PRODUCT MONOGRAPH

pms-TRYPTOPHAN

(L-Tryptophan)
500 mg & 1 g Tablets
500mg Capsules

Adjunct in the Management of Affective Disorders

PHARMASCIENCE INC.

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(L-Tryptophan) 500 mg & 1 g Tablets
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THERAPEUTIC CLASSIFICATION

Adjunct in the Management of Affective Disorders

ACTION AND CLINICAL PHARMACOLOGY

The rationale for the use of L-tryptophan in affective disorders is based on clinical findings more than 20 years ago, that L-tryptophan increases 5-HT (serotonin) synthesis in the central nervous system of humans. It has been demonstrated in clinical trials that oral ingestion of L-tryptophan in humans caused a significant increase in the level of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in the lumbar cerebrospinal fluid, indicating an increased turnover of serotonin in the CNS.

L-tryptophan is one of the eight essential amino acids. The minimum daily requirements are said to be 0.25 g for males and 0.15 g for females. It is present in the hydrolysates of most proteins, the average western diet containing between 1 and 3 grams per day. There are two major metabolic pathways for L-tryptophan, the first to serotonin, the second to nicotinic acid. Approximately 98% of dietary L-tryptophan is metabolized into nicotinic acid and only a very small amount is being metabolized to serotonin via the intermediary stage of 5-hydroxy-tryptophan (5-HTP). Tryptophan hydroxylase, the enzyme responsible for this step, is the rate-limiting enzyme for serotonin production and is normally only about half-saturated. Central nervous system serotonin is metabolized by monoamine oxidase to 5-HIAA.

A comparative bioavailability study was performed using pms-TRYPTOPHAN 1 g tablets (Pharmascience Inc.) *versus* TRYPTAN® 1 g tablets (ICN Canada Ltd.) in 16 healthy male volunteers. A single 1 g oral dose was administered. The results are summarized in the following table:

SUMMARY OF COMPARATIVE BIOAVAILABILITY DATA
[after oral administration (1 x 1 g tablet) in the fasting state]

pms-TRYPTOPHAN 1 g Tablets (Pharmascience Inc., Canada -- Lot #591022) vs.
TRYPTAN® 1g Tablets (ICN Canada Ltd.) -- Lot #OC5428

Parameter	**Geometric Mean Arithmetic Mean (CV %)**		**Ratio of Geometric Means (90% Conf. Limit)**
	Test	**Reference**	
AUC_T (mcg·h/mL)	294.44 297.02 (13.6)	299.18 303.79 (17.9)	98.4
C_{max} (mcg/mL)	47.51 48.21 (17.6)	49.50 50.40 (19.1)	96.0
T_{max} (hr)	1.19 (0.44)	1.44 (0.31)	--
$T_{½el}$ (hr)	4.72 (2.21)	4.78 (2.39)	--

T_{max} and $T_{½el}$ -- arithmetic mean with standard deviation in parenthesis

A comparative bioavailability study was performed using pms-TRYPTOPHAN 500 mg capsules (Pharmascience Inc.) *versus* TRYPTAN® 500 mg capsules (ICN Canada Ltd.) in 36 healthy male volunteers. A single 500 mg oral dose was administered. The results are summarized in the following table:

SUMMARY OF COMPARATIVE BIOAVAILABILITY DATA
[after oral administration (1 x 500mg capsule) in the fasting state]

pms-TRYPTOPHAN 500 mg Capsules (Pharmascience Inc., Canada -- Lot #671202) *vs.* TRYPTAN® 500mg Capsules (ICN Canada Ltd.) -- Lot #7K2892

Parameter	**Geometric Mean Arithmetic Mean (CV %)**		**Ratio of Geometric Means**
	Test	**Reference**	
AUC_T (mcg·h/mL)	36.77 40.23 (41.5)	37.92 42.46 (55.4)	97
$AUC_{:c}$ (mcg·h/mL)	41.21 44.57 (40.8)	39.91 46.06 (66.0)	103
C_{max} (mcg/mL)	17.34 18.78 (36.4)	18.26 19.01 (27.0)	95
T_{max} (hr)	1.00 (57.5)	1.00 (41.7)	---
$T_{½el}$ (hr)	1.17 (74.7)	1.20 (96.8)	---

