27 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1/2

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

/s/

Sherita McLamore
10/13/2006 08:54:34 AM
CHEMIST

Ramesh Sood
10/13/2006 10:15:34 AM
CHEMIST

NDA 21-703

PrismaSol™ Solutions

Gambro Renal Products

HFD 110

Sherita D. McLamore, Ph.D.
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-703

2. REVIEW #1:

3. REVIEW DATE: June 20, 2006

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
n/a	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	September 27, 2005
Amendment	April 28, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Gambro Lundia AB
Address:	P.O. Box 10 101 Se-220 10 Lund, Sweden
Representative:	FEI Law 1845 Mason Avenue Daytona Beach, FL 32117
Telephone:	386-274-02811900

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: PrismaSol
b) Non-Proprietary Name (USAN): n/a
c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Continuous Renal Replacement Therapy

11. DOSAGE FORM: Sterile Solution

12. STRENGTH/POTENCY:

(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^{2+}	3.5	0	3.5		2.5	0		2.5	0
Magnesium	Mg^{2+}	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

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

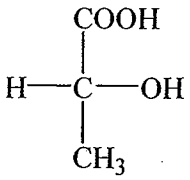
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

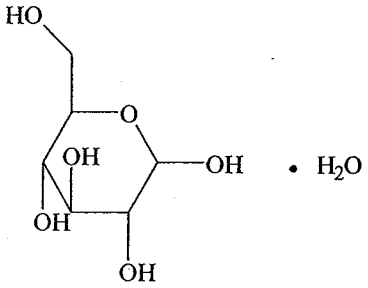
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: Calcium Chloride Dihydrate, Sodium Chloride, Magnesium Chloride Hexahydrate, Sodium Bicarbonate, Potassium Chloride, Lactic Acid and Dextrose Monohydrate

Molecular Weights: 147.015, 58.4425, 203.30, 84.0066, 74.551, 90.0779 and198.1712
Molecular Formula: $CaCl_2 \cdot 2H_2O$, NaCl, $MgCl_2 \cdot 6H_2O$, $NaHCO_3$, KCl



Lactic Acid



Dextrose

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III			1	Adequate	6/20/06	none

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	Sherita McLamore, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Acceptable	Acceptable	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Categorical Exclusion 21 CFR 25 31(b) *Acceptable*	5/1/06	Sherita McLamore, Ph.D.
Microbiology	Approval	May 15, 2006	John W. Metcalfe, Ph.D.

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 21-703

The Executive Summary

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-703 is approvable. The approval from a CMC standpoint is contingent on an acceptable recommendation from the Office of Compliance and an adequate response to the CMC deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

Calcium Chloride Dihydrate, Sodium Chloride, Magnesium Chloride Hexahydrate, Sodium Bicarbonate, Potassium Chloride, Lactic Acid and Dextrose Monohydrate were identified as drug substances. All drug substances are compendial grade. The applicant includes pertinent information for each of the drug substances including the manufactures, acceptance criteria, certificates of analyses and methods of manufacture.

The drug product, PrismaSol™ Solution, is clear sterile, bicarbonate infusate solution. The drug product will be used as replacement solutions in hemofiltration (HF) and hemodiafiltration (HDF) procedures during continuous renal replacement therapy (CRRT). Upon reconstitution, the drug product is 5, 000mL. It is available in nine different formulations and is provided in a pre-packaged, five liter, two compartment polyvinylchloride bag. The smaller compartment has a 250 mL capacity and contains the electrolyte solution. The larger compartment contains the buffer solution and has a capacity of 4,750 mL. Reconstitution is achieved by breaking a frangible pin which is contained between the two compartments. Each of the nine solutions contain 32 mEq/L of bicarbonate, 3.0 mEq/L of lactate and 140 mEq/L of sodium, however, amounts of calcium, magnesium, potassium, chloride and dextrose vary for each of the nine formulations. The exact formulations for each of the nine solutions are contained in the table below. The nine PrismaSol™ formulations are currently used in PrismaSate solutions. PrismaSate solutions are dialysis solutions manufactured by Gambro and regulated by the agency as medical devices.

	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)	[redacted]							
# 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)	[redacted]							
# 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

The applicant indicates that drug product will be manufactured and packaged by Gambro Renal Products of Daytona Beach, FL. Stability testing will be completed by Gambro BCT of Lakewood, CO. All of the concentrations of the drug product will be packaged in 5 L clear, two compartment PVC bags which contain a frangible pin, three tubes, a stopper, an injection port and a luer connector. The bags will be overwrapped with a film made of [redacted] The applicant includes a complete description of each of the packaging component including manufacturers, certificates of analyses, drawings, diagrams and specifications for each of the packaging components.

The applicant has requested a 12 month shelf life for the drug product and a 24 hour expiry for the diluted solution. This stability protocol utilizes a bracketed and matrixing approach. PrismaSol solutions 4 and 9 were utilized in the stability studies. As indicated in the stability section of this review, the applicant included 3 months of long term and accelerated stability for three full scale batches of the two aforementioned strengths of the drug product. In addition to the primary stability data, the applicant includes 12 months of supportive stability data for the drug product. The supportive data came from three industrial scale batch of the European product, Prismasol 4. Prismasol 4 differs from the PrismaSol 4/3.5 solution in the amount of Dextrose present (100 mg/dL for PrismaSol and 110 mg/dL for Prismasol 4). Prismasol 4 is packaged in the same two compartment PVC bag as the drug product and manufactured via a similar method. The applicant also provided data at time 0 for the reconstituted drug product. The reconstituted solutions were tested at 0, 18 and 24 hours. Under room temperature and under accelerated conditions.

All data (primary, reconstituted and supportive stability data) were acceptable and within the prescribed acceptance criteria., however, a decision on the expiry will be made once the stability update has been received and evaluated.

B. Description of How the Drug Product is Intended to be Used

PrismaSol™ is being developed for use as replacement solutions in hemofiltration (HF) and hemodiafiltration (HDF) procedures during continuous renal replacement therapy (CRRT). PrismaSol™ is identical in composition to PrismaSate. PrismaSate is a FDA approved sodium bicarbonate infusate solution. The applicant includes reconstitution instruction in the package insert.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-703 is Approvable from a Chemistry standpoint due to chemistry, manufacturing and controls concerns related to the drug substance and the drug product as outlined in this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
RSood

C. CC Block

Orig. NDA 21-703

Appears This Way
On Original

69 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2/2

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

/s/

Sherita McLamore
7/10/2006 03:23:49 PM
CHEMIST

Ramesh Sood
7/10/2006 04:32:50 PM
CHEMIST