

PRODUCT MONOGRAPH

**TENUATE®
(diethylpropion hydrochloride)**

Tablets, 25 mg

**TENUATE® DOSPAN®
(diethylpropion hydrochloride)**

Continuous Release Tablets, 75 mg

Anorexiant

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Submission Control No. 104730

Date of Revision:
March 23, 2006

s-a Version 1.1 dated July 11, 2008

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THERAPEUTIC CLASSIFICATION

Anorexiant

ACTION

TENUATE® (diethylpropion hydrochloride) is a psychomotor stimulant with anorectic, sympathomimetic and other effects similar to those of amphetamines. As with all other drugs of this class in which the phenomenon has been studied, the initial rate of weight loss decreases until a plateau is reached; a regain of weight thereafter even though drug administration is continued has been reported. As with similar drugs, rebound weight gain also may occur after discontinuation of TENUATE®.

INDICATIONS AND CLINICAL USE

A psychomotor stimulant used as an adjunct in the short-term (i.e. a few weeks) to continued dietary treatment in the medical management of obesity, in patients who have not responded to an appropriate weight reducing regimen (diet and/or exercise) alone. TENUATE® is recommended only for obese patients with an initial body mass index $\geq 30 \text{ kg/m}^2$, or $\geq 27 \text{ kg/m}^2$ in the presence of other risk factors (e.g. hypertension, diabetes, hyperlipidaemia).

Below is a chart of Body Mass Index (BMI) based on various heights and weights. BMI is calculated by taking the patient's weight, in kilograms, divided by the patient's height in meters and squared. Metric conversions are as follows:

Pounds(lbs)/2.2 = kilograms (kg)
 Feet (ft) x 0.3048 = meters (m)
 Inches x 0.0254 = meters (m)

BODY MASS INDEX (BMI), kg/m²

Weight (pounds)	Height (feet, inches)					
	5'0"	5'3"	5'6"	5'9"	6'0"	6'3"
140	27	25	23	21	19	18
150	29	27	24	22	20	19
160	31	28	26	24	22	20
170	33	30	28	25	23	21
180	35	32	29	27	25	23
190	37	34	31	28	26	24
200	39	36	32	30	27	25
210	41	37	34	31	29	26
220	43	39	36	33	30	28
230	45	41	37	34	31	29
240	47	43	39	36	33	30
250	49	44	40	37	34	31

When prescribing anorectic agents it should be borne in mind that the role of these drugs in the management of obesity is strictly limited, since patients treated with anorectics lose, on average, only a fraction of a pound per week more than those who are on a weight reducing diet alone. Furthermore, the rate of weight loss tends to decrease within a few weeks and a plateau is reached. Prolonged administration of diethylpropion should also be strictly avoided since it can lead to drug dependence and abuse (see WARNINGS). Therefore, even short-term use of an anorectic drug is not recommended unless a carefully supervised weight reduction regimen by itself is not successful.

CONTRAINDICATIONS

TENUATE® (diethylpropion hydrochloride) is contraindicated:

- during therapy with monoamine oxidase inhibitors or within 14 days following withdrawal of these agents, hypertensive crisis may result;
- in patients with pulmonary artery hypertension;
- in patients with glaucoma;
- in patients with hyperthyroidism;
- in patients with advanced arteriosclerosis;
- in patients with severe hypertension;
- in patients with known heart murmur or valvular heart disease;
- in patients with agitated states;
- in patients with known hypersensitivity or idiosyncrasy to sympathomimetic amines;
- in emotionally unstable individuals who are known to be susceptible to or have a history of drug abuse;
- in combination use with other anorectic agents.

WARNINGS

Primary Pulmonary Hypertension:

ANOREXIGENS (APPETITE SUPPRESSANTS), INCLUDING DIETHYLPROPION, INCREASE THE RISK OF DEVELOPING PRIMARY PULMONARY HYPERTENSION (PPH), AN OFTEN FATAL DISORDER.¹

An epidemiological study has indicated that use of anorexigens, including diethylpropion, for longer than 3 months was associated with a 23-fold increase in the risk of developing PPH. There was no significant increase in risk for persons who had used these agents for 3 months or less. Obesity itself (body mass index ≥ 30 kg/m²) was also independently associated with an increase of about two-fold in the risk of developing PPH. In the general population, the yearly occurrence of PPH is estimated to be about 1-2 cases per 1,000,000 persons. Therefore, the estimated risk associated with the long-term use of anorexigen drugs is about 23-46 cases per million persons exposed per year. The study further suggested that the risk of PPH rises with increasing duration of use of these drugs. The effect of intermittent compared to continuous use of anorexigens on the risk of PPH has not been determined. Increased risk with intermittent repeated courses of therapy cannot be excluded. There have been reports of primary pulmonary hypertension associated with the use of TENUATE®.

The onset or aggravation of exertional dyspnea, or unexplained symptoms of angina pectoris, syncope, or lower extremity edema suggest the possibility of occurrence of pulmonary hypertension. Under these circumstances, treatment should be immediately discontinued, and the patient should be evaluated for the possible presence of PPH.

Valvular Heart Disease:

Valvular heart disease associated with the use of some anorectic agents such as fenfluramine, dexfenfluramine, both independently and specially used in combination, has been reported. Possible contributing risk factors include use for extended period of time, higher than recommended dose, and/or use in combination with other anorectic agents.

Valvular heart disease has been very rarely reported with TENUATE® but the causal relationship remains uncertain.

