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APPLICATION NUMBER for: 020182, S006

MEDICAL REVIEW(S)

Memorandum

December 14, 1999

12/14/99

To: the File NDA 20-182/S-006 Carnitor (levocarnitine injection)
From: Solomon Sobel M.D. Director, Division of Metabolic and
Endocrine Drug Products

Subject: Approval of Efficacy Supplement for use in End Stage
Renal Disease

The new indication will be for prevention and treatment of carnitine deficiency in patients with end stage renal disease who are undergoing dialysis.

Carnitor has been granted orphan drug status for this indication. Carnitine is derived from diet and endogenous synthesis. Excess free carnitine in the serum is eliminated after glomerular filtration in the urine.

Hemodialysis induces carnitine deficiency because carnitine is cleared during dialysis.

The supplement rests on clinical data derived from two twenty-four week placebo-controlled studies on patients treated with dialysis for end stage renal disease.

The response variable for efficacy is the increase/maintenance of serum carnitine levels. Improvement of clinical symptoms associated with carnitine normalization was not clearly demonstrated in these studies.

Thus, the approval rests on a biochemical endpoint which is a plausible surrogate.

Conclusion: the Division recommends approval of this efficacy supplement.


Solomon Sobel

cc:

NDA 20-182/S-006

HFD-510/Div. File

HFD-510/EHerman/DOrloff/DLewis/DWu/RShore/HAhn/MHess

HFD-715/JGebert/TSahlroot

NDA 20-182/S-006

Carnitor (Levocarnitine) injection

Sigma Tau (Gaithersburg, MD)

Date of submission: January 29, 1999

Date of review: October 12, 1999

SE-1: New indication for the treatment of carnitine deficiency in patients with end-stage renal disease (ESRD) on dialysis

Background

The history of the sNDA dates to NDA 19-823 for VitaCarn (20% Levocarnitine Injection), Kendall McGaw Labs, Inc., dated January 27, 1988. On February 1, 1989, the Division issued an NA letter citing deficiencies that amounted to a failure to provide adequate evidence of a clinical benefit associated with carnitine supplementation in patients with ESRD on dialysis. The current submission includes reanalyses of some of the clinical trial data submitted in 1988 as well as additional pharmacokinetic data in patients on dialysis. These latter data provide indirect evidence of the efficacy of levocarnitine in the secondary carnitine deficiency state that occurs in patients on chronic hemodialysis. By way of further background, approximately 80% of the use of IV carnitine is in hemodialysis patients. In addition, Carnitor has been granted orphan drug status for the indication for use in ESRD on dialysis. Finally, it is interesting to note that worldwide, levocarnitine is indicated not only for use in carnitine deficiency states, but also (partial listing) in acute and chronic coronary insufficiency, angina, congestive heart failure, for arrhythmias and T-wave inversion due to tricyclic administration, and porto-systemic encephalopathy.

Carnitine physiology and metabolism

Carnitine serves two major functions in cellular physiology. The first is the transport of long-chain fatty acids into the mitochondrial matrix to undergo beta-oxidation as a source of energy. This occurs mainly in liver, heart, and skeletal muscle. The second major role of carnitine is to modulate intracellular CoA homeostasis. In this pathway, acyl-CoA esters derived from beta-oxidation are transesterified to acylcarnitines. These then cross the mitochondrial membrane in exchange for free carnitine via a translocase, permitting regeneration of intramitochondrial free CoA for further beta-oxidation.

Carnitine is derived from diet and endogenous synthesis. Nutritional sources of carnitine are red meat, poultry, fish, and dairy products. Carnitine is also synthesized in the liver and kidney from lysine and methionine. Muscle cells cannot synthesize carnitine and are therefore dependent upon uptake of circulating carnitine. Plasma carnitine concentrations are regulated by the kinetics of carnitine reabsorption by the kidney. The proximal tubule reabsorbs ~90% of filtered carnitine at normal plasma concentration. The renal excretory threshold for carnitine is 40 micromoles/L, the approximate normal plasma concentration (~50 micromoles/L). Therefore, excess free carnitine in serum is filtered at the glomerulus and rapidly excreted in the urine.

