PRODUCT MONOGRAPH

[Pr]ODAN LEVOCARNITINE

Levocarnitine Oral Solution, USP

100 mg / mL

Amino Acids and Derivatives

Odan Laboratories Ltd.
325 Stillview Avenue
Pointe-Claire, QC
H9R 2Y6

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ODAN LEVOCARNITINE
Levocarnitine Oral Solution, USP
100 mg/mL

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Solution 1 g / 10 mL (100 mg / mL)	Wild Cherry Flavor, D,L-Malic Acid, Methylparaben, Propylparaben, Purified Water, Sucrose Syrup

INDICATIONS AND CLINICAL USE

ODAN LEVOCARNITINE (levocarnitine oral solution) is indicated for:

- Treatment of primary systemic carnitine deficiency
- Acute and chronic treatment of patients with an inborn error of metabolism which results in a secondary carnitine deficiency

In some patients, particularly those presenting with cardiomyopathy, carnitine supplementation rapidly alleviated signs and symptoms. Treatment should include, in addition to carnitine, supportive and other therapy as indicated by the condition of the patient.

Geriatrics (> 65 years of age):
Limited data are available therefore ODAN LEVOCARNITINE should be used with caution in these patients.

Pediatrics (<18 years of age):
The evaluation of carnitine in primary and secondary carnitine deficiency included pediatric patients.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General

ODAN LEVOCARNITINE (levocarnitine oral solution) contains sucrose. Consideration should be given when used in diabetic patients and those on a low calorie diet.

Carcinogenesis and Mutagenesis

No human data are available. See TOXICOLOGY section.

Gastrointestinal

Rapid consumption of ODAN LEVOCARNITINE may result in gastrointestinal reactions.

Renal

The safety and efficacy of oral levocarnitine have not been evaluated in patients with renal insufficiency.

The chronic use of, or administration of high doses in excess of 1 gram per dose of the oral formulations of levocarnitine for long periods of time, are not recommended in patients with severely compromised renal function or in ESRD patients on dialysis due to the fact that major metabolites formed following oral administration (trimethylamine [TMA] and trimethylamine-N-oxide [TMAO]) will accumulate. Increased levels of TMA in dialysis patients have been reported to be associated with possible neurophysiologic effects. Also, the inefficient removal of TMA may result in the development of "fish odor" syndrome.

In ESRD patients on hemodialysis, only the intravenous form of levocarnitine is indicated for use.

Special Populations

Pregnant Women:
Reproductive studies have been performed in rats and rabbits at doses up to 3.8 times the human dose on the basis of surface area and have revealed no evidence of impaired fertility or harm to the fetus due to levocarnitine. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Women:
Levocarnitine has not been studied in lactating women. Levocarnitine should only be used by nursing mothers if benefit to the mother outweighs any potential risks to the child from excess carnitine exposure. Studies in dairy cows indicate that the concentration of levocarnitine in milk is increased following exogenous administration of levocarnitine. In nursing mothers receiving levocarnitine, any risks to the child of excess carnitine intake need to be weighed against the benefits of levocarnitine supplementation to the mother. Consideration may be given to

discontinuation of nursing or of levocarnitine treatment.

Geriatrics (> 65 years of age):
Limited data are available therefore ODAN LEVOCARNITINE should be used with caution in these patients.

Pediatrics (<18 years of age):
The evaluation of carnitine in primary and secondary carnitine deficiency included pediatric patients. Evidence from clinical studies and experience suggests that use in the pediatric population is not associated with differences in safety or efficacy.

Monitoring and Laboratory Tests

Reports of International Normalised Ratio (INR): INR levels should be monitored in patients treated concomitantly with levocarnitine and anticoagulant drugs[1, 6].

Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations and overall clinical condition.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Various mild gastrointestinal complaints have been reported during the long-term administration of oral L- or D,L-carnitine; these include transient nausea and vomiting, abdominal cramps, and diarrhea. Mild myasthenia has been described only in uremic patients receiving D,L-carnitine.

Gastrointestinal adverse reactions with levocarnitine oral solution dissolved in liquids might be avoided by a slow consumption of the solution or by a greater dilution. Decreasing the dosage often diminishes or eliminates drug-related patient body odor or gastrointestinal symptoms when present.

