate-buffered substitution: Na^+: 142.6 mmol/L Cl: 104.5 mmol/L HCO_3^-: 39.7 mmol/L Lactate: 2.9 mmol/L Ca^{2+}: 1.75 mmol/L Mg^{2+}: 0.50 mmol/L Dextrose: 1 g/L	Lactate-buffered substitution: Na^+: 138/142 mmol/L K^+: 2/0 mmol/L Cl: 111.5/103 mmol/L HCO_3^-: - Lactate: 34/44.5 mmol/L Ca^{2+}: 2.0 mmol/L Mg^{2+}: 0.75 mmol/L Dextrose: -	- subjective feeling: pruritus, headache, nausea/vomiting, - acid-base balance (pH, base excess, standard bicarbonate); - blood dextrose, lactate and potassium, - metabolic parameters - blood pressure, heart rate.	*Part A of the study: Lac vs. Bic type I* All parameters of acid-base balance showed a better control of metabolic acidosis in lactate-buffered HF phases than in bicarbonate-buffered HF. *Part B of the study: Lac vs. Bic type II* The parameters of acid-base balance showed a better control during bic-type II, than bic-type I, and were similar to the lac-buffered phase. In the steady state phase of the treatment, (day 7-9, week 3) parameters of acid-base balance rose more to normal values during bic-type II phase, than during lactate -buffered one. No differences in hemodynamic parameters between the 3 types of buffer.	*Due to the technique or the replacement fluid:* Pruritus tended to be lower during both bicarbonate-buffered HF phases than during the lactate one. Complaints of headache and nausea/vomiting were unchanged. No adverse reaction or deterioration of the clinical condition or specific complaints of the patients occurred.

Study 7. Regulation of base balance in bicarbonate HF. (Int J Artif Organs 1994; 17: 27-36). The study was performed to investigative the feasibility of bicarbonate as a substitute for acetate and lactate in HF solutions using a two-chamber bag. No buffer-related effects were reported. **The bicarbonate concentration was tested in the range of 30-40mEq/L with acetate of 4mEq/L.** Other details of the study were summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)	Assesement criteria	Results efficacy	Adverse events
Int J Artif Organs 1994; 17: 27-36.	Regulation of base balance in bicarbonate hemofiltration. Santoro A, Ferrari G, Bolzani R, Spongano M, Zucchelli P	Prospective study	24 patients (14 men, 10 women) Mean age= 63.2±15.4 (range: 41-75)	- patients with end stage renal failure with regular dialysis treatment - no diabetes mellitus, no congestive heart failure, no severe cardiac arrhythmias.	One HF cycle.	Solution Bic 30 (12 patients) Na^+: 140 mEq/L K^+: 1.5 mEq/L Ca^{2+}: 4 mEq/L Mg^{2+}: 1.5 mEq/L Cl: 113 mEq/L Acetate: 4 mEq/L Bicarbonate : 30 mEq/L Solution Bic 35 (7 patients) Na^+: 140 mEq/L K^+: 1.5 mEq/L Ca^{2+}: 4 mEq/L Mg^{2+}: 1.5 mEq/L Cl: 113 mEq/L Acetate: 4 mEq/L Bicarbonate : 35 mEq/L Solution Bic 40 (5 patients) Na^+: 140 mEq/L K^+: 1.5 mEq/L Ca^{2+}: 4 mEq/L Mg^{2+}: 1.5 mEq/L Cl: 113 mEq/L Acetate: 4 mEq/L Bicarbonate : 40 mEq/L	- pCO_2, total CO_2, - lactate, pyruvate and acetate. - Ca^{2+} conc. - Blood pH - Plasma HCO_3^- conc. (calculated)	The Net Base Gains were respectively: - 73.7 ± 92 with Bic 30 - 138.2 ± 97 with Bic 35 ($p<0.05$ vs. Bic 30) - 201± 65.9 with Bic 40 ($p<0.0001$ vs. Bic 30). The use of bicarbonate in the substitution fluid can lead to an optimal positive buffer balance tailored to the individual patient's needs.	None reported

Study 8. New reinfusate composition in high UF HDF: Electrolyte solution combined with bicarbonate. (Nephrol dial Transplant 1993; 8: 54-59). This is a prospective, crossover, non-randomized study to evaluate whether bicarbonate can be infused together with an electrolyte solution in high ultra-filtration HDF in 12 stable patients with chronic renal failure. Data indicated that bicarbonate can be infused along with an electrolyte solution, thus avoiding the use of unphysiological levels of other buffers, and improving vascular stability. **The bicarbonate concentration was 32mEq/L.** Results were summarized in the below table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)	Assessment criteria	Results efficacy	Adverse events
Nephrol Dial Transplant 1993; 8: 54-59.	New reinfusate composition in high UF haemodiafiltration: electrolyte solution combined with bicarbonate. Gonella M, Calabrese G, Pratesi G, Baldin C, Mazzotta A, Vagelli G.	Prospective Cross over study	Study I: 12 patients (8 men, 4 women) mean age= 60 ± 15 years. Study II: 5 patients (5 women) Mean age= 66.2 (range : 59 – 86)	Study I: - patient with no residual renal function. - stable patients with chronic replacement therapy (range: 13 to 136 months) - patients without signs of water retention Study II: - patient with no residual renal function and with vascular instability	Study I: Parameters assessed during the 12-mid-week sessions. (one for each patient). Four weeks after the reinfusate change, the same parameters have been re-evaluated during the 12-mid-week sessions. (one for each patient). Study II: No information	AR-HDF • *Dialysate:* Na^+: 141±2 mEq/L K^+: 2.5 mEq/L Ca^{2+}: 3.5 mEq/L Mg^{2+}: 0.7 mEq/L Cl^-: 104±3 mEq/L Acetate: 3 mEq/L Bicarbonate : 40±2 mEq/L • Reinfusate solutions: Around 20 liters of solution: Na^+: 138 mEq/L K^+: 2 mEq/L Ca^{2+}: 3.5 mEq/L Mg^{2+}: 1 mEq/L Cl^-: 109.5 mEq/L Acetate: 35 mEq/L and 2 liters of : Na^+: 145 mEq/L Bicarbonate: 100 mEq/L Cl^-: 45 mEq/L BR-HDF • Reinfusate solutions: Na^+: 139 mEq/L K^+: 2 mEq/L Ca^{2+}: 3.5 mEq/L Mg^{2+}: 1 mEq/L Cl^-: 105.5 mEq/L Acetate: 4 mEq/L Bicarbonate:36 mEq/L • Same dialysate as AR-HDF except: Bicarbonate: 34±2 mEq/L Cl^-: 111 ±2 mEq/L	- urea and creatinine clearances - pH, blood gazes - plasma bicarbonate and base excess - plasma electrolytes	Study I: - Mean clearances were not significantly different between both treatments. - Intradialytic mass balance was negative for Na, K, and Mg and positive for Ca. No significant differences were observed between both treatments. - pre- and post dialytic pH, pCO_2, pO_2, bicarbonate and base excess were not significantly different between both treatments. - Plasma K, Mg decreased during AR and BR-HDF. Plasma Ca increased during AR and BR-HDF. - Plasma acetate increased markedly during AR-HDF, whereas it remains normal during BR-HDF. Study II: In 3 patients, the clinical status improved both during the session and in the interdialytic period on BR-HDF, with a better stability on BP. In 1 patient, no difference in BP was observed between the two techniques, but during BR-HDF it was possible to reduce the body weight keeping a good vascular stability and relieving the previous signs of mild hydrosodic retention.	No adverse effect due to the reinfusate were observed during the entire period of study.

Study 9. CRRT: Does technique influence electrolyte and bicarbonate control. (Int Artif Organs 2003; 26: 289-296). This retrospective study was performed to determine whether CVVHDF or CVVH would achieve better control of serum sodium, potassium and bicarbonate concentrations in critically ill patients. **The bicarbonate concentration was 37.5mEq/l.** Data indicated that bicarbonate can be used both in CVVH and CVVHDF (see below table).

