PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrTRYPTAN®

L-Tryptophan
250 mg; 500 mg; 750 mg tablets
1 g Tablets
500 mg Capsules
Oral

Adjunct in the Management of Affective Disorders

Bausch Health, Canada Inc.
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Laval, Quebec
H7L 4A8

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RECENT MAJOR LABEL CHANGES

NONE	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TRYPTAN is indicated:

as a valuable adjunct to antidepressant drug treatment in the management of patients suffering from depressive disorders (bipolar affective disorders).

2 CONTRAINDICATIONS

TRYPTAN is contraindicated in patients with known sensitivity to L-tryptophan or any other compound in the formulation (see 7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Clinical reports on the use of TRYPTAN 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 TRYPTAN, given in 3-4 equally divided doses.

- **Special Populations and Conditions**

A small number of bipolar patients are particularly sensitive to TRYPTAN and will not tolerate higher doses than 1 or 2 g/day. Patients on concomitant medication should be monitored for possible reduction of the concomitant medication since TRYPTAN may enhance their efficacy.

If TRYPTAN 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 TRYPTAN is added because of increased side effects. In these patients TRYPTAN 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 TRYPTAN (see 8.1 Adverse Reaction Overview; 9.4 Drug-Drug interactions).

With some of the more sedative neuroleptics and antidepressants, if TRYPTAN is added, an increased incidence of sedation may occur (see 9.4 Drug-Drug interactions).

4.4 Administration

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 (see 9.5 Drug-Food Interactions).

5 OVERDOSAGE

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 (see 7 WARNINGS AND PRECAUTIONS, General, Serotonin syndrome).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	500 mg Capsules	Magnesium Stearate and Talc
Oral	250 mg, 500 mg, 750 mg and 1g Tablets	Calcium Phosphate, Croscarmellose Sodium, Magnesium Stearate, Methylcellulose, Opadry II White, Film Coating Base Solution (includes: Polyvinyl Alcohol, Macrogol/PEG, Titanium Dioxide, and Talc)

- ***TRYPTAN 500 mg capsules:*** each opaque white capsule, size No. 00 imprinted with ICN T17, contains 500 mg of L-tryptophan, USP. Bottles of 100 capsules.
- ***TRYPTAN 250 mg tablets:*** each white, oval-shaped film coated tablet, embossed 'TRYPTAN' on one side, and “250 mg” on the other side, contains 250 mg of L-tryptophan, USP. Bottles of 100 tablets.
- ***TRYPTAN 500 mg tablets:*** each white, oval-shaped, biconvex film coated tablet embossed 'TRYPTAN' on one side, and “500 mg” on the other, contains 500 mg of L-tryptophan, USP. Bottles of 100 tablets.
- ***TRYPTAN 750 mg tablets:*** each white, oval-shaped film coated tablet, embossed 'TRYPTAN' on one side and “750 mg” on the other side, contains 750 mg of L-tryptophan, USP. Bottles of 100 tablets.
- ***TRYPTAN 1 g tablets:*** each white, oval-shaped film coated tablet, embossed 'TRYPTAN' 1 g’ on one side, contains 1 g of L-tryptophan, USP. Bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

General

- **Monoamine Oxidase Inhibitors (MAOIs)**

TRYPTAN is not recommended in patients taking monoamine oxidase inhibitors (MAOIs including linezolid, 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 9.4 Drug-Drug Interactions).

- **Serotonin Syndrome**

There have been rare reports of serotonin syndrome with the concomitant use of TRYPTAN and serotonergic drugs. Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported during the use of TRYPTAN. Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

If concomitant treatment with TRYPTAN and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Carcinogenesis and Mutagenesis

To minimize the risk of bladder cancer, it may be recommended to give vitamin B6 supplements if the TRYPTAN 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 TRYPTAN and to reduce the metabolites to normal levels. A large study carried out by the National Cancer Institute did not find TRYPTAN to produce cancer in either rats or mice. Elevated levels of TRYPTAN metabolites in the urine have been reported 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 (see 16 NON CLINICAL TOXICOLOGY, Carcinogenicity).

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Xanthurenic acid, which is increased on TRYPTAN 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 (see 16 NON CLINICAL TOXICOLOGY, General).

Gastrointestinal

In ruminants, oral TRYPTAN caused pulmonary edema and emphysema, mediated by bacterial conversion of TRYPTAN 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 TRYPTAN reaches the bacterial populations lower in the gastrointestinal tract due to malabsorption.

Ophthalmologic

Animal data suggest that photooxidation of TRYPTAN and some of its metabolites, such as kynurenine, may be involved in cataract formation. Although there is no evidence that this occurs in humans, TRYPTAN 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.

Sensitivity/Resistance

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

TRYPTAN should not be given to patients suffering from the above conditions or should be prescribed only under close supervision (see 2 CONTRAINDICATIONS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

- TRYPTAN, 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 (see 4.4 Administration).
- 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.
- TRYPTAN, when given with lithium, might increase some side effects associated with

lithium therapy by potentiating the lithium effect (nausea, vomiting, dermatological eruptions, psoriasis, alopecia) (see 9.4 Drug-Drug Interactions).

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Drug interactions between tryptophan and other central nervous system (CNS) affecting drugs have been reported. A higher occurrence of side effects was reported when tryptophan was given in combination with mono-amino-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 behavior, 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 (see 7 WARNINGS AND PRECAUTIONS, General, Serotonin Syndrome and 16 NON CLINICAL TOXICOLOGY, General).

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.

An adjunctive effect has been observed in some case when TRYPTAN 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 shown little or no effect. Clinical observations suggest the possibility that the combination of lithium and TRYPTAN may reduce the need for the higher, more toxic doses of lithium necessary to control acute mania.