Carnitine deficiency

Clinical manifestations of carnitine deficiency do not ensue until levels in the plasma and tissues fall to 10-20% of normal. Carnitine deficiency can be either primary or secondary. Primary deficiency is defined as a decrease in intracellular carnitine content that impairs fatty acid oxidation and that is not associated with another identifiable systemic illness that might deplete tissue carnitine stores. The possible causes of primary deficiency include defective biosynthesis, increased degradation, and defective transport affecting uptake or release of carnitine from tissues. To date the defects described have been in the transport of carnitine from serum to cell in affected tissues. These are rare defects and only about 30 patients with systemic carnitine deficiency have been described in the literature. In about half, there was a history of a sibling who died suddenly or due to cardiac disease. The most frequent findings in the dead sibs were fatty infiltration of the liver and cardiac muscle in the presence of markedly reduced tissue carnitine levels. Manifestations in affected individuals include failure to thrive, recurrent respiratory infections, recurrent hypoglycemia. The mean age at onset is 2 years with three types of presentations: progressive cardiomyopathy, hypoketotic hypoglycemia encephalopathy, and myopathy.

Treatment consists of carnitine repletion at daily doses of 100-200 mg/kg.

Secondary carnitine deficiency may be associated with inborns metabolic errors, acquired medical conditions, or iatrogenic states. Hemodialysis induces secondary carnitine deficiency because plasma carnitine is cleared during dialysis. Similarly, carnitine deficiency due to increased renal clearance occurs with treatment with pivalic acid containing penicillins and certain anti-retroviral drugs. Valproic acid, by complexing with carnitine, interferes with carnitine active transport across the plasma membrane, thus inducing tissue carnitine deficiency in the setting of normal serum carnitine concentrations. With the exception of valproate-associated deficiency, secondary carnitine deficiency states respond well to carnitine supplementation.

Information pertinent to the current sNDA

As stated above, clinical manifestations (fatigue, muscle weakness, etc.) of carnitine deficiency do not ensue until plasma and tissue levels fall to less than 5 to 10% of normal. Under current standard of care for hemodialysis patients, which includes intravenous carnitine supplementation, clinically manifest carnitine deficiency does not occur. Furthermore, it would be unethical to subject patients to the risks and discomforts of frank deficiency in order to prove a clinical benefit of carnitine supplementation. Suffice it to say that there is ample evidence that carnitine is an essential metabolic intermediate and that carnitine deficiency (whether primary or secondary) can be a serious and life-threatening condition. Finally, there is likewise ample evidence that hemodialysis depletes serum and, by extension, tissue carnitine stores. As such, and in light of the safety of carnitine, efficacy in the treatment of carnitine deficiency may be inferred from data showing that carnitine levels are maintained or actually increase in patients subject to carnitine depletion and/or low/falling carnitine levels, even if not frankly carnitine deficient at the time of study.

Data presented in the current submission

The current submission presents data from two 24-week, placebo controlled studies in ESRD patients on dialysis. These have been reviewed and summarized by Dr. Gebert of Biometrics in his draft review of this sNDA. The tables summarizing the plasma carnitine data are contained in Dr. Gebert's review.

In study ST-96001, patients were randomized to receive placebo, Carnitor 10, 20, or 40 mg/kg 3 times per week after each dialysis. Treatment groups contained approximately 30 patients and >90% of patients completed the 6-month study. Groups were matched at baseline for average carnitine levels. In the placebo group, the median serum carnitine level did not change over the study period and remained at approximately 40 micromoles/L (normal ~50 mcmol/L). By contrast in the carnitine groups, there was a dose dependent marked increase in carnitine levels pre-dialysis. The median carnitine concentrations were 209, 374, and 807 micromoles/L at 24 weeks for the groups receiving 10, 20, and 40 mg/kg iv carnitine, respectively.

Study ST-96002 studied carnitine 20 mg/kg three times weekly after dialysis versus placebo and yielded similar results.

In addition, a pharmacokinetic study in 12 ESRD patients on chronic dialysis was conducted. Patients on dialysis at least 6 months were treated with levocarnitine 20 mg/kg 3 times per week following dialysis for a total period of 2 months. Average baseline carnitine was 20 mcmol/L. Not reviewed here, the results reportedly show initial high plasma levels that drop rapidly over 6-8 hours with a t_{1/2} of about 2-3 hours. This pattern persisted at steady state. Finally, post-dialysis carnitine levels increased into the normal range on this treatment regimen.