T_{max} and $T_{½el}$ -- arithmetic mean with standard deviation in parenthesis

INDICATIONS AND CLINICAL USE

pms-TRYPTOPHAN is used as a valuable adjunct to antidepressant drug treatment in the management of patients suffering from depressive disorders (bipolar affective disorders). An adjunctive effect has been observed in some case when L-tryptophan is given in combination with lithium in bipolar patients with mania or depression for whom lithium alone or in combination with neuroleptics or tricyclics has been shown little or no effect. Clinical observations suggest the possibility that the combination of lithium and L-tryptophan may reduce the need for the higher, more toxic doses of lithium necessary to control acute mania.

CONTRAINDICATIONS

pms-TRYPTOPHAN is contraindicated in patients with known sensitivity to L-tryptophan or any other compound in the formulation.

WARNINGS

Monoamine Oxidase Inhibitors (MAOIs): L-tryptophan is not recommended in patients taking monoamine oxidase inhibitors (MAOIs including linezolide, methylene blue) or within 14 days of such therapy. The combination of MAOIs and tryptophan has been reported to cause behaviour and neurologic syndromes including disorientation, confusion, amnesia, delirium, agitation, hypomanic signs, ataxia, myoclonus, hyperreflexia, shivering, ocular oscillations and Babinski signs (see DRUG INTERACTIONS).

Serotonin Syndrome: There have been rare reports of serotonin syndrome with the concomitant use of L-tryptophan and serotonergic drugs. Caution is advise particularly during treatment initiation and dose increases when prescribing pms-TRYPTOPHAN with serotonergic drugs such as selective serotonin re-uptake inhibitor (SSRI) or serotonin norepinephrine re-uptake inhibitor (SNRI) products, as well as with tricyclic antidepressants (TCAs), and other serotonergic drugs (e.g. lithium, triptans and MAOIs). Treatment should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma, and supportive symptomatic treatment should be initiated (see DRUG INTERACTIONS).

Allergic Reactions: There have been reports of hypersensitivity reactions (myalgia, oedema, pruritus, rash, urticaria and wheezing) with the use of L-tryptophan. Patients should be instructed to see their doctor if they develop any of these signs or symptoms.

L-tryptophan should not be given to patients suffering from the following conditions or should be prescribed only under close supervision.

Bladder Cancer: To minimize the risk of bladder cancer, it may be recommended to give vitamin B6 supplements if the L-tryptophan doses are many times in excess of those consumed normally in dietary protein. An increased incidence rate of bladder cancer has been observed in experimental

animals after implantation of pellets containing any of the seven tryptophan metabolites formed by tryptophan pyrrolase. Active metabolites included kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranillic acid, and xanthurenic acid, but not tryptophan itself. Vitamin B6 has been reported to correct the metabolism of L-tryptophan and to reduce the metabolites to normal levels. A large study carried out by the National Cancer Institute did not find L-tryptophan to produce cancer in either rats or mice. Elevated levels of L-tryptophan metabolites in the urine have been reported both in bladder cancer patients relative to controls, in patients who had a recurrence of cancer relative to those who did not, and in patients taking oral contraceptives or hormones.

Diabetes Mellitus: Xanthurenic acid, which is increased on L-tryptophan loading, has a diabetogenic action in animals, possibly due to its ability to bind insulin, suggesting caution in the use of tryptophan in patients with a family history of diabetes.

Achlorhydria / Malabsorption: In ruminants, oral L-tryptophan caused pulmonary edema and emphysema, mediated by bacterial conversion of L-tryptophan to skatole (3-methylindole). This is not normally of concern in humans except where bacteria exist high in the gastrointestinal tract due to conditions such as achlorhydria, or where L-tryptophan reaches the bacterial populations lower in the gastrointestinal tract due to malabsorption.

Cataract Formation: Animal data suggest that photooxidation of L-tryptophan and some of its metabolites, such as kynurenine, may be involved in cataract formation. Although there is no evidence that this occurs in humans, L-tryptophan administration is likely to raise lenticular tryptophan and kynurenine concentrations, and this might make subjects more susceptible to cataract formation, particularly if exposed to ultraviolet light.

