CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20849

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

McCart
JUN 17 1998

Clinical Pharmacology and Biopharmaceutics Review

NDA:	**20-849**
SUBMISSION DATE:	**August 25, 1997**
BRAND NAME:	**20% ProSol™ sulfite -free (Amino Acid) Injection in PL 146® Plastic Container**
REVIEWER:	**Carolyn D. Jones, Ph.D.**
SPONSOR:	**Baxter Healthcare Corporation Round Lake, IL**
Type of Submission:	**Original New Drug Application**

APPEARS THIS WAY ON ORIGINAL

SYNOPSIS:

APPEARS THIS WAY ON ORIGINAL

20% ProSol™-sulfite free (Amino Acid) Injection in PL 146® Plastic Container is a sterile, nonpyrogenic, hypertonic solution of essential and nonessential amino acids in Pharmacy Bulk Package. The product will come in 500, 1000 and 2000 mL containers that will be packaged in The formulation contains only approved drug substances already contained in other Baxter amino acid products. 20% ProSol™ -sulfite-free (Amino Acid) Injection is indicated as an adjunct in the treatment of negative nitrogen balance in patients where: 1) the alimentary tract cannot or should not be used, 2) gastrointestinal absorption of protein is impaired, or 3) metabolic requirements for protein are substantially increased, as with extensive burns. As a result of the drug's higher concentration, this product can supply an amino acid dose equivalent to lower concentration products but in a smaller volume, thereby reducing fluid intake. The drug is very important in the treatment of fluid restricted patients.

APPEARS THIS WAY ON ORIGINAL

No new controlled or uncontrolled clinical studies were conducted to demonstrate safety or efficacy. The sponsor is requesting that the NDA be considered under section 505(b)(2) of the Food, Drug and Cosmetic Act. 20% ProSol™ - sulfite free (Amino Acid) Injection is qualitatively similar to several other marketed parenteral amino acid solutions.

APPEARS THIS WAY ON ORIGINAL

(b)(4) [redacted]

(b)(4) [redacted] In regards to individual amino acid concentrations, the two solutions were comparable for twelve of the amino acids and different for five---glycine, histidine, methionine, serine and threonine.

BACKGROUND:

(b)(4)

[redacted]

At the time of submission the product was named Travasol®. Based on Agency feedback, the brand name was changed to ProSol™ to differentiate between the new product and existing Baxter amino acid products.

APPEARS THIS WAY
ON ORIGINAL

The sponsor has submitted this current application under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, relying on clinical investigations which were not conducted by Baxter and for which Baxter has not obtained the right of reference to demonstrate the safety and efficacy of the proposed drug product. Aggregate data from published studies were submitted to support the safety and efficacy of the product.

The Division of Metabolic and Endocrine Drug Products is taking the position that this application should be submitted as a 505(b)(1) application. The division's rationale is that 1) the sponsor owns the referenced approved product and 2) the literature reports that were submitted as part of the NDA do not provide the basis for approval.

DRUG FORMULATION:

APPEARS THIS WAY

Baxter's amino acid injections in concentrations up to 15% have been available world-wide . The 5.5, 8.5 and 10% Travasol products were available in 1976 in glass and 1993 in plastic. 20% Travasol®[2] was approved in Canada in 1996 (see Appendix for approved Baxter products).

In Table 1, the sponsor has included several commercially available parenteral amino acid solutions that 20% ProSol was compared to.

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ON ORIGINAL

Table 1. Comparison of 20% ProSol™ to Qualitatively Similar Commerical Parenteral Amino Acid Solutions (Normalized to a 20% Amino Acid Concentration)