Seizures have been reported to occur in patients with or without pre-existing seizure activity, receiving either oral or intravenous levocarnitine. In patients with pre-existing seizure activity, an increase in seizure frequency and/or severity has been reported.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The table below lists the adverse events that have been reported in two double-blind, placebo-controlled trials in patients on chronic hemodialysis. Events occurring at ≥5% are reported without regard to causality.

Table 1 % of Patients With Adverse Events Occurring at a Frequency ≥5% Regardless of Causality by Body System

	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	3	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

	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)
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
Metabolic/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				
Nervous					
Anxiety	5		2		1
Depression	3	6	5	6	5
Dizziness	11	18	10	15	13
Drug dependence	2	6			2
Hypertonia	5	3			1
Insomnia	6	3	6		4
Paresthesia	3	3	3	12	5
Vertigo		6			2
Respiratory					
Bronchitis			5	3	3
Cough increase	16		10	18	9
Dyspnea	19	3	11	3	7
Pharyngitis	33	24	27	15	23
Respiratory disorder	5				
Rhinitis	10	6	11	6	9
Sinusitis	5		2	3	2

	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)
Skin And Appendages					
Pruritus	13		8	3	5
Rash	3		5	3	3
Special Senses					
Amblyopia	2		6		3
Eye disorder	3	6	3		3
Taste perversion			2	9	3
Urogenital					
Urinary tract infect	6	3	3		2
Kidney failure	5	6	6	6	6

Less Common Clinical Trial Adverse Drug Events (<5%)

Listed below are adverse events categorized by body system that have been reported in two double-blind, placebo-controlled trials in patients on chronic hemodialysis occurring <5% without regard to causality.

Body as Whole: body odor, chills, cyst, face edema, neck pain, neoplasm, tuberculosis reactivated

Cardiovascular: aortic stenosis, AV block First Degree, AV block Second Degree, coronary artery disorder, heart arrest, inverted T wave, postural hypotension, supraventricular tachycardia, vascular anomaly, vasodilation

Digestive: cholelithiasis, colitis, dry mouth, duodenitis, flatulence, gastritis, gastroenteritis, gingivitis, hematemesis, hepatitis, ileus, liver function tests abnormal, nausea and vomiting, peptic ulcer, periodontitis (pyorrhea), tooth caries, tooth disorder, tongue discoloration, ulcerative colitis

Hemic/Lymphatic: coagulation disorder, ecchymosis, erythrocytes abnormal, hypochromic anemia, leukopenia, thrombocytopenia

Metabolic/Nutritional: avitaminosis, edema, hyperphosphatemia, hypocalcemia, hypoglycemia, acidosis

Musculo-Skeletal: arthralgia, arthritis, bursitis, generalized spasm, myopathy, osteoporosis, pathological fracture (bone fracture spontaneous), tendon disorder, tenosynovitis

Nervous: abnormal gait, agitation, amnesia, convulsions, diplopia, hallucinations, hypotonia, peripheral neuritis

Respiratory: asthma, atelectasis, epistaxis, hemoptysis, hiccup, lung disorder, lung edema, pleural effusion, pneumonia

Skin and Appendages: acne, dry skin, skin carcinoma, skin disorder, skin ulcer, sweat, urticarial, vesiculobullous rash

Special Senses: conjunctivitis, ear disorder, ear pain, eye pain, glaucoma, eye hemorrhage, keratoconjunctivitis tinnitus

Urogenital: dyspareunia, endometrial disorder, female lactation, urinary tract disorder, urinary urgency, vaginal hemorrhage, vaginal moniliasis

Abnormal Hematologic and Clinical Chemistry Findings

Anemia, hypercalcemia, and hyperkalemia were seen in the two double-blind, placebo-controlled trials conducted in patients on chronic hemodialysis (see Table 1).

Post-Market Adverse Drug Reactions

Additional reports of serious adverse events temporally associated with levocarnitine during worldwide post-marketing experience are included below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to levocarnitine exposure.