PRECAUTIONS

Neurologic: Patients should be instructed to not drive, use machinery, or do any activity that requires alertness until they are sure they can perform such activities safely.

DRUG INTERACTIONS

Drug interactions between tryptophan and other CNS-affecting drugs have been reported. A higher occurrence of side effects was reported when tryptophan was given in combination with monoamine oxidase inhibitors (MAOI). The most common side effects caused by this drug combination were dizziness, nausea and headache. At a dosage of 20–50 mg/kg tryptophan in addition to MAOI, the following side effects have been reported: ethanol-like intoxication, drowsiness, hyperreflexia and clonus. Single case reports of adverse reactions to the drug combination include hypomanic behaviour, ocular oscillation, ataxia, and myoclonus. Some of these reactions resemble the "serotonin syndrome" seen in experimental animals, which consists of tremor, hypertonus, myoclonus, and hyperreactivity. These symptoms disappear soon after cessation of tryptophan, and no detrimental long-term effects have been reported.

When tryptophan was given in combination with fluoxetine, the following side-effects have been reported, but disappeared as soon as the medication was discontinued. Neither drug alone caused

similar side-effects: agitation, restlessness, poor concentration, nausea, diarrhea, and worsening of obsessive-compulsive disorder.

Patients taking high doses of L-tryptophan should not be protein deprived since an amino acid imbalance can ensue.

ADVERSE REACTIONS

L-tryptophan, in doses below 5 g/day may cause dry mouth and drowsiness. In higher doses (9–12 g/day) nausea, anorexia, dizziness and headache have been reported.

Side effects disappear when medication is continued and in most cases only a light dizziness may persist.

Sexual disinhibition has been reported in some patients with emotional disorders.

L-tryptophan, when given with lithium, might increase some side effects associated with lithium therapy by potentiating the lithium effect (nausea, vomiting, dermatological eruptions, psoriasis, alopecia).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

According to the toxicity described, symptoms of overdosage would include vomiting and might include serotonin syndrome symptoms. Treatment of overdosage would be symptomatic with close monitoring and support of vital systems as necessary.

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

DOSAGE AND ADMINISTRATION

Clinical reports on the use of L-tryptophan as an adjunct in the management of affective disorders have indicated the dose of 8–12 g/day to be the most effective one. Lower doses have been reported to be effective in combination with other antidepressants. Some patients may not tolerate 12 g/day but might still benefit from doses reduced to 8 g/day.

The treatment might be initiated with 12 g per day of pms-TRYPTOPHAN (L-tryptophan), given in 3–4 equally divided doses. Administration with meals or snacks is recommended to reduce the incidence of nausea. The dose and frequency of administration may have to be adjusted to the patients need and tolerance.

Special Populations and Conditions

A small number of bipolar patients are particularly sensitive to L-tryptophan and will not tolerated higher doses than 1 or 2 g/day. Patients on concomitant medication should be monitored for

possible reduction of the concomitant medication since pms-TRYPTOPHAN may enhance their efficacy.

If pms-TRYPTOPHAN is used in the acute treatment of mania in conjunction with lithium, it will potentiate some of the side effects associated with lithium such as nausea and vomiting. Thus, often it will be necessary to decrease the lithium dosage, especially when it is given in doses above 900–1200 mg/day. In manic-depressive illness chronically treated with lithium, the lithium dose may need to be decreased when pms-TRYPTOPHAN is added because of increased side effects. In these patients, pms-TRYPTOPHAN tends to produce an increase in lithium concentrations, thus it is important to monitor the lithium concentration closely for at least two weeks after the addition of pms-TRYPTOPHAN.

With some of the more sedative neuroleptics and antidepressants, if pms-TRYPTOPHAN is added, an increased incidence of sedation may occur.

PHARMACEUTICAL INFORMATION

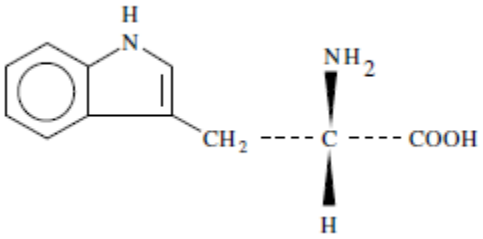
Drug Substance

Brand Name: pms-TRYPTOPHAN

Proper Name: L-Tryptophan

Chemical Name: L-2-Amino-3-(indol-3-yl) propionic acid

Structural Formula:



Molecular Formula: $C_{11}H_{12}N_2O_2$

Molecular Weight: 204.23 g/mol

Physical form: White to slightly yellowish white crystals or crystalline powder, having a slightly bitter taste.