Manufacturer	20% ProSol™ Baxter	10% Travasol Baxter	15% Novamine (in glass) Pharmacia	10% Aminosyn II Abbott	10% Aminosyn-PF Abbott	10% TrophAmine McGaw
Protein concentration	20%	10%	15%	10%	10%	10%
Nitrogen g/100 mL	3.21	1.65	3.16	3.06	3.04	3.10
Essential Amino Acids (mg/100 mL)						
Histidine	1180	480	1192	600	624	960
Isoleucine	1080	600	999	1320	1520	1640
Leucine	1080	730	1387	2000	2400	2800
Lysine	1350	580	1573	2100	1354	1640
Methionine	760	400	999	344	360	680
Phenylalanine	1000	560	1387	596	854	960
Threonine	980	420	999	800	1024	840
Tryptophan	320	180	333	400	360	400
Valine	1440	580	1280	1000	1346	1560
Nonessential Amino Acids (mg/100 mL)						
Alanine	2760	2070	2893	1986	1396	1080
Arginine	1960	1150	1960	2160	2454	2400
Proline	1340	680	1192	1444	1624	1360
Serine	1020	500	789	1060	990	760
Taurine	-	-	-	-	140	50
Tyrosine	50	40	52	-	88	88
N-Acetyl-L-Tyrosine	-	-	-	540	-	480
Glycine	2060	1030	1387	1000	770	720
Cysteine	-	-	-	-	-	<32
Glutamic Acid	1020	-	999	1476	1640	1000
Aspartic Acid	600	-	577	1400	1054	640
mOsmol/L	1835	1000	1851	1740	1658	1750
pH	6.0	6	5.6	5.8	5.4	5-6
Potassium metabisulfite	-	-	-	-	Present	Present
Sodium hydrosulfite	-	-	-	Present	-	-
Sodium metabisulfite	-	-	Present	-	-	-

Baxter's processes for manufacturing amino acid solutions in plastic containers make it possible to manufacture a stable product, free of bisulfite. The Novamine solution is qualitatively identical with this one exception. The Aminosyn II solutions differ from 20% ProSol in that they contain N-acetyl-L-tyrosine. The Aminosyn-PF solution differs from 20% ProSol in that it contains taurine. The TrophAmine product differs from 20% ProSol in that it contains N-acetyl-L-tyrosine, taurine and trace amounts of cysteine.

Table 2 below highlights the 20% ProSol that was used in the pharmacokinetic study.

Table 2. 20% ProSol Formulation Used in Human Pharmacokinetic Study.

*** The 20% ProSol™ Amino Acid Formulation used in this study was as follows: Each 100 mL of the finished dosage form contained:**

Valine, USP	1.44 g
Lysine (added as lysine acetate), USP	1.35 g
Histidine, USP	1.18 g
Isoleucine, USP	1.08 g
Leucine, USP	1.08 g
Phenylalanine, USP	1.00 g
Threonine, USP	980 mg
Methionine, USP	760 mg
Tryptophan, USP	320 mg
Alanine, USP	2.76 g
Glycine, USP	2.06 g
Arginine, USP	1.96 g
Proline, USP	1.34 g
Glutamic Acid	1.02 g
Serine, USP	1.02 g
Aspartic Acid	600 mg
Tyrosine, USP	50 mg
Glacial Acetic Acid, USP	for pH adjustment

APPEARS THIS WAY ON ORIGINAL

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

I. Bioavailability

The study was begun in May 1995 and completed in July 1995. The primary study objective was to compare plasma amino acid concentrations in normal human fasted volunteers at baseline and at steady-state after receiving a peripheral amino acid/dextrose

infusion. The 20% ProSol product was compared to Novamine 15%. The to-be-marketed formulation was used in this study.

Sixteen normal healthy volunteers at a single site participated in a blinded, crossover study. The study consisted of 8 males and 8 females between the age incl[illegible] Eighty-seven percent of the subjects were Caucasian with the remainder including one Black and one Hispanic. The study was conducted over two days. On the first infusion day, half of the subjects received a peripherally infused dose of amino acids equal to 0.054 g of amino acids/kg of body weight/hour of either the test or reference drug. The total dose over the 4.5 hour infusion period was 0.24 g/kg of body weight. On the second day they were crossovered with whichever drug they did not obtain on Day 1. Plasma amino acid concentrations were measured at baseline prior to infusion and at steady-state at two hours and at four hours after initiation of infusion.

RESULTS:

Table 3. Change in Total Amino Acid Concentration and Total Essential Amino Acid Concentration from Baseline to Equilibrium Value

	20% ProSol™		15% Novamine®		
	LS Mean (µmol/L)	SEM (µmol/L)	LS Mean (µmol/L)	SEM (µmol/L)	Comparable at 95% Confidence Level?[a]
Total Amino Acid Concentration	901.1	72.6	560.9	72.6	Yes
Total Essential Amino Acid Concentration	385.0	29.6	316.6	29.6	Yes

LS Mean = Least Squares Mean; SEM = Standard Error of Mean

a Comparability is at both 90% and 95% confidence levels, unless otherwise noted.

This study showed that the two amino acid solutions were comparable in their change from baseline for total amino acid concentration and total essential amino acid concentration (Table 3). In regards to the individual amino acid concentrations, the two solutions had comparable effects for twelve (12) of the amino acids (Table 4). They were not comparable for glycine, histidine, methionine, serine and threonine.

