CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20849

MEDICAL REVIEW(S)

MEDICAL REVIEW

of

NDA 20-849

Drug: Prosol 20% Amino Acid Solution

Indication: Parenteral Nutrition

Sponsor: Baxter

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ON ORIGINAL

Date of Submission: 8/25/97

Date of Review: 4/7/98

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/S/ 4/10/98

Eric Colman, MD

cc: NDA Arch
McCort/Lewis/Troendle

Background

The sponsor of this 505 (b)(2) NDA proposes to market a new 20% amino acid solution - ProSol - as part of a pharmacy bulk package. This product, if approved, would be the most concentrated amino acid solution on the market. ProSol consists of essential and nonessential amino acids as shown below.

Essential AA	**Nonessential AA**
histidine	alanine
isoleucine	arginine
leucine	proline
lysine	serine
methionine	tyrosine
phenylalanine	glycine
threonine	glutamic acid
tryptophan	aspartic acid
valine	

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The amino acid (AA) composition of ProSol is qualitatively the same as other marketed AA solutions (i.e., Novamine 15%), but is quantitatively different from all other products. For example, if ProSol were diluted to a 15% AA solution and compared with Novamine 15% the actual amounts of AA would be as follows:

Essential AA	**Novamine**	**ProSol**	**Nonessential AA**	**Novamine**	**ProSol**
	mg/100ml			**mg/100ml**	
histidine	894	1180	alanine	2170	2760
isoleucine	749	1080	arginine	1470	1960
leucine	1040	1080	proline	894	1340
lysine	1180	1350	serine	592	1020
methionine	749	760	tyrosine	39	50
phenylalanine	1040	980	glycine	1040	2060
threonine	749	980	glutamic acid	749	1020
tryptophan	250	320	aspartic acid	433	600
valine	960	1440			

According to the sponsor, the quantitative changes were made for chemistry (stability) not clinical reasons. It can be seen from the above comparison that for all but one amino acid (pheylalanine), ProSol supplies more of the essential and non-essential amino acids than Novamine 15%.

The proposed labeling states that ProSol is indicated as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance. This is a standard indication for amino acid solutions used as part of a total parenteral nutrition (TPN) admixture. Because of the higher concentration of ProSol the sponsor has added the following indication: "ProSol injection offers

a clinical advantage to fluid restricted patients who require TPN." This represents the first amino acid solution to be marketed with an indication for use in patients requiring fluid restriction.

Data submitted in support of approval of ProSol and deemed appropriate by this Reviewer include two studies from the published literature that compare Novamine 15% to 10% amino acid solutions in patients requiring fluid restriction.

The sponsor, at the request of the previous review Division, has also conducted a "bioequivalency study" comparing ProSol with Novamine 15%. This study will provide critical data on the efficacy, and to a lesser extent, the safety of ProSol 20%.

Literature on Fluid Restriction

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Study #1

Fluid Balance in Fluid-Restricted Patients Receiving 10% Amino Acids or 15% Amino Acids as Part of Parenteral Nutrition

Hospital Pharmacy, 24, Dec. 1989 - this study was funded by Clintec

Objectives: To compare delivery of parenteral nutrition (PN) solutions and fluid balance in fluid-restricted ICU patients.

Design: This was a 7 to 14-day study of 23 ICU patients. Patients were randomly assigned to receive one of two PN solutions: 500 ml of 70% dextrose and 500 ml of 10% amino acids (10PN) or 500 ml of 70% dextrose and 335 ml of 15% amino acids (15PN). The composition of the two solutions are shown below. Solutions were isonitrogenous and isocaloric as well.

Component	10PN	15PN
Amino acids (ml)	500	335
Dextrose 70% (ml)	500	500
Volume/unit (ml)	1000	635
Amino acid/unit (g)	50	50
Nitrogen/unit (g)	8	8
Nonprotein kcal/unit	1190	1190

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PN was initiated at 25-50 ml/hour and advanced as tolerated to a protein goal of 1.0 gram/kg/da and an energy goal of 30 kcal/kg/day. PN intake was then adjusted based on the patient's volume status and urine urea nitrogen excretion. Standard electrolytes and vitamins and minerals were added to the PN solutions. Fat emulsions were provided either two times per week or continuously as a calorie source, depending on the clinical condition of the patient.