Solubility: Soluble in water; slightly soluble in alcohol or soluble in hot alcohol; practically insoluble in ether; soluble in dilute hydrochloric acid.

pKa and pH values: The pH of a 1 in 100 solution is between 5.5-7.0

Partition co-efficient: Log P (octanol water partition coefficient) -1.06

Melting point: 280-285 °C

Composition
pms-TRYPTOPHAN tablets contain: L-Tryptophan and as non-medicinal ingredients: carboxymethylcellulose sodium, croscarmellose sodium, Macrogol/PEG 3350, magnesium stearate, polyvinyl alcohol part hydrolyzed, purified water, talc, titanium dioxide.

pms-TRYPTOPHAN capsules contain: L-Tryptophan and as non-medicinal ingredients: carboxymethylcellulose sodium, croscarmellose sodium, magnesium stearate, gelatin, titanium dioxide.

Stability and Storage Recommendations

Store at room temperature (15-30°C). Keep bottles tightly closed; protect from heat and light.

AVAILABILITY OF DOSAGE FORMS

pms-TRYPTOPHAN 500 mg:
Each white, opaque, size # 00 Coni-snap capsule printed "P" logo and "T 500" in black ink on both body and cap**,** contains 500 mg of L-Tryptophan, USP. Bottles of 100 and 250 capsules.

Each white to off-white, oblong, film-coated tablet is debossed with "P" logo on one side and "T5" on the other side and contains 500 mg of L-Tryptophan, USP. Bottles of 100, 250 and 500 tablets.

pms-TRYPTOPHAN 1 g:
Each white, oblong, film-coated tablet is debossed with "P" logo on one side and "T1" on the other side and contains 1 g of L-Tryptophan, USP. Bottles of 100 and 250 tablets.

INFORMATION TO THE CONSUMER

For better results, pms-TRYPTOPHAN should be taken with a protein-low, carbohydrate-rich snack or meal.

TOXICOLOGY

In animals the toxicity of parenterally administered tryptophan and other amino acids is attributed to ammonia poisoning. In rabbits, it causes histopathological changes in the kidney tubules, and large amounts given in conjunction with a low-protein diet cause death within a few days. It provokes a severe hyperglycemia which in the case of the l-isomer is not sustained since the animals die in a hypoglycemic state. L-tryptophan in toxic doses also causes marked glycosuria and loss of glycogen from skeletal muscle and liver. Some L-tryptophan metabolites cause experimental lymphomas or leukemias. The LD50 for L-tryptophan in the rat is 1.6 g/kg.

Carcinogenicity of L-tryptophan has been reviewed based on early findings relating bladder tumors in rats to aromatic amines and l-tryptophan. Experiments designed to provoke urinary bladder tumors by oral or subcutaneous administration of L-tryptophan or its metabolites, have generally given negative results. Tests performed on behalf of the National Cancer Institute (Bethesda, MD), using male and female rats and mice given large supplements of L-tryptophan for prolonged periods, did not show a statistically significant occurrence of neoplasms as compared to controls. Under the bio-assay, L-tryptophan was not carcinogenic for the strains of animals used. L-tryptophan and its tested metabolites have not exhibited intrinsic carcinogenic action. L-tryptophan has, however, been reported to promote or inhibit the carcinogenic action of a variety of known carcinogens.

L-tryptophan has been shown to cause hyperglycemia in rat and man, to inhibit gluconeogenesis in rat and man and to promote lipogenesis both in the fasted rat and the fed animal. Patients with scleroderma may exhibit abnormal L-tryptophan metabolism and studies have been carried out in an attempt to reveal a possible relationship between tryptophan and scleroderma. Serotonin given subcutaneously in a high dose for 30 days or more to rats was found to result in a scleroderma-like lesion. It is conceivable that the appearance of a sclerodermatous lesion can be initiated by different factors, among them a high level of kynurenine or metabolites of that amino acid, or of serotonin.

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