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)		Assessment criteria	Results efficacy	Adverse events
Int J Artif Organs 2003; 26: 289-296.	Continuous renal replacement therapy: Does technique influence electrolyte and bicarbonate control. Morimatsu H, Uchino S, Bellomo R, Ronco C.	Retrospective controlled study Note: fluid and /or electrolyte management was similar in both groups.	CVVHDF 49 patients CVVH 59 patients The two cohorts were similar in age. However, according to APACHE II score, patients treated with CVVHDF were more severely ill on admission than those in CVVHF group.	- critically ill patients with acute renal failure treated by either CVVHDF or CVVH in two different ICU.	Assessment of the criteria for 2 weeks of treatment.	CVVHDF *Dialysate:* Dianeal 1.5% with: Na^+: 132 mmol/L Cl^-: 95 mmol/L HCO_3^-: - Lactate: 40 mmol/L Ca^{2+}: 1.25 mmol/L Mg^{2+}: 0.25 mmol/L *Replacement fluid:* Na^+: 150 mmol/L Cl^-: 112.5 mmol/L HCO_3^-: 37.5 mmol/L Lactate: - Ca^{2+}: 0.55 mmol/L Mg^{2+}: 1.25 mmol/L	CVVH Na^+: 140 mmol/L K^+: 1 mmol/L Cl^-: 100 mmol/L HCO_3^-: - Lactate: 46 mmol/L Ca^{2+}: 1.6 mmol/L Mg^{2+}: 0.8 mmol/L	- demographic data, details of initial clinical presentation and biochemical information, APACHE II score. - retrieval of daily morning serum sodium and potassium concentration and bicarbonate concentration.	Sodium: - *Before treatment:* most common disorder= hyponatremia - *After treatment:* significant increase of Na conc., especially with CVVHDF. In addition, CVVHDF was more likely to achieve serum Na conc. within the normal range than CVVH (74.1% vs. 62.8%, p=0.0026) Potassium: - *Before treatment:* most common disorder= hyperkalemia - *After treatment:* both treatments corrected hyperkalemia within 24hours. Bicarbonate: - *Before treatment:* most common: metabolic acidosis - *After treatment:* over the first 48 hours, both groups showed significant increase in mean arterial bicarbonate. However CVVH was associated with a lower incidence of metabolic acidosis (CVVH: 13.8% vs. CVVHDF : 34.5%, p<0.0001) and a higher incidence of metabolic alkalosis (38.9% vs. 1.1%, p<0.0001).	Not specified

6.1.4.2. Justification of the use of calcium concentration

In the published literatures, solutions generally used for CRRT contain electrolytes in concentrations similar to those unbound to proteins in blood plasma. The calcium concentrations in replacement solutions for CRRT are usually in the range of 3 to 5mEq/L. Replacement solutions can also be calcium free and $CaCl_2$ is added to the solutions as needed. Calcium-free replacement solution was mainly used in patients with chronic renal failure accompanied with hypercalcemia and high level of parathyroid hormone based on the literature reports. However, the literature is scarce for the consequence and use of calcium-free solutions in patients with acute renal failure and treated with CRRT. To assess the role of calcium concentration in the solution, most data come from hemodialysis studies and pharmacologic studies and address cardio-vascular endpoints and PTH regulation in end stage renal failure that are not relevant to acute renal failure. Study reports from literatures were summarized in the followings.

Study 10. Physiological mechanisms for calcium induced changes in systemic arterial pressure in stable dialysis patients. (Hypertension 1989; 13:213-218). This is a controlled, randomized, crossover, double blind study to investigate the hemodynamic effects due to changes in blood ionized calcium in 8 stable hemodialysis patients. The dialysates were only difference in calcium concentrations at 1, 3, and 5mEq/L. Results indicated that there were no calcium-related effects. **The calcium concentrations were in the range of 1 to 5mEq/L.** Data were summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)	Assessment criteria	Results efficacy	Adverse events
Hypertension 1989; 13: 213-218.	Physiological mechanisms for calcium-induced changes in systemic arterial pressure in stable dialysis patients. Fellner SK, Lang RM, Neumann A, Spencer KT, Bushinsky DA, Barrow KM.	Prospective Randomized Crossover Double blind	8 patients (4 men and 4 women) mean age= 45±5 yrs (range: 32 - 60)	- patients with stable chronic renal failure, undergoing regular hemodialysis for a median 34±18 months (range 5 to 135). - no suggestive ischemic heart disease, no congestive heart failure or abnormal cardiac rhythm, - no abnormal left ventricular regional wall (detected by two-dimensional echocardiography) - no antihypertensive medications, nitrates, ß-blockers, digitalis or calcitriol.	Each patient underwent hemodialysis three times within a single week with one of the three proposed dialysate.	Low calcium dialysate Ca^{2+}: 0.5 mmol/L Na^+: 140 mmol/L K^+: 2.5 mmol/L Mg^{2+}: 0.75 mmol/L Cl^-: 111.5 mmol/L Acetate: 36 mmol/L Dextrose: 138.7 mg/dL Medium calcium dialysate Ca^{2+}: 1.75 mmol/L Na^+: 140 mmol/L K^+: 2.5 mmol/L Mg^{2+}: 0.75 mmol/L Cl^-: 111.5 mmol/L Acetate: 36 mmol/L Dextrose: 138.7 mg/dL High calcium dialysate Ca^{2+}: 2.5 mmol/L Na^+: 140 mmol/L K^+: 2.5 mmol/L Mg^{2+}: 0.75 mmol/L Cl^-: 111.5 mmol/L Acetate: 36 mmol/L Dextrose: 138.7 mg/dL	Immediately on completion of the hemodialytic procedures: - determination of Ca^{2+}, arterial blood gases, total calcium, electrolytes, creatinine, BUN, magnesium, hematocrit. After a 15-minute rest; systemic, diastolic and mean blood pressure were measured (oscillometric method). Minimum 10 readings during the next 15 to 45 minutes. - dimensions and volumes of left ventricular end-systolic and end-diastolic	*Biochemical changes:* Arterial blood gases, electrolytes, creatinine, BUN, magnesium, hematocrit did not differ among the 3 studies in each patient. Arterial Ca^{2+} concentration was significantly different: - with low Ca^{2+}: 1.04±0.04 mmol/L - with medium Ca^{2+}: 1.40±0.03 mmol/L - with high Ca^{2+}: 1.66±0.06 mmol/L *Hemodynamic changes:* Heart rate did not differ between treatments groups. Systolic and diastolic blood pressures increased with higher levels of Ca^{2+}. The correlation coefficient for systolic pressure vs. Ca^{2+} 0.74 ($p<0.001$) and for diastolic pressure: 0.46 ($p<0.02$). Higher levels of Ca^{2+} resulted in increased left ventricular stroke volume and cardiac output. In contrast, total vascular resistance, and left ventricular end-diastolic dimension did not change at the higher levels of Ca^{2+}.	Not specified

Study 11. Changes in intact parathyroid hormone levels during hemodialysis following exposure to either differing dialysate calcium concentrations or calcium-free dialysis with varying calcium infusion rates. (Clinical Nephrology 1990; vol 34 (2):84-87). To determine the optimal infusion rate for calcium, when using a calcium-free dialysate, 6 patients were treated sequentially, in random order with 6 different dialysates. Results indicated that with increasing the calcium infusion, the ionized calcium tends to increase after dialysis. With increasing ionized calcium levels, there is suppression of PTH. **The infusion rates of $CaCl_2$ 10% was 10 to 20ml/h. The controlled standard bicarbonate dialysate with the calcium concentrations of 2.5, 3 or 3.5 mEq/L.** Data were summarized in the following table (in next page):

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)		Assessment criteria	Results efficacy	Adverse events
Clinical Nephrology 1990; vol 34 (2): 84-87	Changes in intact parathyroid hormone levels during hemodialysis following exposure to either differing dialysate calcium concentrations or calcium-free dialysis with varying calcium infusion rates Kaye M, Fisher D.	Prospective study	6 patients	- stable hemodialysis patients	3 dialyses with standard bicarbonate and 3 dialyses with calcium-free dialysate.	Calcium free dialysate: Na^+: 142 mmol/L Cl^-: 108 mmol/L HCO_3^-: 34 mmol/L Mg^{2+}: 0.85 mmol/L + $CaCl_2$ 10% injectable, USP was infused into the drip chamber after the dialyzer at infusion rates: EITHER 10 mL/h OR 15 mL/h OR 20 mL/h	Standard bicarbonate dialysate: Na^+: 140 mmol/L Cl^-: 106 mmol/L HCO_3^-: 30 mmol/L Mg^{2+}: 0.78 mmol/L WITH EITHER Ca^{2+}: 1.25 mmol/L OR Ca^{2+}: 1.50 mmol/L OR Ca^{2+}: 1.75 mmol/L	- ionized calcium, total calcium - PTH	With increasing the calcium infusion, the ionized calcium tends to increase after dialysis. Concomitantly there will be a positive calcium balance. With increasing ionized calcium levels, there is suppression of PTH. Changes with $CaCl_2$ infused at 15 mL/h, were similar to those of 1.5mmol/L calcium in standard bicarbonate. More PTH suppression and higher end dialysis calcium resulted from 20 mL/h infusion or 1.75 mmol/L dialysate calcium.	Not specified