Body as Whole: anaphylaxis

Dermatological: toxic epidermal necrolysis

Gastro-intestinal: cholecystitis

Hematologic: necrotic granuloma formation, INR increase, vitamin K deficiency, prothrombin level abnormal

Infection: sepsis

Metabolic: hypoglycemia

Musculoskeletal: rhabdomyolysis

Nervous system: psychosis, seizures

Respiratory: bronchospasm, laryngeal edema

DRUG INTERACTIONS

Drug-Drug Interactions

Anticoagulants: There is evidence that co-administration of anticoagulant drugs such as acenocoumarol or warfarin with levocarnitine may lead to increase the INR. INR levels of patients taking levocarnitine with concomitant anticoagulant drugs should be monitored appropriately and treatment should be revised. The mechanism of action of this drug interaction is unknown. (see WARNINGS AND PRECAUTIONS section) .

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ODAN LEVOCARNITINE (levocarnitine oral solution) may be consumed alone or dissolved in drink or other liquid food. Doses should be spaced evenly throughout the day (every three or four hours) preferably during or following meals and should be consumed slowly in order to maximize tolerance. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit.

Recommended Dose and Dosage Adjustment

The recommended dosage of levocarnitine is 1 to 3 g / day for a 50 kg subject, which is equivalent to 10 to 30 mL / day of ODAN LEVOCARNITINE. Dosage should start at 1 g / day (10 mL / day), and be increased slowly while assessing tolerance and therapeutic response. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit.

Geriatrics (>65 years of age):
Limited data are available therefore ODAN LEVOCARNITINE should be used with caution in these patients.

Pediatrics (<18 years of age):
The recommended dosage of levocarnitine is 50 to 100 mg / kg / day which is equivalent to

0.5 mL / kg / day ODAN LEVOCARNITINE . Dosage should start at 50 mg / kg / day, and be increased slowly to a maximum of 3 g / day (30 mL / day) while assessing tolerance and therapeutic response. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit.

Missed Dose

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule.

Administration

ODAN LEVOCARNITINE (levocarnitine oral solution):
For oral use only.

OVERDOSAGE

No toxicity has been reported. Levocarnitine is easily removed from plasma by dialysis. Overdosage should be treated with supportive care.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Levocarnitine is a naturally occurring substance required in mammalian energy metabolism. It has been shown to facilitate long-chain fatty acid entry into cellular mitochondria, thereby delivering substrate for oxidation and subsequent energy production. Fatty acids are utilized as an energy substrate in all tissues except the brain. In skeletal and cardiac muscle, fatty acids are the main substrate for energy production.

Pharmacodynamics

Primary systemic carnitine deficiency is characterized by low concentrations of levocarnitine in plasma, red blood cell (RBC), and/or tissues. It has not been possible to determine which symptoms are due to carnitine deficiency and which are due to an underlying organic acidemia, as symptoms of both abnormalities may be expected to improve with levocarnitine. The literature reports that carnitine can promote the excretion of excess organic or fatty acids in patients with defects in fatty acid metabolism and/or specific organic acidopathies that bioaccumulate Acyl-coenzyme A (acylCoA) esters.[2,3,4,5,8,9]

Secondary carnitine deficiency can be a consequence of inborn errors of metabolism or

iatrogenic factors such as hemodialysis. Levocarnitine may alleviate the metabolic abnormalities of patients with inborn errors that result in accumulation of toxic organic acids. Conditions for which this effect has been demonstrated are: glutaric aciduria II, methyl malonic aciduria, propionic acidemia, and medium chain fatty acylCoA dehydrogenase deficiency.[11,12]

Autointoxication occurs in these patients due to the accumulations of acylCoA compounds that disrupt intermediary metabolism. The subsequent hydrolysis of the acylCoA compound to its free acid results in acidosis which can be life-threatening. Levocarnitine clears the acylCoA compound by formation of acylcarnitine, which is quickly excreted. Carnitine deficiency is defined biochemically as abnormally low plasma concentrations of free carnitine, less than 20 μmol / L at one week post term and may be associated with low tissue and/or urine concentrations. Further, this condition may be associated with a plasma concentration ratio of acylcarnitine/levocarnitine greater than 0.4 or abnormally elevated concentrations of acylcarnitine in the urine. In premature infants and newborns, secondary deficiency is defined as plasma levocarnitine concentrations below age-related normal concentrations.