Table 4. Change in Individual Amino Acid Concentration from Baseline to Equilibrium Value

	20% ProSol™		15% Novamine®		
Amino Acid	LS Mean (µmol/L)	SEM (µmol/L)	LS Mean (µmol/L)	SEM (µmol/L)	Comparable at 90% and 95% Confidence Level?
Alanine	144.8	18.3	87.1	18.3	Yes
Arginine	60.8	4.7	58.9	4.7	Yes
Aspartic Acid	2.6	0.5	2.8	0.5	Yes
Glutamic Acid	13.2	3.2	13.0	3.2	Yes
Glutamine	40.1	18.1	-19.0	18.1	Yes
Glycine	166.4	11.2	66.2	11.2	No
Histidine	42.7	5.6	33.1	5.6	No
Isoleucine	41.4	2.6	26.5	2.6	Yes
Leucine	14.9	3.4	24.6	3.4	Yes
Lysine	62.0	9.7	59.0	9.7	Yes
Methionine	32.4	1.6	36.5	1.6	No
Phenylalanine	27.2	1.8	36.8	1.8	Yes
Proline	60.0	9.6	22.9	9.6	Yes
Serine	39.2	4.2	24.1	4.2	No[a]
Threonine	58.0	5.1	32.7	5.1	No[a]
Tyrosine	-10.9	1.7	-11.7	1.7	Yes
Valine	106.3	6.6	67.4	6.6	Yes

LS Mean = Least Squares Mean; SEM = Standard Error of Mean

a Serine and Threonine levels are comparable at a 90% confidence level but not at a 95% confidence level.

Urea nitrogen excretion results during the 24 hour period including the infusion period were almost identical between the two solutions. The two solutions had similar effects on the plasma concentration of albumin, prealbumin and transferrin, however, post -levels of pre-albumin and transferrin were higher for 20% ProSol (i.e. took longer to return to baseline levels).

Table 5. Urinary Urea Nitrogen (Urinary urea nitrogen g/kg body weight/24 hours). From Repeated Measurers Analysis

Treatment	Sequence*	N	Mean	SEM	LS Mean	SEM
All	All	16	65.720	2.690	---	---
	AB	16	66.858	2.592	66.858	3.915
	BA	16	64.852	3.677	64.582	3.915
20% ProSol™	All	16	65.930	2.711	65.930	3.200
	AB	8	69.959	3.661	69.959	4.526
	BA	8	61.901	3.668	61.901	4.526
15% Novamine®	All	16	65.510	3.613	65.510	3.200
	AB	8	63.757	3.557	63.757	4.526
	BA	8	67.262	6.514	67.262	4.526

LS Mean = Least Squares Mean; SEM = Standard Error of Mean

* A= 20% ProSol™; B= 15% Novamine®

	p-value
Treatment	0.8978
Sequence	0.6872
Period	0.0934

Table 6. Plasma Protein Concentrations (Albumin, Pre-albumin and Transferrin)

	ProSol™/Novamine®			Novamine®/ProSol™		
	N	Mean	SEM	N	Mean	SEM
Albumin (g/dL)						
Screen	8	4.60	0.152	8	4.65	0.124
Check-in	8	4.85	0.145	8	4.71	0.064
Pre-Infusion 1	8	4.08	0.121	8	4.23	0.136
Pre-Infusion 2	8	4.15	0.154	8	4.08	0.092
Post	8	4.89	0.152	8	4.75	0.089
Pre-Albumin (mg/L)						
Pre-Infusion 1	8	269.88	11.737	8	273.88	17.293
Pre-Infusion 2	8	272.13	12.765	8	261.00	16.720
Post	8	301.88	11.710	8	271.75	15.300
Transferrin (mg/dL)						
Pre-Infusion 1	8	306.25	12.368	8	301.13	18.877
Pre-Infusion 2	8	316.13	13.890	8	300.38	16.645
Post	8	329.00	8.131	8	305.00	16.901

The adverse events reported were minor and related to soreness at the injection site. No difference was observed based on which formulation was being administered. No differences in hematology, serum chemistry or urinalysis were observed.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the current NDA submission. The sponsor has demonstrated that the 20% ProSol solution is similar in its performance to 15% Novamine, a marketed product for the indication of malnourishment. Although not identical in its formulation, 20% ProSol is capable of supporting protein and amino acid metabolism in parenteral nutrition therapy.