9.5 Drug-Food Interactions

Patients taking high doses of TRYPTAN should not be protein deprived since an amino acid imbalance can ensue (see 4.4 Administration).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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.

10.3 Pharmacokinetics

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.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature (15 - 30ºC). Protect from heat and light

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this product.

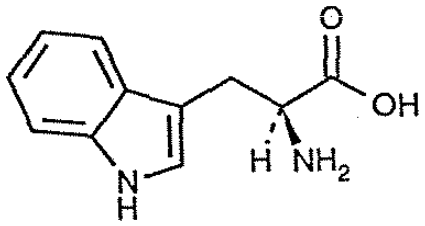
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	L-tryptophan, USP
Chemical name:	L-2-Amino-3-(indol-3-yl) propionic acid
Molecular formula and molecular mass:	$C_{11}H_{12}N_2O_2$, 204.23 g/mol

Structural formula:



Physicochemical properties:

Description:	White to slightly yellowish-white crystals or crystalline powder with a slightly bitter taste.
Solubility:	It is soluble in 11.4 g in 1 L of water, slightly soluble in alcohol; practically insoluble in chloroform and ether; soluble in hot alcohol and solutions of dilute acids and alkali hydroxides.
pH:	A 1 % solution in water has a pH of 5.5 to 7.0.

14 CLINICAL TRIALS

The clinical trial data based on which the original indication was initially authorized are not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 LD_{50} for L-tryptophan in the rat is 1.6 g/kg.

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. A high dose of serotonin administered subcutaneously 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 L-tryptophan, or of serotonin.

Carcinogenicity

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 bioassay, 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.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTRYPTAN®
L-Tryptophan
250 mg; 500 mg; 750 mg tablets
1 g Tablets
500 mg Capsules

Read this carefully before you start taking **TRYPTAN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TRYPTAN**.

What is TRYPTAN used for?

TRYPTAN is used in addition to antidepressants to depressive disorders.

How does TRYPTAN work?

TRYPTAN contains L-Tryptophan, one of the eight essential amino acids. It works by increasing the level of serotonin (a neurotransmitter) in the central nervous system in the body.

What are the ingredients in TRYPTAN?

Medicinal ingredients: L-Tryptophan

Non-medicinal ingredients:

- ***Tablets:*** Magnesium Stearate and Talc
- ***Capsules:*** Calcium Phosphate, Croscarmellose Sodium, Magnesium Stearate, Methylcellulose, Opadry II White, Film Coating Base Solution (includes: Polyvinyl Alcohol, Macrogol/PEG, Titanium Dioxide, and Talc)

TRYPTAN comes in the following dosage forms:

- Capsules; 500 mg
- Tablets; 250 mg, 500 mg, 750 mg and 1g Tablets

Do not use TRYPTAN if:

- you have a known allergy to TRYPTAN or to any of the other ingredients TRYPTAN contains.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRYPTAN. Talk about any health conditions or problems you may have, including if you:

- have ever had an allergic reaction (swelling, itching, rash, hives, and wheezing) to TRYPTAN or any of the inactive ingredients TRYPTAN contains
- have diabetes or have family history of diabetes

Other warnings you should know about:

- There have been rare cases of a condition called "serotonin syndrome" in patients taking TRYPTAN with other drugs that affect your serotonin levels. Symptoms may include involuntary muscle movements or spasms, tremors, agitation, and overactive reflexes. Talk to your healthcare professional if you notice any of these symptoms.
- Your doctor may prescribe you a vitamin B6 supplement while you are taking TRYPTAN. This may help your body process (metabolize) TRYPTAN better.
- TRYPTAN may make you drowsy, or dizzy. Before driving a vehicle or doing activities that require alertness, wait to see how you feel after taking TRYPTAN.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TRYPTAN:

- Lithium
- Monoamine oxidase inhibitors (e.g., moclobemide, phenelzine, tranylcypromine)
- Selective norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine)
- Selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, fluvoxamine, paroxetine, sertraline)

How to take TRYPTAN:

Take TRYPTAN as directed by your healthcare professional. The usual recommended adult dose of TRYPTAN is 8 g to 12 g daily taken in 3 to 4 equally divided doses. Take with meals or snacks to help reduce nausea.

For better results TRYPTAN should be taken with a protein-low, carbohydrate rich meal.

Overdose:

If you think you, or a person you are caring for, have taken too much TRYPTAN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose of TRYPTAN take it as soon as possible, then just carry on with the regular times you take your medication. If you remember your missed dose close to the time for your next dose, do not take the missed dose.

What are possible side effects from using TRYPTAN?

These are not all the possible side effects you may have when taking TRYPTAN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may be due to TRYPTAN or due to other drugs taken with TRYPTAN. Side effects may include:

- agitation
- confusion
- diarrhea
- disorientation
- drowsiness
- loss of appetite
- overactive reflexes
- poor coordination / concentration
- restlessness
- sexual disinhibition (unusual sexual behaviour)
- shivering
- sudden or involuntary moves or spasms (myoclonus)
- sweating
- talking or acting with excitement you cannot control
- trembling or shaking
- twitching
- vomiting

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Insomnia, dizziness, nausea, headache		√	
RARE			
Allergic reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada 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.

Storage:

- Store at controlled room temperature (15 - 30ºC).
- Protect from heat and light.
- Do not use TRYPTAN tablets after the expiry date. All expired medications should be returned to your pharmacist.

Keep out of reach and sight of children.

If you want more information about TRYPTAN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.bauschhealth.ca, or by calling 1-800-361-4261.

This leaflet was prepared by

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