Fluid balances during each 24-hour period of PN administration were calculated by the differences between fluid intake and output. Fluid input included PN solutions, other intravenous solutions, and blood products. Fluid output included all urine excretion and fluids lost from

nasogastric suction, ostomies, or drains. Stool output was not calculated in the output, unless the patient had a rectal tube placed for severe diarrhea.

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Patient Population: All ICU patients receiving PN during a 9 month period in two teaching hospitals were considered for this study. Patients were judged to be in need of fluid restriction if: 1) they had a condition in which fluid restriction is an accepted treatment (i.e., SIADH, ARDS, or CHF); 2) they had elevated central venous pressure or pulmonary capillary wedge pressure; or 3) they were receiving a volume of intravenous antibiotics, pressor agents, blood products, or other fluids which would make the administration of optimal PN improbable. Patients were excluded if they had acute oliguric renal failure or severe liver failure.

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Statistical Analyses:

Analysis of variance and Duncan's new multiple range test were used to determine statistical significance between the two groups.

Results

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Patient Demographics and Disposition

Twenty-three patients were entered into the study and 20 (10 in each group) completed at least 7 days of PN. Three subjects (2 in 15PN and 1 in 10PN) were excluded because they received less than 7 days of PN.

Patient demographics are shown in the following table.

Demographic Characteristic	10PN	15PN
# Patients	10	10
# Male/female	5/5	7/3
# Black/white	6/4	7/3
Age (years)	49	42
Weight (kg)	63	71
Length of PN (days)	11	10

Although no statistics are reported for the comparison of demographic characteristics between groups at baseline, the authors state that "they appear to be well matched." This unsubstantiated comment is not unreasonable. Any differences between groups are not likely to influence the primary outcomes of this study.

The major diagnoses for the patients were varied and included in the 10PN group: liver transplant (2), SIADH, SBR, ARDS, Crohn's, sepsis with RI, CRF (2), and polycystic kidney disease. The diagnoses in the 15PN were as follows: hepatitis, gangrenous gallbladder, CHF, pancreatitis, liver transplant, SBR, trauma with sepsis, nonoliguric RF, and CRF (2). The mean BUN values prior to PN were 35 and 33 mg/dl in the 10 and 15% groups, respectively; the mean

creatinine values were 2.3 and 2.7 mg/dl, respectively; and the mean albumin values were 2.5 and 2.4 mg/dl, respectively. No statistical comparisons are provided by the authors, however, the values do not appear to be significantly different, at least from a clinical standpoint.

The table below summarizes the fluid balance data for the two groups.

Fluid Parameter	10PN	15PN
Intake (ml/d)	2806	2764
Output (ml/d)	2116	2060
Balance (ml/d)	690	704
PN intake (ml/d)*	1246	1059
% of fluid as PN†	48	41
Energy intake (kcal/kg/d)	28	24
Protein intake (g/kg/d)	1.0	0.9

*p=0.002, †p=0.01

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Both PN intake in ml/day and the percent of fluid intake as PN were significantly lower in the 15PN compared with the 10PN group.

No significant safety data are reported. Of note, however, the mean plasma creatinine value in the 10PN group went from 2.3 mg/dl pre-TPN to 2.8 mg/dl post-treatment, while the mean value pre-TPN in the 15PN group decreased from 2.7 mg/dl to 2.3 mg/dl post-treatment.

Investigator's Conclusions

Although the use of a 15% amino acid solution in PN does decrease the amount of fluid from TPN infused, we were unable to demonstrate a significant difference in total fluid intake or fluid balance.

Medical Officer's Conclusions

As expected, the use of a 15% vs. 10% amino acid solution in PN in a population of patients who require fluid restriction resulted in less fluid supplied as PN. That the two groups did not differ in fluid balance is of interest, but hardly a surprise. As the author's point out, the inclusion of patients with CRF and renal insufficiency with varying degrees of urine output may have obscured differences between the two groups. Additionally, the patients with CRF (2 in each group) were on peritoneal dialysis, but no measure of fluid loss *via* this route was made. It is also possible that fluid losses in the feces were significantly different in the two groups, yet fecal fluid loss was not reported by the investigators.