End Stage Renal Disease (ESRD) patients on maintenance hemodialysis may have low plasma carnitine concentrations and an increased ratio of acylcarnitine/carnitine because of reduced intake of meat and dairy products, reduced renal synthesis and dialytic losses. Certain clinical conditions common in hemodialysis patients such as malaise, muscle weakness, cardiomyopathy and cardiac arrhythmias may be related to abnormal carnitine metabolism.

Pharmacokinetics

Absorption:
Following oral administration of levocarnitine the time to maximum plasma concentration (T_{max}) occurs at 3.3 hours.

The absolute bioavailability is 15.1 ± 5.3% for levocarnitine tablets and 15.9 ± 4.9% for levocarnitineoral solution calculated after correction for circulating endogenous plasma concentrations of levocarnitine.

Distribution:
The mean total body clearance of levocarnitine (Dose/area under the curve [AUC] including endogenous baseline concentrations) is 4.00 L / hr.

The mean steady state volume of distribution (Vss) of the intravenously administered dose above baseline endogenous levels is 29.0 L ± 7.1 L (approximately 0.39 L / kg).

The mean distribution half-life is 0.585 hours and the mean apparent terminal half-life is 17.4 hours.

Levocarnitine does not bind to plasma protein or albumin.

Metabolism:
58 to 65% of oral L-carnitine is recovered in the urine and feces in 5 to 11 days.

After oral administration, the unabsorbed levocarnitine is metabolized in the gastrointestinal tract by the bacterial microflora to trimethylamine and γ-butyrobetaine. Trimethylamine is absorbed and converted to trimethylamine N-oxide which is primarily excreted in urine. γ-butyrobetaine is excreted primarily in feces (0.44% to 45% of administered dose).

Excretion:
Urinary excretion of oral levocarnitine is 4% to 9% of the dose.

Fecal excretion of total carnitine is less than 2% of the administered oral dose.

Following a single i.v. administration of levocarnitine , 73.1% ± 16% of the levocarnitine dose may be excreted in the urine during the 0–24 h interval.

Special Populations and Conditions

Geriatrics (> 65 years of age): No data available.

Pediatrics (< 18 years of age): No data available.

Renal Insufficiency:

The safety and efficacy of the oral formulations of levocarnitine have not been evaluated in patients with renal insufficiency.

The pharmacokinetics of levocarnitine in 12 ESRD patients undergoing hemodialysis for at least 6 months was studied following single and multiple post-dialysis i.v. administration of 20 mg / kg of levocarnitine , three times a week for nine consecutive weeks. Prior to dosing with levocarnitine , endogenous plasma levels of levocarnitine in these patients were approximately 20 nmol / mL pre-dialysis and 5.6 nmol / mL post-dialysis. Endogenous plasma levels of levocarnitine in normals are approximately 40-50 nmol / mL. Following repeated post-dialysis i.v. administration of 20 mg / kg of levocarnitine , the pre-dose, post-dialysis plasma concentration of levocarnitine was restored to physiological levels (40 nmol / mL) in about 8 weeks.

Plasma levels were determined in 2 controlled clinical trials in patients on dialysis for at least 6 months. Levels before levocarnitine administration were below normal. Intravenous administration of levocarnitine increased levels in a similar manner to the pharmacokinetics study. A linear relationship between levocarnitine plasma levels and i.v. doses of levocarnitine (10, 20 and 40 mg / kg) was found.

STORAGE AND STABILITY

ODAN LEVOCARNITINE (levocarnitine oral solution) should be stored at room temperature (15-30 °C). Avoid excessive heat. Protect from freezing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ODAN LEVOCARNITINE (levocarnitine oral solution) 1 g / 10 mL (100 mg / mL) is a clear, cherry flavored oral solution supplied in 118 mL multiple-unit plastic containers. **For oral use only.** Each 118 mL container of ODAN LEVOCARNITINE contains 1 g of levocarnitine / 10 mL (100 mg / mL). Also contains: Wild Cherry Flavor, D,L-Malic Acid, Purified Water, Sucrose Syrup. Methylparaben and Propylparaben are added as preservatives. The pH is approximately 5.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