Study 12. Calcium-free hemodialysis for the management of hypercalcemia (Nephrol 1996; 72: 424-428). This is a prospective study to investigate the influence of a calcium-free dialysate in 6 hypercalcemic patients. Results shown that calcium free hemodialysis is indicated when presence of severe renal failure prevents the administration of large volumes of intravenous fluids to hypercalcemic patients. The amount of dialysis can be used to predict the decrease in plasma calcium concentration during calcium-free hemodialysis. Detailed data were summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)	Assessment criteria	Results efficacy	Adverse events
Nephrol 1996; 72: 424-428	Calcium-free hemodialysis for the management of hypercalcemia Koo WS, Jeon DS, Ahn SJ, Kim YS, Yoon YS, Bang BK	Prospective study	6 patients were included in the analysis: 4 men, 2 women mean age= 57 years (range: 42 - 65)	- patients with hypercalcemia and renal failure - treatment with force saline diuresis without success.	12 sessions of calcium free dialysis The duration of dialysis was 2-3 hours.	Calcium free dialysate: Na^+: 135 mmol/L K^+: 2.5 mmol/L Cl^-: 108 mmol/L HCO_3^-: 30 mmol/L Mg^{2+}: 0.75 mmol/L pH= 7.8	- plasma concentration of total calcium, inorganic phosphorus, urea nitrogen, creatinine and ionized calcium. - hypocalcemic ad signs	Plasma calcium concentrations: - before dialysis: 2.92±0.21 mmol/L - post dialysis: 2.16±0.33 mmol/L there was a significant positive correlation between the decrease in plasma calcium concentration and the K/V urea.	*Due to the technique:* None reported *Due to the replacement fluid:* None reported The rate of decrease in plasma calcium did not appear to produce adverse effects.

Study 13. Ionised calcium changes and parathyroid hormone secretion in HDF in relation to substitution fluid calcium content. (Nephrol Dial Transplant 1991; suppl.2: 104-107). This study was performed on 11 patients to evaluate the acute effect of different substitution fluid calcium concentrations and infusion rates on PTH response during HDF. Results indicated that

when calcium balance was slightly positive after the infusion of the substitution fluid containing calcium 3.5mEq/L, the PTH decreased slightly. Data were summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)		Assessment criteria	Results efficacy	Adverse events
Nephrol Dial Transplant 1991; suppl.2: 104-107	Ionised calcium changes and parathyroid hormone secretion in haemodiafiltration in relation to substitution fluid calcium content Malbert F, Surian M.	Within patient Comparative study	11 patients	- patients with chronic HDF treatment	2 to 3 HDF treatments (in different weeks) treatment time of 210 min.	Dialysate composition: Na^+: 138 mmol/L K^+: 1.5 mmol/L Cl^-: 103 mmol/L HCO_3^-: 31 mmol/L acetate: 10 mmol/L Ca^{2+}: 1.75 mmol/L Mg^{2+}: 0.5 mmol/L	Substitution fluids composition: A-HDF Na^+: 140 mmol/L K^+: 1.5 mmol/L Cl^-: 106.5 mmol/L Lactate: 40 mmol/L Ca^{2+}: 1.75 mmol/L Mg^{2+}: 0.5 mmol/L B1/B2-HDF Na^+: 140 mmol/L Cl^-: 100 mmol/L HCO_3^-: 40 mmol/L UF rate for A and B1-HDF: 53 -68 mL/min UF rate for B2-HDF: 75-100mL/min	- calcium balance, - serum ionized calcium - intact parathyroid hormone (PTH)	During A-HDF: - Calcium balance slightly positive - Serum ionized calcium increased from 1.24±0.06 mmol/L to a final 1.46±0.05 mmol/L ($p<0.001$) - PTH decreased from 227±231 pg/mL to 150±123 pg/mL ($p<0.01$) During B1-HDF: - Calcium balance slightly negative - Serum ionized calcium decreased from 1.29±0.05 mmol/L to a final 1.24±0.05 mmol/L ($p<0.05$) - without significant increase of PTH. When UF rate increase (B2-HDF), effect with B-HDF more marked with a significant increase of PTH ($p<0.01$). PTH changes negatively correlated ($r=-0.85$) to ionized calcium changes.	Not specified

6.1.4.3. Justification of the use of magnesium concentration

The replacement solution concentrations in PrimsaSol (1 or 1.5mEq/L) are similar to magnesium concentration in normal plasma (see the attached reference summary tables in Section 10.1). In critically ill patients with acute renal failure, calcium, phosphate and magnesium were commonly abnormal and are only partly correctly by CRRT.

6.1.4.4. Justification of the potassium concentration

In the early stage of patients treated with CRRT, commercial replacement solutions are potassium and phosphate free since most patients with acute renal failure require potassium and phosphate removal at this time. Patients may subsequently require potassium and/or phosphate supplementation. The appropriate concentrations of potassium were from 0 to 4mEq/L.

6.1.4.5. Justification of the use of sodium and chloride concentration

The sodium concentrations for the replacement solutions are within the normal physiological range of concentrations. Chloride is only adjusted to balance the concentrations of the other electrolytes. The ranges of sodium and chloride have been shown the above tables.

6.1.4.6. Justification of the dextrose concentration.

Most published studies use replacement solutions without dextrose and some use replace solutions with 1-2g/L of dextrose. The dextrose concentration to use in replacement solutions should be determined based on the dextrose loss in the ultrafiltrate and administration of dextrose via the same solutions. In the literature, the prevention of hyperglycemia is a prognostic factor in ICU patients.

6.1.4.7. Children

Two hemofiltration studies have shown that PrismaSol solutions match the requirements in composition for those solutions used in these studies including a study from newborn to 17 years old patients. In one study, bicarbonate-based calcium-free substitution fluids were used, in combination with citrate anticoagulation, and $CaCl_2$. Electrolyte disturbances were primarily related to sodium, bicarbonate, and magnesium changes. Data were summarized in the following studies.

Study 14. CRRT in critically ill neonates. (Kidney International 1998; vol 53, suppl 66: S169-S173. Treatments included CAVH, CVVH, CAVHD and CVVHD. The authors described their experience with CRRT in 36 critically ill neonates. **The concentration of bicarbonate buffer was 35mmol/L with 3.16mmol/L lactate. The concentrations of electrolytes were 145, 115, 1.84, 0.53 mmol/L for Na, Cl, Ca, and Mg, respectively. Potassium was added as required to a 4.5mmol/L.** Data were summarized in the following table:

al olume age	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)	Assessment criteria	Results efficacy	Adverse events
Idney ternational 998; vol 53, uppl 66: S 69-S 173	Continuous renal replacement therapy in critically ill neonates Zobel G, Rödl S, Urlesberger B, Kuttnig-Haim M, Ring E.	Retrospective study	36 neonates (22 men, 14 women) mean age= 9.8 ± 1.5 days mean body weight= 3.0 ± 0.1 kg	- CAVH (continuous arterio-venous hemofiltration) : 17 patients; - CVVH (continuous veno-venous hemofiltration) : 15 patients; - continuous ultrafiltration (CUF) during extracorporeal membrane oxygenation (ECMO): 4 patients (because of severe diuretic-resistant hypervolemia).	Mean duration of CRRT= 97±20 hours (range: 14 to 720 hours)	*Substitution fluid:* Na^+: 145 mmol/L Cl: 115 mmol/L HCO_3^-: 35 mmol/L Lactate: 3.16 mmol/L Ca^{2+}: 1.84 mmol/L Mg^{2+}: 0.53 mmol/L K^+ was added as required up to 4.5mmol/L *Bicarbonate dialysate for CHDF:* Na^+: 140 mmol/L Cl: 100- 110 mmol/L HCO_3^-: 35-40 mmol/L Ca^{2+}: 3.5 mmol/L Mg^{2+}: 1. 5 mmol/L Dextrose: 1.5 g/dL K^+ was added as required up to 4.5mmol/L		The overall survival rate was 66%. No significant difference between survivors and non-survivors, except the mean blood pressure (resp. 49.2±1.8 vs. 38.3±1.4 mmHg, p>0.01 and APSC (p<0.01) 24 hours after starting CRRT. CAVH Mean duration= 103 h/patient (range: 12-720) UF rate= 3.3±0.4 mL/min/m² CAVH was well tolerated by all patients. CVVH UF rate= 9.5±1.9 mL/min/m² CUF Improved severe hypervolemia within 48.5±13 hours. CHDF Mean UF rate during CHF= 1.06±0.2mL/min. Adding a dialysate solution at a rate of 5mL/min in a countercurrent fashion to blood flow decreased the UF rate by 20%, whereas urea and creatinine clearances increased by 300%	CAVH - local bleeding at the catheter entrance site (4 patients) - severe bleeding (1 patient) - transient ischemia of the leg (due to femoral artery cannulation) (2 patients) CVVH - partial thrombosis of the vena cava superior or inferior (3 patients) - severe metabolic crisis (cardiocirculatory compromise) (1 patient).