While admittedly an ambitious proposition, the true value of a product in a population of patients requiring fluid restriction and TPN would be assessed by more meaningful clinical outcomes than simple fluid balance. For example, in a group of patients with CHF and

resulting renal insufficiency, assessment of cardiac output, renal function, and need for diuretics, inotropic, and afterload-reducing agent, etc. would be more meaningful endpoints.

In any event, for labeling purposes, this study supports the statement (which is simple intuition) that the use of a more concentrated amino acid solution (15% vs 10%) will help reduce fluid intake in patients requiring TPN and fluid restriction.

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Study #2

Pharmacist Intervention Improve Fluid Balance in Fluid-Restricted Patients Requiring Parenteral Nutrition

The Annals of Pharmacotherapy, 25 Feb. 1991 - this study was funded by the American Pharmacists' Research and Education Foundation.

Objectives: To determine if pharmacist interventions could reduce fluid intake and improve fluid balance in fluid-restricted ICU patients who require parenteral nutrition (PN).

Design and Endpoints: Twenty-four consecutive ICU patients at one institution were randomized to one of two PN treatments: Group 1 received a solution comprised of 10% amino acid, 70% dextrose, and 20% lipid emulsion (10PN); and Group 2 received a solution containing 15% amino acids, 70% dextrose, and a 20% lipid emulsion (15PN). Group 1 received medications as 50 and 100ml piggybacks while Group 2 received medications, when possible, as 25ml piggybacks. Both groups received standard electrolyte and vitamin and mineral supplements. The PN solutions were initiated at and advanced as tolerated to a protein goal of and an energy goal of The PN formulations were prepared to contain the same number of nonprotein calories and grams of protein in each unit. Patients were studied for a minimum of 7 days and a maximum of 14 days.

Fluid intake and output were recorded daily for the duration of the study period. Fluid intake = PN + other IV solutions + piggybacks + blood products + oral/enteral intake. Output = urine + nasograstric tube + abdominal drains + chest tubes + ostomies + and rectal tube (if placed). All diuretic therapy was recorded as was administration of albumin. Nitogren balance was measured on Day 2 of the study and repeated on Day 6. Balance was measured by nitrogen intake and output (calculated by adding 4g to the urea nitrogen excreted during a 24-hour urine collection). Other labs measured on study entry and exit included serum creatinine, BUN, and serum albumin.

Patient Population: Male and female adult ICU patients referred for parenteral nutrition were eligible for this study. Patients were judged to be in need of fluid restriction if: 1) they had a condition in which fluid restriction is an accepted treatment (i.e., SIADH, ARDS, or CHF); 2) they had elevated central venous pressure or pulmonary capillary wedge pressure (>12 mmHg); or 3) they were receiving a volume of intravenous antibiotics, pressor agents, blood products, or other fluids which would make the administration of optimal PN improbable. Patients were

excluded if they had acute or chronic renal failure, thermal injury, protein-losing enteropathy, or severe liver failure.

Statistical Analyses: Student's unpaired t-test for demographics and cumulative fluid balance data. Fluid intake, output, and cumulative balance (repeated measures) between groups were compared by ANOVA with Scheffe's test.

Results

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Patient Demographics and Disposition

Baseline demographic characteristics are provided in the table below.

Demographic Characteristic	10PN	15PN	p-value
N	10	10	
#Male/Female	5/5	8/2	
Age (yrs)	56	46	0.23
Weight (kg)	69	71	0.74
Hospital Days*	10	8	0.66
BUN (mmol/L)	9	9	0.75
Creatinine (umol/L)	124	115	0.68
Albumin (g/L)	24	25	0.74

* Days before PN started

No significant differences existed at baseline; although the number of males/females was not tested.

The medical diagnoses in the 10PN group included exploratory lap (2), pancreatitis, liver transplant (2), head injury, intraabdominal abscess, ovarian cancer, respiratory failure with ileus, sickle cell crisis with ileus and in the 15PN group included exploratory lap (2), pancreatitis (2), liver transplant, head injury with ileus, intraabdominal abscess, CABG with ileus, intraabdominal trauma, and respiratory failure with ileus. The groups appear to have been fairly well balanced in this regard, particularly considering the small sample sizes.

Of the 24 patients enrolled into the study, 20 received at least 7 days of PN and were included in the analysis. Four patients were excluded because they did not receive at least 7 days of PN. One patient from each group died during the study.