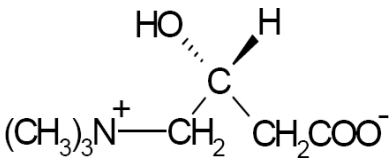
Proper name: Levocarnitine

Chemical name: 3-carboxy-2(*R*)-hydroxy-N,N,N-trimethyl-1-propanaminium, inner salt

Molecular formula: $C_7H_{15}NO_3$

Molecular weight: 161.20

Structural formula:



Physicochemical properties: Levocarnitine is a carrier molecule in the transport of long-chain fatty acids across the inner mitochondrial membrane. As a bulk drug substance it is a white, crystalline, hygroscopic powder with a melting point of 196-197 °C. It is readily soluble in water, hot alcohol, and insoluble in acetone. The pH of a solution (1 in 20) is between 6-8 and its pKa value is 3.8.

CLINICAL TRIALS

Pharmacokinetic and clinical studies with levocarnitine have shown that administration of levocarnitine to ESRD patients on hemodialysis results in increased plasma levocarnitine concentrations. In one study, blood urea nitrogen (BUN), creatinine, and phosphorus blood levels decreased with levocarnitine administration. In another study, increases in hematocrit, decreases in hypotensive episodes, and improvement in wellbeing have been observed, although not statistically significant.

Comparative Bioavailability Studies

In a relative bioavailability study in 15 healthy adult male volunteers, levocarnitine tablets were found to be bioequivalent to levocarnitine oral solution. Following the administration of 6 tablets of Levocarnitine 330 mg b.i.d. or 2 g of levocarnitine oral solution b.i.d., the maximum plasma concentration (C_{max}) was 80 nmol / mL and the time to maximum plasma concentration (T_{max}) occurred at 3.3 hours. Based on confidence – interval testing procedure (two one-sided t test with 90% confidence intervals within 80 -120% range), the two oral formulations were found to be bio-equivalent.

DETAILED PHARMACOLOGY

Metabolism and Excretion

In a pharmacokinetic study where five normal adult male volunteers received an oral dose of [^{3}H-methyl]-L-carnitine following 15 days of a high carnitine diet and additional carnitine supplement, 58 to 65% of the administered radioactive dose was recovered in the urine and feces in 5 to 11 days. Maximum concentration of [^{3}H-methyl]-L-carnitine in serum occurred from 2.0 to 4.5 hr after drug administration. After oral administration, the unabsorbed levocarnitine is metabolized in the gastrointestinal tract by the bacterial microflora to trimethylamine and γ-butyrobetaine. Trimethylamine is absorbed and converted to trimethylamine N-oxide which is primarily excreted in urine. [^{3}H]-γ-butyrobetaine is excreted primarily in feces (0.44% to 45% of the administered dose). Urinary excretion of levocarnitine was 4% to 8% of the dose. Fecal excretion of total carnitine was less than 2% of the administered dose.[10]

After attainment of steady state following 4 days of oral administration of levocarnitine tablets (1980 mg q12h) or oral solution (2000 mg q12h) to 15 healthy male volunteers, the mean urinary excretion of levocarnitine during a single dosing interval (12h) was about 9% of the orally administered dose (uncorrected for endogenous urinary excretion).

Bioavailability/Pharmacokinetics

The plasma concentration profiles of levocarnitine after a slow 3 minute intravenous bolus dose of 20 mg / kg of levocarnitine were described by a two-compartment model. Following a single

i.v. administration 73.1 ± 16% of the levocarnitine dose was excreted in the urine during the 0-24h interval. Using plasma concentrations uncorrected for endogenous levocarnitine, the mean distribution half life was 0.585 hours and the mean apparent terminal elimination half life was 17.4 hours.

The absolute bioavailability of levocarnitine from the two oral formulations oflevocarnitine, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was 15.1 ± 5.3% for levocarnitine tablets and 15.9 ± 4.9% for levocarnitineoral solution.