Study 15. Pediatric CRRT: Normocarb dialysate solution with citrate anticoagulation. (Pediatr Nephrol 2002; 17: 150-154). 14 children from newborn to 17 years of age were treated with CVVHD. Bicarbonate-based calcium-free substitution fluids were used, in combination with citrate anticoagulation, and $CaCl_2$. Electrolyte disturbances were primarily related to sodium, bicarbonate, and magnesium changes. **The compositions of the substitutions included Na: 140mEq/L, Cl: 95mEq/L, HCO_3 40mEq/L, Mg: 1mEq/L, and Dextrose: 100mg/dl.** All children on HF in excess of 7 days developed a metabolic alkalosis, resolved by decreasing the dialysate rate and adding normal saline as replacement fluid. Data were summarized in the following table:

Ref Volume Page	Study	Study methodology	Number of subjects (age, sex)	Diagnosis and inclusion criteria	Treatment duration	Study drugs (dosage and route of administration)		Assessment criteria	Results efficacy	Adverse events
Pediatr Nephrol 2002; 17: 150-154	Pediatric hemofiltration: dormocarb dialysate solution with citrate anticoagulation Bunchman TE, Maxvold NJ, Barnett J, Hutchings A, Benfield MR	Descriptive report, non comparative study	14 children from newborn to 17 yrs of age. Mean weight= 31.6±4.7 kg (range: 3.7-62kg)	- patient requiring HF: sepsis (11 children) and tumor lysis syndrome (3 children).	Mean time: 11.4±3.7 days (range: 6hrs to 67 days)	Bicarbonate-buffered substitution: Na^+: 140 mEq/L Cl: 95 mEq/L HCO_3: 40 mEq/L Mg^{2+}: 1 mEq/L Dextrose: 100mg/dL If needed add: KCl: 2 mEq/L K_2PO_4: 2 mEq/L (this equal to 4 mEq/L of Phosphorus) Solution of $CaCl_2$ 5g/L is added separately.	Normocarb: Na^+: 140 mEq/L Cl: 105 mEq/L HCO_3: 35 mEq/L Mg^{2+}: 1.5 mEq/L If needed add: KCl: 2 mEq/L K_2PO_4: 2 mEq/L (this equal to 4 mEq/L of Phosphorus) Solution of $CaCl_2$ 5g/L is added separately.		No bleeding occurred with citrate anticoagulation. Electrolyte disturbances were primarily related to sodium, bicarbonate, and magnesium changes. In 4 children (less than 6kg), attention to the timing of citrate introduction is important.	- Acute drop in sodium (141mEq/L to 121mEq/L) in 1 patient, corrected with 3% saline infusion. - overload of sodium (152mEq/L) and calcium in 1 patient, corrected by lowering the sodium in the TPN and reducing the $CaCl_2$ in the saline. - all children on HF in excess of 7 days developed a metabolic alkalosis, resolved by decreasing the Normocarb dialysate rate and adding normal saline as replacement fluid. - bradykinin release syndrome in 1 child with sepsis (and no ACE inhibitor), prevented subsequently by introduction of the citrate 5min after the induction of the HF process.

6.1.5 Efficacy Conclusions

Based on the clinical reports from the published data, replacement fluid in most situations should contain physiological concentrations of electrolytes except for those that are protein-bound. In the buffer selection, lactate solutions are usually well tolerated. However, it appears that bicarbonate is the first choice for replacement solutions than the lactate and acetate. Bicarbonate-containing solutions provide benefit to the patient, especially when liver function is compromised, when there is circulatory failure or when a large volume of replacement fluid is used during CRRT. The appropriate concentrations of bicarbonate were in the range of 30 to 40 mmol/L with or without 3mmol/L lactate. Magnesium and sodium solutions should be the same as the normal physiological conditions in the range of 1 to 1.5 mEq/L and about 140mEq/L, respectively. Calcium and potassium concentrations can be variable from 0 to 4mEq/L based on the individual patient conditions, and treatment modalities. Calcium can also be added separately in the calcium-free replacement solutions during CRRT. The dextrose concentration for use in replacement solutions should be determined based on the dextrose loss in the ultrafiltrate and administration of dextrose via the same solutions.

According to the published clinical data, the nine formulations of PrismaSol solution appear to be acceptable for CRRT. In pediatric patients, PrismaSol solutions appear to match the requirements in the CRRT treatment. Based on the similar plasma levels of electrolytes between the children and adults, the PrismaSol should be effective and safe in pediatric use.

7. INTEGRATED REVIEW OF SAFETY

Methods:

PrismaSol solutions for CRRT are a range of products that provide multiple formulations for the prescribing physician in the management of patient with acute renal failure (ARF). No sponsor-generated clinical study related to the safety of these solutions was provided with this application. All data were cited from the published literature.

Findings:

1. According to the published study reports, the mortality rate in ARF patient population is high and can be predicted using APACHE II scores. The expected mortality rate in this patient population is usually over 50%. Regarding the fluid balance errors, the sponsor reported that the incidence rate was 6% based on data from the largest hemofiltration study in which lactate-containing replacement solutions were used and ultrafiltration doses were compared (Lancet 2000; volume 355:26-30).
2. In small studies, a direct comparison between lactate- and bicarbonate-buffered solutions demonstrated a significant reduction in cardiovascular event (volume change-related hypotension, angina, etc.) with bicarbonate-buffered solutions (Kidney International 2000; vol 58:1751-1757).
3. Factors extrinsic to the patient and the solution, such as local medical practice, specific CRRT technique, choice of membrane, and monitoring of the patient, may influence safety of the patient but should not interfere with the safety of the solution used.
4. In term of drug interactions, the mixing of bicarbonate, calcium and magnesium together in a single container raises issues of stability. The double-compartment bag used for PrismaSol can prevent these solution stability problems.
5. The excessive electrolyte/fluid addition or depletion can be prevented by close monitoring of the patients volume and biochemical status. This occurrence can be managed by changes in the flow rates of replacement fluid, or by changes in the concentrations of solute constituents in these fluids.

In conclusion, based on the results of published clinical studies, no significant solution-related safety issues were reported. Although, patient deaths, cardiovascular complications, nausea, vomiting, pruritus, and many other side effects were reported from these studies, these were not considered by this reviewer to be solution-related. The reviewer considered that these published clinical studies adequately evaluate the safety of the PrismaSol formulations in the indicated ARF patient population when used as replacement solutions in CRRT. Even though not all of the formulations have been tested in every condition and age group, the range of concentrations of electrolytes and dextrose proposed in this application is covered by the cited reports. Therefore, this solution itself should have no specific safety issues.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dose regimen and administration depend on the local medical practice, specific CRRT technique, choice of membrane, and monitoring of the patient.

8.2 Drug-Drug Interactions

No additional formal drug interaction studies have been conducted. Based on the published data, citrate was commonly used in patents with hemorrhagic trend and may induce alkalosis if the bicarbonate concentration was not adjusted. In addition, some electrolytes may also need to be changed.

8.3 Special Populations
No formal subgroup analyses were conducted for age, gender or race. No data were available in the condition of pregnancy. Based on the published data, age is an important survival factor in ICU patients treated with CRRT. However, no data confirmed that the compositions of replacement solutions need to be changed with age.