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Nutrition Support Data

Both groups receive a similar number of days of PN (9.7 vs 9.3 days: 10PN vs 15PN; p=0.6), as well as similar protein and energy intakes (data not shown). The nitrogen balance data were also similar for the two groups (Day 2, -6.4 vs. –5.6 g/d; 10PN vs. 15PN, p=0.8) and (Day 6, -1 vs -0.8 g/d; 10PN vs 15PN, p=1).

Concomitant Medications Affecting Fluid Balance

Six patients in each group received albumin during PN treatment: 225 g vs. 265 g; 10PN vs. 15PN) (no stats reported). The 10PN group received 1500ml of blood products and the 15PN group received 1380 ml of blood products (no stats reported). Although the 10PN group received a total of 1850 mg of lasix and the 15PN group only 770 mg, the authors state that this difference was not "significant". The amount of albumin and blood products received by the two groups do not appear to be significantly different between groups, at least not from a clinical perspective. And if anything, the larger amount of lasix received by the 10PN group would move the overall fluid balance in a negative direction.

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Fluid Balance Data

The fluid intake and overall balance were significantly lower in the 15PN group compared with the 10PN group (table below).

Parameter	10PN	15PN	p-value
Intake (ml/d)	3498	3112	<0.02
Output (ml/d)	2789	2966	ns
Balance (ml/d)	708	146	<0.02
Cummulative Balance (ml)	6867	1358	<0.05

No specific safety data were reported.

Investigator's Conclusions

It was intention of this study to demonstrate that simple, "common sense" pharmacist interventions could affect fluid balance in fluid-restricted patients. Patients receiving PN were targeted for this study because PN fluid can exceed 60% of total fluid intake. We conclude that both fluid input and balance can be significantly decreased with comprehensive pharmacist interventions in critically ill patients who require PN and fluid restriction.

Medical Officer's Conclusions

I agree with the investigator's conclusions. I would add, however, that the total intake of fluid for the two groups were not that different (although statistically so) and would surmise that the more concentrated amino acid solution contributed little to the large difference in fluid balance between the two groups. Nonetheless, the availability of a concentrated amino acid solution for TPN admixtures would be helpful to clinicians in their effort to reduce the fluid intake of patients on TPN. From the standpoint of nitrogen balance, the data indicate that both solutions offset a negative nitrogen balance by Day 6.

"Bioequivalency" Study

A Comparison of Plasma Amino Acid Concentrations in Normal Volunteers Following Infusion of 20% ProSol versus 15% Novamine.

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This was a single-center study conducted from May 1995 to July 1995.

Objectives: The primary objective was to compare the plasma AA concentrations in normal volunteers at baseline and at a steady state after receiving a peripheral AA/dextrose infusion of ProSol and 15% Novamine. A secondary objective was to compare 24-hour urinary nitrogen excretion and plasma concentrations of albumin, pre-albumin, and transferin 24-hours post infusion.

Design: This was a double-blind crossover study conducted in 16 subjects. On the first infusion day one half of the subjects were randomized to receive formulation A and the other half to formulation B. Formulation A was ProSol at a total AA dose of 0.243 gm/kg and formulation B was 15% Novamine at a total AA dose of 0.242 gm/kg. Formulation A contained 7.3 g/100ml of dextrose and B contained 6.7 g/100ml of dextrose. These two formulations were isonitrogenous and isocaloric. The infusion period was 4.5 hours. All subjects were served a portion-controlled lunch at least 6 hours after the initiation of the infusion. Dinner and a snack were also provided at between 5:00 and 6:00 and between 8:00 and 9:00 p.m., respectively. On the second infusion day (the day immediately following day of initial infusion) subjects crossed over to the solution that they did not receive on infusion day one.

Patient Population: Both male and female volunteers between the ages were eligible for study participation. Body weight had to be within 15% of ideal for height and frame. Exclusion criteria included: Use of prescription medications within 14 days of study, use of caffeine or alcohol within 72 hours of study, a history of significant medical disease, pregnancy, and positive antibody for HIV.