/S/

APPEARS THIS WAY
ON ORIGINAL

6/15/98
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 6/16/98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 6/17/98

cc: NDA 20-849 (1 copy), HFD-510 (Colman, McCort), HFD-340 (Viswanathan), HFD-870 (Ahn, Jones, M. Chen), CDR (Murphy).

CODE: AE

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ON ORIGINAL

13 PAGES REDACTED

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OCT 10 1997
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

SUBMISSION DATE: March 13, 1995

BRAND NAME: 20% Travasol®

GENERIC NAME: Amino Acid Injection in PL 146® Plastic Container

REVIEWER: Carolyn D. Jones, Ph.D.

SPONSOR: Baxter Healthcare Corporation
Round Lake, IL

APPEARS THIS WAY
ON ORIGINAL

TYPE OF SUBMISSION: IND Submission

SYNOPSIS:

APPEARS THIS WAY
ON ORIGINAL

Baxter Healthcare Corporation submitted an Investigational New Drug (IND) application for the product 20% Travasol (Amino Acid) Injection in PL 146® Plastic Container on March 21, 1995. Although this submission was logged into the Agency on March 21, 1995, it was not received by the Division of Metabolic and Endocrine Drug Products until September 25, 1997. NDA 20-849, the corresponding NDA was submitted to the Agency on August 25, 1997. The name of the product has been changed to 20% ProSol™-sulfite free (Amino Acid) Injection in PL 146® Plastic Container.

RECOMMENDATION:

The information submitted on March 13, 1995 by Baxter Healthcare Corporation to will be reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of Pharmaceutical Evaluation II (DPEII) as part of NDA 20-849. No further review of this submission is necessary

APPEARS THIS WAY
ON ORIGINAL

/S/

10/1/97
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Hae Young Ahn, Ph.D., Team leader /S/

FT initialed by Hae Young Ahn, Ph.D., Team Leade /S/ 10/10/97

cc: HFD-510 (Colman, Snyder, McCort), HFD-870 (Ahn, Jones, M. Chen), CDR (Murphy).

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McCort

OCT 20 1997

NDA 20-849 **Review Completed: October 20, 1997**

Sponsor: Baxter Healthcare Corp.; Round Lake, IL 60073

Date Submitted: August 25, 1997 **Date Received:** August 28, 1997

PHARMACOLOGY REVIEW OF INITIAL NDA SUBMISSION
(Original NDA submission August 28, 1997)

DRUG: 20% ProSol™-Sulfite-free (Amino Acid) Injection in PL 146® Plastic Container.

STRUCTURAL FORMULA: 20% ProSol™-Sulfite-free (Amino Acid) Injection in PL 146® Plastic Container is a mixture of amino acids similar to Novamine®15%, a previously approved product.

CATEGORY: Large volume parenteral used as a source of amino acids for protein synthesis

INDICATION: (Currently) "As an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance in patients where: (1) the alimentary tract cannot or should not be used, (2) gastrointestinal absorption of protein is impaired, or (3) metabolic requirements for protein are substantially increased as with extensive burns."

RELATED NDA: Novamine® 15%- sulfite-free (Amino Acid) in PL 146® Plastic Container.

COMMENTS FROM PHARMACOLOGIST
LABELING REVIEW

APPEARS THIS WAY
ON ORIGINAL

There were no pharmacology data submitted with this NDA. Given the comparisons of relative amino acid contents between the approved product and ProSol, there appear to be no differences in amino acid composition which would result in different toxicity profiles between the products. Thus, no further pharmacology data are required. Pharmacology recommends the approval of NDA 20-849 for 20% ProSol™-Sulfite-free (Amino Acid) Injection in PL 146® Plastic Container.

LABELING COMMENTS:

Since no specific studies on Carcinogenesis, Mutagenesis, Fertility or Pregnancy were performed, labeling is fairly standard in specifying that these studies were not performed. Labeling for these sections is acceptable as it is presently stated. There is no further action required from a pharmacology standpoint.

RECOMMENDATION: No pharmacology data were submitted, nor are any further data required. Labeling is appropriate. Pharmacology recommends approval of NDA 20-849. No further action is required from pharmacology at this time.

APPEARS THIS WAY
ON ORIGINAL

/S/

Ronald W. Steigerwalt, Ph.D.
10/20/97

cc: NDA Arch
HFD510
HFD510/Steigerwalt/McCort