8.4 Pediatrics
Two studies have been shown that CRRT can be used to treat pediatric patients with the similar replacement solutions like PrismSol solutions (see section 6.1.4.7).

8.5 Advisory Committee Meeting
No additional advisory committee meeting is planned at the present time.

8.6 Literature Review
All the clinical data were from literature review. The reviewer also performed a PubMed search using the terms: dialysate, infusate, replacement solution, hemofiltration, hemodiafiltration, and CRRT. There was no new information or unusual solution-related findings.

8.7 Postmarketing Risk Management Plan
Hemosol B0 and PrismaSol 2 and 4 are currently being marketed in Europe. Hemosol B0 is currently commercially available in Canada. Except for a minor difference in the dextrose concentration (100mg/dl in this application instead of 110mg/dl), they are essentially the same as PrismaSol BK0/3.5, PrismaSol BGK2/3.5 and PrismaSol BGK 4/3.5. Pharmacovigilance of these products did not reveal any adverse events related to their use during these treatments. All PrismaSol formulations are within the range of dextrose and electrolytes concentrations contained in the formulation of PrismaSate dialysate which is currently marked in the US and cleared by the FDA under a 510(K) notification K013448

8.8 Other Relevant Materials
N/A

9. Overall Assessment

9.1 Conclusions
In determining the fluid composition, there is general consensus that replacement fluid ——— should contain a buffer and electrolytes in concentrations aiming for physiological levels and taking into account preexisting deficits or excess and all inputs and losses. It should be considered as a pure physiological solution rather than a drug. In most situations, replacement fluid should contain physiological concentrations of electrolytes except for those that are protein-bound. As replacement solutions in CRRT, PrismaSol solutions provide multiple formulations for the prescribing physician in the management of patients with acute renal failure with different primary diseases. These formulations included physiological concentrations of sodium (140mEq/L), chloride (106.5-113.5mEq/L), magnesium (1-1.5mEq/L), bicarbonate (32mEq/L) with lactate (3mEq/L), and different concentrations of dextrose (0-100mEq/L), potassium (0-4mEq/L), and calcium (0-3.5mEq/L). Based on the review of the literature and journal citations, there is sufficient documentation in these articles to adequately evaluate the safety and efficacy of the PrismaSol formulations in the indicated ARF patient population when used as replacement

solutions in CRRT. Even though not all of the formulations have been tested in every condition and age group, the range of concentrations of electrolytes and dextrose proposed in this application is covered by the cited reports.

One major concern regard to PrismaSol solutions as replacement solutions in CRRT is the selection of the different formulations and the monitoring of the fluid balance, electrolytes and acid-base condition in patients. The physician should understand how to select the appropriate formulations. Examples include when to choose the solution with 0, 2.5, or 3.5mEq/L potassium, etc. Inappropriate procedures have been observed from MEDWATCH reports as shown in the following: "FDA has issued an update to its August 2005 preliminary public health notification for the Gambro Prisma(r) Continuous Renal Replacement Therapy (CRRT) device, used for continuous solute and/or fluid removal in patients with acute renal failure or fluid overload. Approximately 1,900 units have been distributed to hospitals in the United States. This device has caused or contributed to a number of serious adverse events by removing excessive amounts of fluid from patients undergoing CRRT. FDA is aware of 9 deaths and 11 serious injuries associated with the excessive fluid removal problem. Special caution must be used and caregivers must adhere strictly to the labeled operating instructions, including the Manufacturer's Instructions for Use, Operator's Manual, and the User Interface on the Prisma(r) System control panel". Therefore, the reviewer recommended that the indications of each formulation of PrismaSol solutions in CRRT should be labeled in detail to avoid the imbalance of body volume and acid-base, and disturbance of plasma electrolytes.

The other issue during the CRRT is the application of citrate. Citrate is used for regional anticoagulation of the extracorporeal circuit during CRRT and is particularly appealing of patients at risk of bleeding. Since citrate can be converted to bicarbonate by the liver and by the muscle in a 1:3 ratio, the plasma concentration of bicarbonate will significantly increase and metabolic alkalosis may be a consequence after the long-term use of this anticoagulant agent. The sodium and calcium concentrations may also change significantly. Therefore, the formulations of the PrismSol solutions need to be adjusted. This information should be added to the labeling. In addition, PrismSol solutions do not contain phosphate and phosphate supplementation is generally required at some stage during CRRT. Customized solutions may be necessary in patients with some electrolyte imbalances. This is not a major concern but should be added into the labeling.

The reviewer recognizes that the PrismaSate solutions which are the similar as the PrismaSol are currently available on the US market as dialysate solutions that received FDA clearance in 510 (K) notification from CDRH. In addition, the various formulations, with their changes in solute concentrations were considered as changes in 'dose' of the various electrolytes and sugars by the division. Therefore, the approval, then, would be a single NDA for a range of electrolyte concentrations, for use in as a renal replacement solution. From this reviewer's perspective, this NDA should be approved

9.2 Recommendation on Regulatory Action

1. It is recommended that PrismaSol be approved as replacement solutions for the indication of CRRT to treat the adult and pediatric patients with acute renal failure.

9.3 Recommendation on Postmarketing Actions:
N/A

9.4 Labeling Review:
Labeling review will be submitted separately.

This reviewer has recommended:

1. It is recommended that PrismaSol be approved for the indication as a replacement solution in continuous renal replacement therapy (CRRT) to treat the patients with acute renal failure.

2. When citrate is used as an anticoagulant agent during CRRT, adjustment of the composition of PrismaSol solutions may be needed. This should be added to the labeling.

3. Phosphate which is not in the PrismaSol solutions may be required at some stage during CRRT. This should be added to the labeling.

Comments to Applicant
The recommendations should be conveyed to the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

Concentrations of electrolytes and buffers that were used in CRRT from published literature compared to PrismaSol solutions were summarized in the following tables.

Number of patients per concentration of electrolytes and solutes

					Gambro sodium : 140 mEq/L				Gambro potassium : 0-4 mEq/L				
					sodium				potassium				
N°	Paper	Ther-apy	Disease	Proc-edure	< 138 mEq/L	138 - 142 mEq/L	> 142 mEq/L	comment s 4	0 mEq/L	< 2 mEq/L	2 - 4 mEq/L	> 4mEq/L	comments 5
1	Barenbrock, Kidney Int 2000	HF	ARF	CRRT	56	61			NA		NA		K^+: 2mEq/L or K-free are chosen according to the patients' serum potassium values.
3	Heering, Intensive Care Med 1999	HF	ARF	CRRT		132			132				
4	Hilton, QJMed 1998	HF	ARF	CRRT		NA			200				
5	Kierdorf, Contrib Nephrol Basel Karger 1995	HF	ARF	CRRT		20			20				
6	Olbricht, Anästh. Intensivther. Notfallmed 1990	HF	ARF	CRRT		7			7				
7	Ronco, Lancet 2000	HF	ARF	CRRT		NA				NA			
9	Tan, Int J Artif Organs 2003	HF	ARF	CRRT		8					8		KCl was added (final conc of 3.7 mEq/L)
10	Thomas, Nephrol Dial Transplant 1997	HF	ARF	CRRT		21	20		NA	NA	NA	NA	"K in the solution 0-6 mEq/L to maintain the serum K between 4.5 and 6.0 mEq/L." Hemosol B0 used
30	Zobel, Kidney Int 1998	HF	C-ARF	CRRT			36		36				K was added as required up to 4.5 mEq/L
31	Bunchman, Pediatr Nephrol 2002	HF	C-ARF	CRRT		14			14				if needed add: KCl 2 mEq/L
32	Bunchman, Am J of Kid Dis 2003	HF	C-ARF	CRRT		9			9				if needed add: KCl 2 mEq/L
2	Böhm, Clinical Nephrology 1994	HF	ESRD	IT		11	11		11				bicarbonate buffered sol: K^+ free, but lactate buffered solution K^+ 0/2 mEq/L according to patients' values
8	Santoro, Int J Artif Organs 1994	HF	ESRD	IT		24				24			
33	Splendiani, Artificial Organs 2000	HF	Toxic	CRRT		NA				NA			
11	Bellomo, Am J of Kid Dis 1993	HDF	ARF	CRRT		NA			110				
34	Bironneau, Renal Failure 1996	HDF	Toxic	CRRT									