Endpoints: Thirty minutes prior to the drug infusion on Day 1 baseline plasma levels of AA, albumin, prealbumin, and transferrin were collected. The 24-hour urinary collection also began just prior to drug infusion in order to determine urinary urea nitrogen excretion. Blood samples were taken at 2 and 4 hours into the infusion for measurement of AA. On Day 2 just prior to initiation of the drug, the first 24-hour urine collection was completed and the second collection was begun. Other procedures were followed as done on Day 1. Twenty-four hours after initiation of the infusion of Day 2 the second urine collection was completed and blood was collected for determination of albumin, prealbumin, and transferrin.

Statistical Analyses: For the primary endpoint of plasma AA concentration following infusion of the two formulations, a two-way crossover ANOVA was used as the statistical analysis. Comparability between ProSol and Novamine was evaluated by determining whether confidence limits (90 and 95%) fell within an interval defined as one quarter of the reference range. Confidence intervals were derived using the error term from the repeated measured cross-over ANOVA.

Results

Patient Disposition and Demographics

Eight male and 8 female subjects were enrolled into and completed both phases of the study. All but two of the volunteers were Caucasian and the average age was 29 years.

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Post-Infusion Plasma Amino Acid Concentrations

The sponsor stated *a priori* that the sequence of drug infusion would not have an effect on baseline AA concentrations. When this was tested it was found not to be true. The baseline concentration for total amino acid was higher prior to the second infusion regardless of the solution ($p<0.001$) administered on Day 1. This finding suggests that the wash-out period of approximately 20 hours was not adequate. Because of this carryover effect a more appropriate analysis is one in which comparisons are made between the two products during period 1 only; in essence this becomes a parallel design study. With this approach one is also able to log transform the data and use the traditional bioequivalency analysis: drugs are considered bioequivalent if the 90% confidence interval is contained within 0.8 to 1.25. The table below provides this analysis.

Amino Acid	Pro/Nov	90% CI	Pass or Fail?	Amino Acid	Pro/Nov	90% CI	Pass or Fail?
Histidine	0.97	0.89, 1.07	P	Alanine	1.23	1.05, 1.45	F
Isoleucine	1.25	1.12, 1.40	F	Arginine	1.11	0.99, 1.25	P
Leucine	0.97	0.85, 1.11	P	Asparagin	1.27	0.99, 1.63	F
Lysine	0.98	0.86, 1.13	P	Aspartate	0.83	0.61, 1.13	F
Methionin	0.91	0.82, 1.02	P	Glutamate	1.05	0.73, 1.50	F
Phenylala	0.92	0.83, 1.02	P	Proline	1.08	0.93, 1.26	F
Threonine	1.07	0.91, 1.24	P	Serine	1.05	0.85, 1.29	F
Tryptopha	NA			Glutamine	1.08	0.98, 1.20	P
Valine	1.17	1.04, 1.30	F	Glycine	1.24	1.02, 1.51	F
Cystine	1.09	0.88, 1.35	F				
Tyrosine	1.00	0.84, 1.19	P	**Total Essential**	**1.04**	**0.94, 1.16**	**p**

Test value was the average of the 2 and 4 hour post-dosing concentrations
NA Tryptophan was not measured because of stated deficiencies with the analytic method

It can be seen from the above that in every case where an amino acid, other than aspartic acid, a non-essential amino acid, falls outside of the stated reference range (fails), the concentration of the ProSol amino acid is higher than the corresponding Novamine amino acid (ratio > 1.0). Thus from an efficacy standpoint these data support the notion that ProSol 20% would support nitrogen balance as well as Novamine 15%.

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Given the increased concentration of some of the ProSol amino acids compared with the Novamine amino acids it is reasonable to look at the frequency of subjects with amino acid levels that exceeded 1.5 times the upper limit of the fasting normal range. At the 2 and 4 hour post-dosing time points, methionine was the only amino acid in which levels were consistently above

the 1.5 threshold and was so for both ProSol and Novamine; the difference between the two products, however, was not statistically significant.

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Urinary Urea Nitrogen Excretion

The mean values of urinary urea nitrogen for subjects randomized to ProSol and Novamine were the same: 66 g/kg/24hr. It should be kept in mind that these data are not tantamount to nitrogen balance. Typically, nitrogen balance is studied after at least several days and takes into account fecal and insensible losses of nitrogen.