Total body clearance of levocarnitine (Dose/AUC including endogenous baseline concentrations) was a mean of 4.00 L / hr. Endogenous baseline levels were not subtracted since total body clearance of levocarnitine does not distinguish between exogenous sources of levocarnitine and endogenously synthesized levocarnitine. The steady state volume of distribution (Vss) of the intravenously administered dose above baseline endogenous levels was calculated to be a mean of 29.0 L ± 7.1 L (approximately 0.39 L / kg) which is an underestimate of the true Vss since plasma levocarnitine is known to equilibrate slowly with, for instance, muscle levocarnitine.

Levocarnitine was not bound to plasma protein or albumin when tested at any concentration or with any species including the human.[7]

The pharmacokinetics of levocarnitine in 12 ESRD patients undergoing hemodialysis for at least six months was studied following single and multiple post-dialysis i.v. administration of 20 mg / kg of levocarnitine , three times a week for nine consecutive weeks. Prior to dosing with levocarnitine , endogenous plasma levels of levocarnitine in these patients were approximately 20 nmol / mL pre-dialysis and 5.6 nmol / mL post-dialysis. Endogenous plasma levels of levocarnitine in normals are approximately 40-50 nmol / mL. Following repeated post-dialysis i.v. administration of 20 mg / kg of levocarnitine, the pre-dose, post-dialysis plasma concentration of levocarnitine was restored to physiological levels (40 nmol / mL) in about eight weeks.

Plasma levels were determined in 2 controlled clinical trials in patients on dialysis for at least 6 months. Levels before levocarnitine administration were below normal. Intravenous administration of levocarnitine increased levels in a similar manner to the pharmacokinetics study. A linear relationship between levocarnitine plasma levels and i.v. doses of levocarnitine (10, 20 and 40 mg / kg) was found.

TOXICOLOGY

Levocarnitine as the inner salt or hydrochloride salt was evaluated in acute, subacute, subchronic, chronic, reproductive tests and mutagenic evaluation.

Toxicity

Acute studies were performed in the mouse and rat (i.v., i.p., and i.m.) and in the rabbit intravenously. Subacute tests were performed in the rabbit (i.v.) and the dog (orally).

Subchronic toxicity was evaluated in the rat (per os and intravenously). The rat and dog were both evaluated for chronic toxicity orally and intramuscularly.

In mice, the LD_{50} orally ranged between 8,400 and 30,000 mg / kg. The intravenous LD_{50} was between 2,000 and 5,000 mg / kg. The rat had an LD_{50} orally from 6,100 to 18,000 mg / kg with the intravenous range being 2,000 to 5,500 mg / kg. The rabbit had an intravenous LD_{50} higher than 7,800 mg / kg. The predominant signs of toxicity included transient diarrhea, depression, and slight clonic convulsions. Deaths occurred within one hour to within 72 hours, depending upon the route and the rate of administration.

In the multidose toxicity studies in rats, rabbits and dogs, levocarnitine caused liquid feces, vomiting and a slight retardation in body weight gain in the dogs. A number of hematologic and serum chemistry differences from the control groups were observed, but values were mostly within normal limits and inconsistent within and between studies. No overt toxicity was observed orally or parenterally.

Teratogenesis and Mutagenesis

Fertility and reproduction were studied in the rat (orally). Fetotoxicity and teratogenicity were studied in two species as well (rat and rabbit - orally and i.m.). Peri- and post-natal safety studies were run in the rat and rabbit (orally). Mutagenicity was evaluated with reverse mutation, gene conversion, forward mutation and in the micronucleus test in the mouse.

In the reproduction or teratogenicity studies in rats and rabbits, levocarnitine caused no adverse effects. All five mutagenicity tests were negative. On the basis of the above results, it is concluded that levocarnitine, tested in a broad spectrum of oral and parenteral toxicity studies at high dosage levels, caused no significant adverse effects.

Mutagenicity tests have been performed in *Salmonella typhimurium, Saccharomyces cerevisiae*, and *Schizosaccharomyces pombe* that do not indicate that levocarnitine is mutagenic. Long-term animal studies have not been conducted to evaluate the carcinogenicity of the compound.