					Gambro sodium : 140 mEq/L				Gambro potassium : 0-4 mEq/L				
					sodium				potassium				
N°	Paper	Ther-apy	Disease	Proc-edure	< 138 mEq/L	138 - 142 mEq/L	> 142 mEq/L	comments 4	0 mEq/L	< 2 mEq/L	2 - 4 mEq/L	> 4mEq/L	comments 5
12	Gonella, Nephrol Dial Transplant 1993	HDF	ESRD	IT		17					17		
13	Malberti, Nephrol Dial Transplant 1991	HDF	ESRD	IT		11				11			
14	Morimatsu, Int J Artif Organs 2002	HDF	ARF	CRRT		49	49		49	50			CVVHDF: 49 patients CVVH: 50 patients (lactate RF)
15	Morimatsu, Int J Artif Organs 2003	HDF	ARF	CRRT									
16	Movilli, Am J of Kid Dis 1996	HDF	ARF	CRRT		12					12		
17	Bouffard, Kidney Internation al 1993	HD	ARF	CRRT		NA			NA				
24	Leblanc, Am J of Kid Dis 1995	HD	ARF	CRRT	13		50	In lactate buffered dialysate, Na^+: 132 mEq/L; in bicar dialysate, Na^+: 144±3 mEq/L			50		
29	Zimmerma n, Nephrol Dial Transplant 1999	HD	ARF	CRRT		26			26				KCl was added if the serum potassium dropped below 3.5mmol/L
25	Leunissen, Nephron 1986	HD	ARF	IT		9				9			
23	Koo, Nephrol 1996	HD	ARF Ca^{2+}	IT			6			6			
18	Fellner, Hypertensi on 1989	HD	ESRD	IT			8				8	8	8
19	Gutierrez, Kidney Int 1994	HD	ESRD	IT		8				8			K^+: 1-2 mEq/L
20	Henrich, N Engl J Med 1984	HD	ESRD	IT			8				8		
21	Kaye, Clinical Nephrology 1990	HD	ESRD	IT		6			6				
22	Kaye, Clinical Nephrology 1993	HD	ESRD	IT		39			39				

					Gambro sodium : 140 mEq/L				Gambro potassium : 0-4 mEq/L				
					sodium				potassium				
N°	Paper	Ther-apy	Disease	Proc-edure	< 138 mEq/L	138 - 142 mEq/L	> 142 mEq/L	comments 4	0 mEq/L	< 2 mEq/L	2 - 4 mEq/L	> 4mEq/L	comments 5
26	Mansell, Nephrol Dial Transplant 1967	HD	ESRD	IT	18	18		In acetate buffered dialysate, Na^+: 138 mEq/L; in bicar dialysate, Na^+: 135-140mEq/L		18	18		
27	Pietilä, Nephrol Dial Transplant 1989	HD	ESRD	IT				25 patients with Na^+: 135-140mEq/L			25		
28	Williams, Nephrol Dial Transplant 1997	HD	ESRD	IT		46					46		

					Gambro Magnesium: 1 - 1.5 mEq/L					Gambro calcium: 0mEq/L, 2.5 mEq/L and 3.5 mEq/L				
					Magnesium					Calcium				
N°	Paper	Ther-apy	Disease	Proc-edure	0 - <0.5 mEq/L	0.5 - <1.0 mEq/L	1 - 1.5 mEq/L	> 1.5 mEq/L	comments 6	0	≤ 2.5 mEq/L	2.5 - 3.5 mEq/L	> 3.5 mEq/L	comments 7
1	Barenbrock, Kidney International 2000	HF	ARF	CRRT			117					61	56	with bicar sol, Ca^{2+}: 3mEq/L; with lactate sol, Ca^{2+}: 3.7mEq/L
3	Heering, Intensive Care Med 1999	HF	ARF	CRRT			100	32				48	84	with bicar sol, Ca^{2+}: 3mEq/L; with lactate sol, Ca^{2+}: 4mEq/L with acetate sol, Ca^{2+}: 4mEq/L
4	Hilton, QJMed 1998	HF	ARF	CRRT		NA			Mg salts were infused but conc.NA					Ca salts were infused but conc.NA
5	Kierdorf, Contrib Nephrol Basel Karger 1995	HF	ARF	CRRT			20					20	20	with bicar sol, Ca^{2+}: 3.5mEq/L; with lactate sol, Ca^{2+}: 4mEq/L
6	Olbricht, Anästh. Intensivther. Notfallmed 1990	HF	ARF	CRRT			7					7		
7	Ronco, Lancet 2000	HF	ARF	CRRT		NA								
9	Tan, Int J Artif Organs 2003	HF	ARF	CRRT			8	8	in bicarb. sol, Mg^{2+}: 1 mEq/L in lactate sol, Mg^{2+}: 1.6 mEq/L			8		
10	Thomas, Nephrol Dial Transplant 1997	HF	ARF	CRRT			21	20					41	
30	Zobel, Kidney Int 1998	HF	C-ARF	CRRT			36						36	
31	Bunchman, Pediatr Nephrol 2002	HF	C-ARF	CRRT			14			14				CaCl2 is added separately
32	Bunchman, Am J of Kid Dis 2003	HF	C-ARF	CRRT			9			9				CaCl2 is added separately
2	Böhm, Clinical Nephrology 1994	HF	ESRD	IT			11					11	11	with bicar sol, Ca^{2+}: 3.5mEq/L; with lactate sol, Ca^{2+}: 4mEq/L
8	Santoro, Int J Artif Organs 1994	HF	ESRD	IT			24						24	

					Gambro Magnesium: 1 - 1.5 mEq/L					Gambro calcium: 0mEq/L, 2.5 mEq/L and 3.5 mEq/L				
					Magnesium					Calcium				
N°	Paper	Ther-apy	Disease	Proc-edure	0 - <0.5 mEq/L	0.5 - <1.0 mEq/L	1 - 1.5 mEq/L	> 1.5 mEq/L	comments 6	0	≤ 2.5 mEq/L	2.5 - 3.5 mEq/L	> 3.5 mEq/L	comments 7
33	Splendiani, Artificial Organs 2000	HF	Toxic	CRRT		NA					NA			
11	Bellomo, Am J of Kid Dis 1993	HDF	ARF	CRRT		NA			Mg salts were infused but conc. NA					Ca salts were infused but conc NA
34	Bironneau, Renal Failure 1996	HDF	Toxic	CRRT										
12	Gonella, Nephrol Dial Transplant 1993	HDF	ESRD	IT			17		Mg in the reinfusate : 1 mEq/L Mg in the dialysate : 0.7 mEq/L			17		
13	Malberti, Nephrol Dial Transplant 1991	HDF	ESRD	IT			11					11		
14	Morimatsu, Int J Artif Organs 2002	HDF	ARF	CRRT				99				50		CVVH ca: 3.2 mEq/L. CVVHDF replacement fluid: 1.1 mEq/L but CVVHDF dialysate: 2.5 mEq/L
15	Morimatsu, Int J Artif Organs 2003	HDF	ARF	CRRT										
16	Movilli, Am J of Kid Dis 1995	HDF	ARF	CRRT			12					12		
17	Bouffard, Kidney Int 1993	HD	ARF	CRRT		NA								
24	Leblanc, Am J of Kid Dis 1995	HD	ARF	CRRT			50					50		
29	Zimmerman, Nephrol Dial Transplant 1999	HD	ARF	CRRT			21							calcium was given by infusion at 2.8 mEq/hour if necessary.
25	Lounissen, Nephron 1986	HD	ARF	IT			9					9		
23	Koo, Nephrol 1996	HD	ARF Ca^{2+}	IT			6			6				
18	Fellner, Hypertension 1989	HD	ESRD	IT			8				8	8	8	