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Plasma Protein Concentrations

Plasma concentrations of albumin, pre-albumin, and transferrin were measured at baseline and 24 hours post-amino acid infusion. Because of a possible carry-over effect, plasma protein values will be compared after infusion period 1only. Pre-albumin was the only variable that was significantly different following the two treatments: the mean value increased by 2.25 mg/L following ProSol and decreased by 13 mg/L following Novamine (p=0.01). It is difficult to imagine that a single infusion of an amino acid solution would significantly affect the levels of pre-albumin, a compound with a half-life of 2-3 days, when measured over a 24-hour period. Nevertheless, the numbers for pre-albumin favor ProSol over Novamine.

Safety Results

There were no deaths or serious adverse events reported.

Four subjects receiving each infusion reported an adverse event. The adverse events included headache (1-ProSol), constipation (1-Novamine), nausea (2-Novamine) and soreness at IV site (3 each product).

There were no significant changes in the mean levels of serum chemistry or hematology or urinalysis following treatment with ProSol compared with post-Novamine treatment. Similarly, there were no worrisome trends in the number of outliers for serum chemistry or hematology or urinalysis parameters in either group.

There did not appear to be any significant adverse trends for vital sign changes in either of the two groups.

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Sponsor's Conclusions

Peripheral vein infusion of two amino acid solutions with different amino acid compositions or profiles but the same quantity of total amino acids has comparable effects on plasma amino acid concentrations, urinary urea nitrogen excretion, and plasma protein concentrations. Both amino acid solutions have the capability of supporting protein and amino acid metabolism in parenteral nutrition therapy. The solutions do not result in clinically significant adverse effects.

Medical Officer's Conclusions

I agree with the Sponsor's conclusions, but would emphasize the fact that an inadequate washout period and resulting carryover effect hampered the originally planned analysis for bioequivalency. Therefore, in a standard bioequivalency analysis conducted by Karen Higgins, an FDA statistician, in all but one case (aspartic acid, a non-essential amino acid), the levels of amino acids averaged at 2 and 4 hours post-dosing were higher for ProSol as compared with Novamine 15%. These data support the contention that ProSol 20% is bioequivalent to Novamine 15%. And while this was a short-term study and nitrogen balance was not measured, the urinary nitrogen excretion for the two products were the same; this suggests that – if dosed properly — the two drugs would have equal abilities to offset nitrogen loss.

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Labeling Review

1. **Description** - acceptable

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2. **Clinical Pharmacology** - acceptable

3. **Indications and Usage** - 1st paragraph - recommend deleting

There is no evidence that the use of ProSol, or any other concentrated amino acid solution, provides a clinical advantage to patients who require fluid restriction and TPN. I know of no data that indicate fluid restriction improves survival, decreases morbidity, or has any other favorable affect on a hard clinical endpoint. It seems more appropriate to say something along these lines:

2nd and 3rd paragraphs - recommend bolding the last sentence of each paragraph.

4. **Contraindications** - acceptable.

5. **Warnings** - acceptable.

6. **Precautions** - recommend bolding the last paragraph which mentions that the product should not be directly infused.

Pediatric Use subsection - not acceptable. The sponsor needs to make a statement about the safety and efficacy of the product in the pediatric population.

7. **Adverse Reactions** - acceptable.

8. **Overdose** - acceptable.

9. **Dosage and Administration** - acceptable.

10. **How Supplied** - acceptable.

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The above labeling comments were conveyed to the sponsor the week of August 3, 1998, and their response was as follows:

A. Under Indications and Usage

Reviewer's comment: the sponsor's proposal is acceptable.

B. Under Precautions, Pediatric Use: the sponsor proposes to include the wording from the Indications and Usage section, the Dosage and Administration section, as well as information about hyperammonemia and inborn errors of metabolism.

Reviewer's comments: the sponsor's proposals are not acceptable. ProSol 20% has not been studied in the pediatric population and its lack of taurine, a conditionally essential amino acid for infants, make it unsuitable for this population. Therefore, it is recommended that the Pediatric Use section read as follows: The safety and effectiveness of ProSol 20% in pediatric patients have not been established.

In a conversation with the sponsor on the morning of August 7, 1998, they agreed with this Reviewer's proposed wording for the Pediatric Use subsection.

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Conclusion

Based on data from published literature and a comparative bioequivalency study, this Reviewer recommends approval of ProSol 20% injection.

/S/
Eric Colman, MD

8/10/98

Good Review

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