While the data clearly support the efficacy of iv levocarnitine in maintaining or increasing carnitine serum levels in ESRD patients on dialysis, they do not support improvements in clinical status or exercise tolerance, nor do they provide convincing evidence for decreases in BUN, creatinine, phosphorus, for increases in hematocrit, and for decreases in hypotensive episodes. These latter claims should not be included in labeling.

Safety

In studies ST-96001 and 96002, 130 patients were exposed to Carnitor at doses up to 40 mg/kg three times weekly for 6 months. There were few adverse events that occurred more frequently among carnitine patients than in placebo. Hypertension occurred in 9 of 63 (14%) placebo patients and in 26 of 130 (20%) carnitine patients. There was no apparent effect of dose on incidence across the carnitine groups. Hypercalcemia occurred in 3% of placebo patients and in 9% of carnitine patients, again with no dose-response. Hypotension and hypervolemia occurred more frequently among placebo patients than among carnitine patients (placebo rates of 19 and 17% respectively; carnitine rates of 14 and 5 %, respectively).

Labeling

Clinical pharmacology

Delete sentence beginning line 73 and sentence that follows. Not supported by data. Await Biopharm comments on other labeling in this section.

Indications and Usage

Line 162. Change to [redacted]

There is no evidence from the trials that this therapy ameliorates the signs and symptoms of frank carnitine deficiency in these patients.

Adverse reactions

Line 222. Change to "[redacted]"

Three AE's are listed twice each in the table of AE's. These are [redacted]. These repetitions should be deleted from the table.

Dosage and Administration

Await comments from Biopharm

Summary

Substantial evidence exists in the literature regarding the essential place for carnitine in intermediary metabolism and for the clinical significance of frank carnitine deficiency. Hemodialysis is an established cause of secondary carnitine deficiency.

This sNDA provides substantial evidence for the efficacy and safety of intravenous levocarnitine in patients on hemodialysis. Evidence suggests that post-dialysis administration of levocarnitine maintains or increases pre-dialysis serum carnitine levels and supports the conclusion that this is a means by which to treat or prevent clinical carnitine deficiency. No major safety issues arise from the data on ESRD patients treated with intravenous levocarnitine at the doses recommended in proposed labeling.

Recommendation

Pending agreement on final labeling for Carnitor, this sNDA may be approved.

David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

Recommendation code: AP

[redacted] 10-12-99
J. Orloff [redacted] 12-14-99

NDA 20-182
Carnitor (Levocarnitine) Injection

August 24, 1999
Sigma-Tau Pharmaceuticals, Inc

Review and Evaluation of Clinical Data
Submission dated 01-29-99; S-006

This submission provides for a new indication: to be used as a supplement in end-stage renal disease (ESRD) patients who have been placed on hemodialysis and who have secondary carnitine deficiency. This secondary deficiency of carnitine occurs in ESRD patients on hemodialysis and results from both the actual dialysis procedure as well as changes in the endogenous physiological process involved in synthesis and maintenance of normal levocarnitine levels. The intended use is to replace the levocarnitine lost in ESRD patients on hemodialysis and to establish levels back to the normal range again. The clinical benefits resulting from this correction include the obvious correction as well as prevention of those complications that may result from carnitine deficiency. Among these complications one of the more notable effects important to patients are the cardiac complications. Additionally, BUN, phosphorus, and creatinine levels were reduced in a controlled clinical trial in those patients not receiving epoetin as well as improvements in hypotensive events and overall patient well being. Finally, improvements in the response to epoetin in certain patients have also been suggested.

The manifestations of secondary carnitine deficiency could include those associated with primary carnitine deficiency as well as other reported secondary deficiencies. Symptoms of this condition include hypotension, muscle weakness, failure to thrive, encephalopathy, hypoketotic hypoglycemia, and/or cardiomyopathy.