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PART III: CONSUMER INFORMATION

Pr ODAN LEVOCARNITINE
(Levocarnitine Oral Solution, USP)

This leaflet is Part III of a three-part "Product Monograph" published when ODAN LEVOCARNITINE was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about ODAN LEVOCARNITINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ODAN LEVOCARNITINE is used to treat carnitine deficiency, a rare disorder in which body levels of carnitine, an amino acid, is less than what is needed for the normal function of the body.

What it does:
ODAN LEVOCARNITINE is given to supplement the normal diet with carnitine to be able to process foods, especially fats and convert them to energy to work the muscles and organs in the body properly.

When it should not be used:
Do not use ODAN LEVOCARNITINE if you are allergic to carnitine or any of the ingredients in the product (see below).

What the medicinal ingredient is:
levocarnitine

What the nonmedicinal ingredients are:

Wild Cherry Flavor, D,L- Malic Acid, Purified Water, Sucrose Syrup. Methylparaben NF and Propylparaben NF are added as preservatives.

What dosage forms it comes in:
Oral Solution 1 g / 10 mL (100 mg / mL)

WARNINGS AND PRECAUTIONS

BEFORE you use ODAN LEVOCARNITINE talk to your doctor or pharmacist if you:

- have kidney disease
- have diabetes or are on a low-calorie diet as ODAN LEVOCARNITINE contains sucrose
- are pregnant or could be pregnant
- are breastfeeding
- have a history of seizures

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ODAN LEVOCARNITINE include:

- anticoagulants (acenocoumarol and warfarin)

PROPER USE OF THIS MEDICATION

Usual dose:

ODAN LEVOCARNITINE Oral Solution may be taken alone or dissolved in a drink or other liquid food. Doses should be spaced evenly throughout the day (every three or four hours) preferably during or following meals and should be consumed slowly in order to limit side effects.

Adults
The recommended oral dosage is 1 to 3 g / day for a 50 kg person, which is equivalent to 10 to 30 mL / day of ODAN LEVOCARNITINE Oral Solution. Dosage should start at 1 g / day (10 mL / day), and be increased slowly.

Pediatrics (<18 years of age)
The recommended oral dosage for infants and children is 50 to 100 mg / kg / day which is equivalent to 0.5 mL / kg / day ODAN LEVOCARNITINE Oral Solution. Dosage should start at 50 mg / kg / day, and be increased slowly to a maximum of 3 g / day (30 mL / day).

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If a dose of this medication has been missed, it should be taken as soon as possible unless it is almost time for the next dose. In this case, skip the missed dose and go back to the regular dosing schedule. Do not take 2 doses together.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects include:

- vomiting, nausea, upset stomach, diarrhea, abdominal cramps
- abnormal taste
- body odour ("fishy" smell)
- headache

If any of these affects you severely, tell your doctor or pharmacist.

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SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	**High Blood Pressure:** headache, dizziness, vision problems, shortness of breath		✓	
	Abnormal Heartbeat: palpitations		✓	
	Decreased Platelets: bleeding or bruising, fatigue and weakness		✓	
	Anemia: fatigue, loss of energy, weakness, shortness of breath		✓	
	Bronchitis: coughing and difficulty breathing		✓	
	Increased levels of calcium: increased thirst, frequent urination, nausea, vomiting, constipation, bone pain, confusion and fatigue		✓	
Uncommon	**Allergic Reaction:** difficulty swallowing or breathing, hives, swelling of the face, lips, tongue or throat, rash			✓
	Seizure			✓
Rare	**Low Blood Sugar**		✓	
	Rhabdomyolysis: muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine			✓
Very Rare	**Injection Site Reaction:** redness, swelling, tenderness		✓	
	Signs of dermatitis exfoliative: Rash, redness, widespread blistering or peeling of the skin and mucosa (mouth)			✓

This is not a complete list of side effects. For any unexpected effects while taking ODAN LEVOCARNITINE, contact your doctor or pharmacist.

HOW TO STORE IT

ODAN LEVOCARNITINE Oral Solution should be stored at room temperature (15-30°C). Avoid high temperatures or heat such as in hot weather and direct contact from the sun. Protect from freezing.

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to the Canada Vigilance Program by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Odan Laboratories Limited at: 1-800-387-9342.

This leaflet was prepared by Odan Laboratories Ltd.

Date prepared: September 5, 2019