



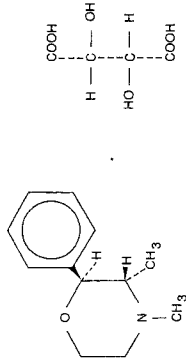
BONTRIL®
SLOW RELEASE
BRAND OF
PHENDIMETRAZINE TARTRATE
SLOW-RELEASE CAPSULES
105 mg

Rx Only

DESCRIPTION

Phendimetrazine tartrate, as the dextro isomer, has the chemical name of (+)-3,4-Dimethyl-2-phenylmorpholine Tartrate.

The structural formula is as follows:



$C_{12}H_{17}NO \cdot C_4H_6O_6$

M.W. 341.36

Phendimetrazine tartrate is a white, odorless powder with a bitter taste. It is soluble in water, methanol and ethanol.

Bontril® Slow-Release capsules contain FD&C Yellow No. 6 as a color additive.

CLINICAL PHARMACOLOGY

Phendimetrazine tartrate is a sympathomimetic amine with pharmacological activity similar to the prototype drugs of this class used in obesity, the amphetamines. Actions include central nervous system stimulation and elevation of blood pressure. Tachyphylaxis and tolerance have been demonstrated with all drugs of this class in which these phenomena have been looked for.

Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics". It has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions or metabolic effects may be involved.

Adult obese subjects instructed in dietary management and treated with anorectic drugs lose more weight on the average than those treated with placebo and diet, as determined in relatively short term clinical trials.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks. The possible origin of the increased weight loss due to the various drug effects is not established. The amount of weight loss associated with the use of an anorectic drug varies from trial to trial, and the increased weight loss appears to be related in part to variables other than the drug prescribed, such as the physician investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration, thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically limited.

The active drug 105 mg of phendimetrazine tartrate in each capsule of this special slow-release dosage form approximates the action of three 35 mg non-time release doses taken at 4 hour intervals.

The major route of elimination is via the kidneys where most of the drug and metabolites are secreted. Some of the drug is metabolized to phendimetrazine and also phendimetrazine-N-oxide.

The average half-life of elimination when studied under controlled conditions is about 1.9 hours for the non-time and 9.8 hours for the slow-release dosage form. The absorption half-life of the drug from conventional non-time 35 mg phendimetrazine tablets is approximately the same. These data indicate that the slow-release product has a similar onset of action to the conventional non-time-release product and, in addition, has a prolonged therapeutic effect.

INDICATIONS

Phendimetrazine tartrate is indicated in the management of exogenous obesity as a short term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class (see ACTIONS) should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate and severe hypertension, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. Use in patients taking other CNS stimulants including monoamine oxidase inhibitors.

WARNINGS

Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued.

Use of phendimetrazine within 14 days following the administration of monoamine oxidase inhibitors may result in a hypertensive crisis.

Abrupt cessation of administration following prolonged high dosage results in extreme fatigue and depression. Because of the effect on the central nervous system phendimetrazine tartrate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

PRECAUTIONS

Caution is to be exercised in prescribing phendimetrazine for patients with even mild hypertension.

Insulin requirements in diabetes mellitus may be altered in association with the use of phendimetrazine and the concomitant dietary regimen.

Phendimetrazine may decrease the hypotensive effect of guanethidine.

The least amount feasible should be prescribed or dispersed at one time in order to minimize the possibility of overdose.

Usage in Pregnancy: Safe use in pregnancy has not been established. Until more information is available, phendimetrazine tartrate should not be taken by women who are or may become pregnant unless, in the opinion of the physician, the potential benefits outweigh the possible hazards.

Usage in Children: Phendimetrazine tartrate is not recommended for use in children under 12 years of age.

ADVERSE REACTIONS

Cardiovascular: Palpitation, tachycardia, elevation of blood pressure.

Central Nervous System: Overstimulation, restlessness, dizziness, insomnia, tremor, headache; rarely psychotic episodes at recommended doses; agitation, flushing, sweating, blurring of vision.

Gastrointestinal: Dryness of the mouth, diarrhea, constipation, nausea, stomach pain.

Genitourinary: Changes in libido, urinary frequency, dysuria.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Phendimetrazine is a Schedule III controlled substance.

Dependence: Phendimetrazine tartrate is related chemically and pharmacologically to the amphetamines. Amphetamines and related stimulant drugs have been extensively abused, and the possibility of abuse of phendimetrazine should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with intense psychological dependence and severe social dysfunction. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability,



hyperactivity and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSEAGE

Manifestations of acute overdose may include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states.

Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, hypertension, or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Poisoning may result in convulsions, coma, and death.

Management of acute intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard.

Acidification of the urine increases phendimetrazine tartrate excretion.

Intravenous phenolamine (Regitine) has been suggested for possible acute, severe hypertension, if this complicates overdose.

DOSEAGE AND ADMINISTRATION

One Slow-Release Capsule (105 mg) in the morning, taken 30-60 minutes before the morning meal.

Phendimetrazine Tartrate is not recommended for use in children under twelve years of age.

HOW SUPPLIED

Bontril Slow Release Capsules (phendimetrazine tartrate 105 mg) is available as opaque green and clear yellow capsules, imprinted with "VALEANT" and "BONTRIL 105". Phendimetrazine Slow-Release Capsules are available in bottles of 100 (NDC #0187-0498-01) and 1000 (NDC 0187-0498-02).

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

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