Currently a range of 40 to 60 nmol/ml in blood is considered a normal carnitine range. Standard for efficacy in Protocol P00835 in this submission was to be restoration to and maintenance of carnitine levels in blood at or close to normal range. FDA biostatistician has been asked by team leader to analyze and report on levels of carnitine prior to and after intravenous infusion of levocarnitine that was given at the end of each dialysis session; a control group was to receive an infusion of placebo at the same time. The study was to consist of a four-week baseline period followed by a 26-week treatment period. Minimum requirements of the protocol were satisfied upon the completion of at least 36 drug-treated and 36 placebo-control subjects, for a total of 72 patients at four centers.

Data were analyzed on changes from study entry to subsequent time points; these changes were then compared between the two treatment arms. The primary outcomes were clinical and hematological lab measures (BUN, creatinine, phosphorus, hematocrit),

which are considered here to be markers of product efficacy. Secondary outcomes, also considered to be markers of efficacy, are clinical improvement (a subjective, four-level, physician's assessment of change from study entry), intradialytic complications (asthenia, cramps, hypotension), post-dialysis body weight, muscle anthropometrics, lipids and triglycerides, and exercise tolerance as measured by progressive load cycle ergometry.

Data analyses revealed statistically significant effects of levocarnitine for three of the four primary outcomes: BUN, creatinine, and phosphorus. Beginning in the second or third month after initiation of treatment, significantly lower levels of BUN and creatinine were seen in the levocarnitine group than in the placebo group, although the differences varied with treatment time.

The company states that approximately 80% of the distribution of IV levocarnitine are prescribed in ESRD, although it is an unapproved indication as yet. It is said that within a group of renal insufficiency patients, only patients undergoing hemodialysis are capable of presenting an L-carnitine deficiency. Hemodialysis causes a reduction of 50 to 70% of the plasma level during each session. With repetition of sessions, muscular depletion can occur and can be aggravated by nutritional reduction or by inadequate diet. In parallel fashion, there are qualitative anomalies linked to accumulation of esterified carnitine at the expense of free carnitine.

SAFETY

Carnitor has been marketed in the US in the form of tablets and oral solution since December 1986; the IV form has been available since 1992 for the treatment of secondary carnitine deficiency. Since that time the use of levocarnitine in dialysis patients has grown significantly; at present, about 80% of the distribution of IV Carnitor is in dialysis. Patient exposure approximates 2000 to 3000 patients. No unusual limiting effects have presented for this exposure in seriously ill ESRD patients requiring hemodialysis.

The two adequate and well-controlled studies in patients with ESRD who required hemodialysis are herein submitted; Protocol ST-96001 and ST-96002 included a total of 193 patients. Protocol ST-96001 evaluated the safety and efficacy of levocarnitine 10 mg/kg, 20 mg/kg, or 40 mg/kg vs placebo. Protocol ST-96002 evaluated the safety and efficacy of levocarnitine 20 mg/kg vs placebo. In both of these studies, levocarnitine or placebo was administered as a slow 2-3 minute bolus injection into the venous return line after each dialysis session (TIW). Duration of exposure was six months. The attached table, reproduced from the sponsor's submission, presents a tabulation of adverse events, regardless of causality assessment, by body system from these two studies combined. Based on the results of these two studies, the company proposes to add to the adverse event section of the labeling a table of adverse events with frequency greater than or equal to 5%, regardless of causality. This table would include only events with a frequency greater than or equal 5% in placebo, any individual active treatment group (10 mg/kg, 20 mg/kg, or 40 mg/kg), or in the combination of the active treatment groups.

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The table below lists the adverse events that have been reported in two double-blind, placebo-controlled studies. Events occurring at $\geq 5\%$ are reported without regard to causality.