					Gambro Magnesium: 1 - 1.5 mEq/L					Gambro calcium: 0mEq/L, 2.5 mEq/L and 3.5 mEq/L				
					Magnesium					calcium				
N°	Paper	Ther-apy	Diseas e	Proc-edure	0 - <0.5 mEq/L	0.5 - <1.0 mEq/L	1 - 1.5 mEq/L	> 1.5 mEq/L	comments 6	0	≤ 2.5 mEq/L	2.5 - 3.5 mEq/L	> 3.5 mEq/L	comments 7
19	Gutierrez, Kidney International 1994	HD	ESRD	IT			8					8		
20	Henrich, N Engl J Med 1984	HD	ESRD	IT		8	16		1.2 mEq/L; 1.02 mEq/L; 0.98 mEq/L		8	8	8	2.2 mEq/L; 3.7 mEq/L; 2.6 mEq/L
21	Kaye, Clinical Nephrology 1990	HD	ESRD	IT				6		6	6	12		0; 2.5 mEq/L; 3 mEq/L; 3.5 mEq/L
22	Kaye, Clintcal Nephrology 1993	HD	ESRD	IT				39		20		19		study I: 3mEq/L (10 patients) study II: 3.5 mEq/L (9 patients)
26	Mansell, Nephrol Dial Transplant 1987	HD	ESRD	IT			18					18		
27	Pletilä, Nephrol Dial Transplant 1989	HD	ESRD	IT			25					25		
28	Williams, Nephrol Dial Transplant 1997	HD	ESRD	IT		46					46			

Appears This Way
On Original

					Gambro dextrose: 0 - 1 g/L dextrose				
N°	Paper	Ther-apy	Disease	Proc-edure	0	≤ 1g/L	1 - 2 g/L	> 2g/L	comments 8
1	Barenbrock, Kidney International 2000	HF	ARF	CRRT		61	56		with bicar sol. Dex: 1g/L with lactate sol. Dex: 1.35 and 1.5 g/L
3	Heering, Intensive Care Med 1999	HF	ARF	CRRT	132				
4	Hilton, QJMed 1998	HF	ARF	CRRT	200				
5	Kierdorf, Contrib Nephrol Basel Karger 1995	HF	ARF	CRRT		20			
6	Olbricht, Anästh. Intensivther. Notfallmed 1990	HF	ARF	CRRT	7				
7	Ronco, Lancet 2000	HF	ARF	CRRT					
9	Tan, Int J Artif Organs 2003	HF	ARF	CRRT	8		8		with bicar sol. Dex: 0 g/L with lactate sol. Dex: 1.94 g/L
10	Thomas, Nephrol Dial Transplant 1997	HF	ARF	CRRT	41				
30	Zobel, Kidney International 1998	HF	C-ARF	CRRT	36				
31	Bunchman, Pediatr Nephrol 2002	HF	C-ARF	CRRT		14			bicarbonate based calcium-free sol. contains 1g/L Dex
32	Bunchman, Am J of Kid Diseases 2003	HF	C-ARF	CRRT	9				
2	Böhm, Clinical Nephrology 1994	HF	ESRD	IT		11			
8	Santoro, Int J Artif Organs 1994	HF	ESRD	IT	24				
33	Splendiani, Artificial Organs 2000	HF	Toxic	CRRT		NA			
11	Bellomo, American Journal of Kidney Diseases 1993	HDF	ARF	CRRT	110				
34	Bironneau, Renal Failure 1996	HDF	Toxic	CRRT					
12	Gonella, Nephrol Dial Transplant 1993	HDF	ESRD	IT	17				
13	Maiberti, Nephrol Dial Transplant 1991	HDF	ESRD	IT	11				
14	Morimatsu, Int J Artif Organs 2002	HDF	ARF	CRRT	99				
15	Morimatsu, Int J Artif Organs 2003	HDF	ARF	CRRT					
16	Movilli, American Journal of Kidney Diseases 1996	HDF	ARF	CRRT		12			Bicarbonate dialysis contains 1g/L Dex.
17	Bouffard, Kidney International 1993	HD	ARF	CRRT					
24	Leblanc, American Journal of Kidney Diseases 1995	HD	ARF	CRRT				50	
29	Zimmerman, Nephrol Dial Transplant 1999	HD	ARF	CRRT	21			21	with bicar sol. : no Dex ; with lactate sol. Dex: 15 g/L

					Gambro dextrose: 0 - 1 g/L				
					dextrose				
N°	Paper	Ther-apy	Disease	Proc-edure	0	≤ 1g/L	1 - 2 g/L	> 2g/L	comments 8
25	Leunissen, Nephron 1986	HD	ARF	IT	9				
23	*Koo, Nephrol 1996*	*HD*	*ARF Ca^{2+}*	*IT*	6				
18	Fellner, Hypertension 1989	HD	ESRD	IT				8	Dex: 25g/L
19	Gutierrez, Kidney International 1994	HD	ESRD	IT	8		8		comparison of dialysis fluid without Dex and with Dex (1.98 g/L)
20	Henrich, N Engl J Med 1984	HD	ESRD	IT				8	Dex : approx 2.5 g/L
21	Kaye, Clinical Nephrology 1990	HD	ESRD	IT	6				
22	Kaye, Clinical Nephrology 1993	HD	ESRD	IT	39				
26	Mansell, Nephrol Dial Transplant 1987	HD	ESRD	IT			18		with bicar sol. : no Dex ; with lactate sol. Dex: 1.98 g/L
27	Pietilä, Nephrol Dial Transplant 1989	HD	ESRD	IT	8				
28	*Williams, Nephrol* Dial Transplant 1997	HD	ESRD	IT			46		Dex: 2 g/L

					Gambro bicarbonate: 32 mEq/L			Gambro lactate: 3 mEq/L	
					Bicarbonate solution		bicar + lactate	bicar + acetate	
N°	Paper	Ther-apy	Disease	Proc-edure	<35 mEq/L	≥ 35 mEq/L	bicar + lactate	bicar + acetate	comments 9
1	Barenbrock, Kidney International 2000	HF	ARF	CRRT		61			bicar: 35mEq/L
3	Heering, Intensive Care Med 1999	HF	ARF	CRRT		48			bicar: 35mEq/L
4	Hilton, QJMed 1998	HF	ARF	CRRT					NA
5	Kierdorf, Contrib Nephrol Basel Karger 1995	HF	ARF	CRRT			20		bicar: 34.5mEq/L; lactate: 3 mEq/L
6	Olbricht, Anästh. Intensivther. Notfallmed 1990	HF	ARF	CRRT			7		bicar: 31.4mEq/L; lactate: 2.9 mEq/L
7	Ronco, Lancet 2000	HF	ARF	CRRT					
9	Tan, Int J Artif Organs 2003	HF	ARF	CRRT			8		bicar: 32mEq/L; lactate: 3 mEq/L
10	Thomas, Nephrol Dial Transplant 1997	HF	ARF	CRRT			20		bicar: 40mEq/L; lactate: 3 mEq/L
30	Zobel, Kidney International 1998	HF	C-ARF	CRRT			36		bicar: 35mEq/L; lactate: 3.16 mEq/L
31	Bunchman, Pediatr Nephrol 2002	HF	C-ARF	CRRT		14			bicar: 35 - 40 mEq/L
32	Bunchman, Am J of Kid Diseases 2003	HF	C-ARF	CRRT		9			bicar: 35mEq/L
2	Böhm, Clinical Nephrology 1994	HF	ESRD	IT			11		bicar: 31.4mEq/L; lactate: 3 mEq/L or bicar: 39.7mEq/L; lactate: 2.9 mEq/L
8	Santoro, Int J Artif Organs 1994	HF	ESRD	IT	12	12			Bicar 30mEq/L: 12 patients; Bicar 35-40mEq/L: 7+5 .patients
33	Splendiani, Artificial Organs 2000	HF	Toxic	CRRT		NA			
11	Bellomo, Am J of Kid Dis 1993	HDF	ARF	CRRT					NA
34	Bironneau, Renal Failure 1996	HDF	Toxic	CRRT					
12	Gonella, Nephrol Dial Transplant 1993	HDF	ESRD	IT				17	bicar: 36 mEq/L; acetate: 4 mEq/L
13	Malberti, Nephrol Dial Transplant 1991	HDF	ESRD	IT				11	bicar: 31 mEq/L; acetate: 10 mEq/L
14	Morimatsu, Int J Artif Organs 2002	HDF	ARF	CRRT		49			bicar: 37.5mEq/L
15	Morimatsu, Int J Artif Organs 2003	HDF	ARF	CRRT					
16	Movilli, Am J of Kid Dis 1996	HDF	ARF	CRRT				12	bicar: 35 mEq/L; acetate: 4 mEq/L
17	Bouffard, Kidney Int 1993	HD	ARF	CRRT	8				bicar: 31 mEq/L