	Placebo (n=63)	Levocarnitine 10 mg (n=34)	Levocarnitine 20 mg (n=62)	Levocarnitine 40 mg (n=34)	Levocarnitine 10, 20 & 40 mg (n=130)
Body as Whole					
Abdominal pain	17	21	5	6	9
Accidental injury	10	12	8	12	10
Allergic reaction	5	6			2
Asthenia	8	9	8	12	9
Back pain	10	9	8	6	8
Chest pain	14	6	15	12	12
Fever	5	6	5	12	7
Flu syndrome	40	15	27	29	25
Headache	16	12	37	3	22
Infection	17	15	10	24	15
Injection site reaction	59	38	27	38	33
Pain	49	21	32	35	30
Cardiovascular					
Arrhythmia	5	3		3	2
Atrial fibrillation			2	6	2
Cardiovascular disorder	6	3	5	6	5
Electrocardiogram abnormal		3		6	2
Hemorrhage	6	9	2	5	4
Hypertension	14	18	21	21	20
Hypotension	19	15	19	3	14
Palpitations		3	8		5
Tachycardia	5	6	5	9	6
Vascular disorder	2		2	6	2
Digestive					
Anorexia	3	3	5	6	5
Constipation	6	3	3	3	3
Diarrhea	19	9	10	35	16
Dyspepsia	10	9	6		5
Gastrointestinal disorder	2	3		6	2
Melena	3	6			2
Nausea	10	9	5	12	8
Stomach atony	5				
Vomiting	16	9	16	21	15
Endocrine System					
Parathyroid disorder	2	6	2	6	4
Hemic/Lymphatic					
Anemia	3	3	5	12	6
Hypervolemia	17	3	3	12	5
Muscle/Nutritional					
Hypercalcemia	3	15	8	6	9
Hyperkalemia	6	6	6	6	6
Hypervolemia	17	3	3	12	5
Peripheral edema	3	6	5	3	5
Weight decrease	3	3	8	3	5
Weight increase	2	3		6	2
Musculo-Skeletal					
Leg cramps	13		8		4
Myalgia	6				

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	Placebo (n=63)	Levocarnitine 10 mg (n=34)	Levocarnitine 20 mg (n=62)	Levocarnitine 40 mg (n=34)	Levocarnitine 10, 20 & 40 mg (n=130)
Nervous					
Anxiety	5		2		
Depression	3	6	5	6	1
Dizziness	11	18	10	15	5
Drug dependence	2	6			13
Hypertension	14	18	21	21	2
Hypertonia	5	3			20
Insomnia	6	3	6		1
Leg cramps	13		8		4
Paresthesia	3	3	3	12	4
Stomach atony	5				5
Vertigo		6			
Respiratory					
Bronchitis			5	3	
Cough increase	16		10	18	3
Dyspnea	19	3	11	3	9
Pharyngitis	33	24	27	15	7
Respiratory disorder	5				23
Rhinitis	10	6	11	6	
Sinusitis	5		2	3	9
Skin And Appendages					
Pruritus	13				
Rash	3		8	3	5
Special Senses					
Amblyopia	2		5	3	
Eye disorder	3	6	6		3
Taste perversion			3		3
Urogenital					
Urinary tract infect	6	3	2	9	
Kidney failure	5	6	3	6	3
			6		2
				6	6

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Benefit/Risk Relationship

Potential benefit from levocarnitine supplementation in those ESRD patients on hemodialysis who have secondary carnitine deficiency includes:

1. Correction of the deficiency itself
2. Subsequent avoidance or correction of the medical complications associated with carnitine deficiency

In addition, decreases in BUN, phosphorus, and creatinine have been reported in a controlled trial in patients who were not receiving epoetin alfa (which is now standard therapy in this disorder). BUN increases can occur in a carnitine-deficient state. Improvements have also been reported in intradialytic complications such as hypotension, cramping, and asthenia.

The medical literature, in general, supports a finding of an overall improvement in patient well being. Furthermore, risks associated with development of a long-term carnitine deficiency, especially in patients who remain on dialysis for extended periods, exceed those associated with levocarnitine administration to deficient patients.

LABELING

1. The revised package insert includes a large number of minor editorial revisions, changes of syntax, and rewordings made in order to secure greater clarity. All of these changes are minor, satisfactory, and acceptable.
2. Indications should be reworded to [REDACTED]
3. The new table of adverse events now present in the labeling is satisfactory, but contains several repetitions. For example, [REDACTED] is present under both Hemic/Lymphatic and under Metabolic/Nutritional with exactly the same entries for frequencies in both places. [REDACTED] is included under both Cardiovascular and under Nervous. [REDACTED] are included under both Musculo-Skeletal and under Nervous.

RECOMMENDATIONS:

After the emendations itemized above have been made in the package insert, and unless Statistics has objections or further corrections, this NDA supplement may be approved for this new indication.

[REDACTED]
/s/
Elton Herman