					Gambro bicarbonate: 32 mEq/L			Gambro lactate: 3 mEq/L	
					Bicarbonate solution		bicar + lactate	bicar + acetate	
N°	Paper	Ther-apy	Disease	Proc-edure	<35 mEq/L	≥ 35 mEq/L	bicar + lactate	bicar + acetate	comments 9
24	Leblanc, American Journal of Kidney Diseases 1995	HD	ARF	CRRT				50	bicar: 37±2 mEq/L; acetate: 2-4 mEq/L
29	Zimmerman, Nephrol Dial Transplant 1999	HD	ARF	CRRT			21		bicar: 35mEq/L; lactate: 2-4 mEq/L
25	Leunissen, Nephron 1986	HD	ARF	IT				9	bicar: 35 mEq/L; acetate: 3 mEq/L
23	Koo, Nephrol 1996	HD	ARF Ca^{2+}	IT	6				bicar: 30 mEq/L
18	Fellner, Hypertension 1989	HD	ESRD	IT					acetate: 36 mEq/L
19	Gutierrez, Kidney International 1994	HD	ESRD	IT	8				bicar: 32 mEq/L
20	Henrich, N Engl J Med 1984	HD	ESRD	IT	8				bicar: 25 - 24.1 - 30.5 mEq/L
21	Kaye, Clinical Nephrology 1990	HD	ESRD	IT	6				bicar: 34 mEq/L
22	Kaye, Clinical Nephrology 1993	HD	ESRD	IT	20				bicar: 34.5 mEq/L
26	Mansell, Nephrol Dial Transplant 1987	HD	ESRD	IT				16	bicar: 40 mEq/L; acetate: 2-4 mEq/L
27	Pietilä, Nephrol Dial Transplant 1989	HD	ESRD	IT				8	bicar: 34 mEq/L; acetate: 3 mEq/L
28	Williams, Nephrol Dial Transplant 1997	HD	ESRD	IT				46	bicar: 30 mEq/L; acetate: 2 mEq/L or bicar: 40mEq/L; acetate: 2 mEq/L

10.2 . Pre-NDA meeting minutes.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION

Woodmont II **US Mail address:** 1451 Rockville Pike FDA/CDER/HFD-110 Rockville, MD 20852 5600 Fishers Lane Rockville, MD 20857

Transmitted to FAX Number: 410-531-5088

Attention: David Zuchero (US Agent) Chesapeake Regulatory Group, Inc.

Company Name: Gambro Renal Products

Phone: 410-531-3631

Subject: Pre-NDA Meeting Minutes

Date: January 5, 2004

Pages including this sheet: 6

From: Dianne Paraoan Phone: 301-594-5308
Fax: 301-594-5494
E-mail address: paraoand@cder.fda.gov

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes). Please let me know you received this.

Thank you.

Meeting Date: December 9, 2003

Type of Meeting: Pre-NDA Meeting 21-703

P-NDA Application:

Sponsor: Gambro Renal Products

Classification: B

Meeting Request Date: October 15, 2003

Confirmation Date: October 17, 2003 (faxed confirmation sent)

Briefing Package Received: November 10, 2003

Meeting Chair: Douglas C. Throckmorton, M.D.

Meeting Recorder: Dianne C. Paraoan

Attendees:

Division of Cardio-Renal Drug Products
Douglas C. Throckmorton, M.D. Director, Division Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D. Deputy Director, HFD-110
Thomas Marciniak, M.D. Team Leader, Medical Officer, HFD-110
Albert DeFelice, Ph.D. Team Leader, Pharmacologist, HFD-110
Kasturi Srinivasachar, Ph.D. Team Leader, Chemistry, HFD-810
Carolyn Neuland, Ph.D. Chief, CDRH, Gastroenterology and Renal Devices Branch, HFZ-470
Jeffrey Cooper, D.V.M. Veterinary Medical Officer, CDRH, Gastroenterology and Renal Devices Branch,
Daryl Allis, M.S., F.N.P. Regulatory Health Project Manager, HFD-110
Dianne C. Paraoan. Regulatory Health Project Manager, HFD-110

Gambro Renal Products
Susie Lew, M.D. Clinical/Medical Consultant, GW University
Jeffery Shideman, Ph.D. Director of Therapy Groups Americas, Gambro
Marie-Armelle Mouret, Pharmacist. Regulatory Affairs Group Manager, Gambro
Melanie Voisin, Pharmacist, Regulatory Affairs Deputy Manager, Gambro
David Zuchero, M.S., J.D. Gambro Regulatory Affairs Consultant

BACKGROUND

Gambro Renal Products requested a Pre-NDA meeting to discuss the submission for PrismaSol, a replacement [redacted] solution for use in Continuous Renal Replacement Therapy. When used as a dialysis solution, this product has already been approved as a medical device under a different brand name (PrismaSate). Gambro Renal Products seeks approval of these products as replacement solutions and intends to seek common labeling for both the replacement solution [redacted] so that one product can be used [redacted] as an intravenous replacement solution with the same or similar labeling.

DISCUSSION POINTS

General Discussion

Dr. Throckmorton provided the sponsor with three general recommended guidelines to consider in their NDA submission for PrismaSol Replacement Solutions as an infusate.

1. Claim Structure

The sponsor assured the Division that the product is intended only for the current claim as an infusate in hemofiltration, and that they were not seeking any additional claims. Dr. Throckmorton said that if the sponsor intended to seek additional claims beyond as an infusate, they would need to provide data to support that claim.

2. Chemistry, Manufacturing, and Control (CMC)

The CMC requirements of a dialysate and an infusate differ. Dr. Throckmorton stated to the sponsor that all CMC data would need to meet the CDER standard, and would need to be complete at the time of submission. The sponsor stated that they were aware of and followed the good manufacturing practices and guidances regarding new drug development. The sponsor should provide sufficient evidence that they know enough about modality and can support their indication with sufficient clinical data.

3. General Safety

As a part of the submission, the sponsor must provide data, perhaps in the form of articles, to support their position that the product given as an infusate is just as safe or safer than when used as a dialysate.

Proposed PrismaSol Formulations

Dr. Throckmorton recognized that the sponsor is seeking approval for nine proposed PrismaSol formulations. The ranges of proposed solutes for seven of the nine products are covered by a previous approval of a dialysate by the Center for Devices and Radiological Health (CDRH). Dr. Throckmorton stated that he has proposed that these products be considered dosing changes, rather than substantial differences in composition, such that each one of them will not be seen as new drugs. As soon as the Division knows if this is an acceptable policy by the upper management in CDER they will let the sponsor know as well.

Dr. Throckmorton added that because only seven of the nine products have a basis for predicate approval by CDRH, it may be more difficult for the sponsor to provide sufficient clinical data for the remaining two (Products #7 and 9). [redacted]

Pre-Clinical

Dr. Throckmorton informed the sponsor that based on the information provided, no pre-clinical studies are required. However, the sponsor should submit sufficient references to support their claim in order to support their contention that the infusate has no new safety concerns not seen with the dialysate (as discussed above for the General Safety). The sponsor inquired whether or not the references submitted had to be bicarbonate based versus lactate based solutions. Dr. Throckmorton recognized that lactate based solutions are more common, but encouraged the sponsor to focus on bicarbonate based solutions as their references since their solution is bicarbonate based.

CMC

Dr. Throckmorton suggested that the sponsor arrange a separate meeting to discuss CMC issues. The sponsor will contact Ms. Dianne Paraoan when they are prepared for the CMC meeting.

Labeling

Regulatory Discussion

The sponsor informed the Division that they will be prepared to submit an NDA application by the middle of 2004.

CONCLUSIONS/ RECOMMENDATIONS

The Division recommended the sponsor consider the discussions and suggestions described above in preparing their NDA application. We encouraged them to contact the Division if they need additional assistance.

The sponsor should contact Ms. Dianne Paraoan to arrange a CMC meeting prior to their NDA submission.

Signature recorder: _____
Dianne C. Paraoan

Concurrence, Chair: {See appended electronic signature page}
Douglas C. Throckmorton, M.D.

Draft: 12/22/03

Final: 1/5/04

RD:

Throckmorton: 1/5/2004 Stockbridge:
1/5/2004 Marciniak: 1/5/04 DeFelice:1/2/04
Srinivasachar:1-2-04
Allis: 12/24/03

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/s/

Dianne Paraoan
1/6/04 11:21:02 AM

Doug Throckmorton
1/7/04 08:23:51 AM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shen Xiao
7/11/2006 12:13:07 PM
MEDICAL OFFICER

Norman Stockbridge
7/12/2006 07:18:37 AM
MEDICAL OFFICER