The potential risk of possible serious adverse effects such as valvular heart disease and pulmonary hypertension should be assessed carefully against the potential benefit of weight loss. Baseline cardiac evaluation should be considered to detect preexisting valvular heart diseases or pulmonary hypertension prior to initiation of TENUATE® treatment. Echocardiogram during and after treatment could be useful for detecting any valvular disorders which may occur.

Drug Dependence:

There is a good correlation between a drug's ability to act as a positive reinforcer in animals and its abuse potential in man. Diethylpropion has been shown to serve as a positive reinforcer in various self-administration studies performed in animals (see TOXICOLOGY).

Furthermore, experience with anorectic drugs with amphetamine-like properties such as diethylpropion has established that prolonged use of these drugs can produce tolerance, severe psychological dependence and may lead to extensive abuse. There have been a significant number of reports of abuse of diethylpropion in the last several years. This should be kept in mind when assessing the desirability of using the drug and caution should be exercised not to use the drug in individuals whose histories suggest they may develop dependence or increase the dosage on their own initiative.

If psychological dependence occurs, gradual withdrawal of the medication is recommended. Abrupt cessation following prolonged high dosage may result in extreme fatigue and mental depression and changes in the sleep EEG. Drug abuse may lead to moderate to severe manifestations of chronic intoxication including marked insomnia, irritability, hyperactivity, personality changes and even psychosis.

Tolerance:

In most patients, weight loss during treatment with diethylpropion plateaus after a few weeks. If tolerance develops discontinuation of medication is indicated rather than an increase in the dose. The recommended dose should not be exceeded in an attempt to increase the effect.

Use in Pregnancy:

TENUATE® (diethylpropion hydrochloride) should not be used in women of child-bearing potential unless in the opinion of the prescribing physician the potential benefits of drug therapy outweigh the possible risks to mother and fetus.

Use in Children:

TENUATE® (diethylpropion hydrochloride) is not recommended for use in children under 12 years of age.

Use in Elderly:

TENUATE® (diethylpropion hydrochloride) is not recommended for the elderly.

General

TENUATE® is not recommended for patients who used any anorectic agents within the prior year.

TENUATE® may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle.

PRECAUTIONS

TENUATE® (diethylpropion hydrochloride) should be used with caution in patients with mild cardiovascular disease, or hypertension, and regular monitoring of cardiovascular function and blood pressure is indicated in such patients receiving TENUATE®. TENUATE® should not be used in patients with severe cardiovascular disease including arrhythmias or hypertension. TENUATE® is not recommended in patients with known heart murmur or valvular heart diseases (see CONTRAINDICATIONS).

Prolonged use of TENUATE® may induce dependence with withdrawal syndrome on cessation of therapy (see WARNINGS). Hallucinations have occurred rarely following high doses of the drug. Several cases of toxic psychosis have been reported following the excessive use of the drug, and a very small number have been reported in which the recommended dose appears not to have been exceeded. Psychosis abated after the drug was discontinued.

Reports also suggest that diethylpropion may increase the incidence of convulsions in some epileptic patients. Therefore, caution is required if the drug is administered to epileptic patients. Epileptics receiving TENUATE® should be carefully monitored. Titration of dose or discontinuance of the drug may be necessary.

Driving a Vehicle of Performing Other Hazardous Tasks

See WARNINGS

Interactions

TENUATE® is contraindicated with monoamine (MAO) inhibitors (see CONTRAINDICATIONS).

Efficacy of TENUATE® with other anorectic agents has not been studied and the combined use may have the potential for serious cardiac problems; therefore concomitant use with other anorectic agents is contraindicated.

Arrhythmias have been associated with some sympathomimetic agents given concurrently with general anaesthetics; therefore, caution should be used during general anaesthesia in patients receiving TENUATE®.

TENUATE® may alter the effect of other drugs which act on the central nervous system. Antidiabetic drug requirements (eg, insulin) may be altered in association with the use of TENUATE® and the concomitant dietary regimen. TENUATE® may decrease the hypotensive effect of guanethidine. In addition, drugs of this class may potentiate the pressor effects of exogenous catecholamines.

Pregnancy

TENUATE® should not be used during pregnancy, unless, in the opinion of the prescribing doctor, the potential benefits outweigh the potential risks (see WARNINGS).

Isolated spontaneous reports of congenital malformations have been recorded in humans, but no causal relationship to diethylpropion has been established.

Use during pregnancy may result in withdrawal symptoms in the neonate.

No evidence of teratogenicity has been observed in animal studies. Reproduction studies in rats showed no harm to the fetus at doses up to nine times the human dose. Animal reproduction studies have revealed no evidence of impairment of fertility at doses up to 60 mg/kg/day. Higher doses may cause maternal and/or embryo toxicity.

Lactation

It is not known if diethylpropion hydrochloride and/or its metabolites pass into human milk. Use in a nursing woman is not recommended.

ADVERSE REACTIONS

The most frequently encountered side effects of TENUATE® (diethylpropion hydrochloride) are insomnia, nervousness, dizziness, anxiety, agitation and dry mouth. An epidemiological study has indicated that use of anorexigens for longer than 3 months was associated with an increase in the risk of developing Primary Pulmonary Hypertension (PPH) (see WARNINGS).

Central Nervous System:

Dyskinesia, blurred vision, overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, dysphoria and occasionally depression, tremor, mydriasis, drowsiness, malaise, headache, cerebrovascular accident, and psychotic episodes. Increase in convulsive disorders has been reported.

Cardiovascular:

Tachycardia, precordial pain, arrhythmias (including ventricular), palpitation, increased blood pressure, electrocardiogram changes. One published report described T wave changes in the ECG of a healthy young male after ingestion of diethylpropion. There have been reports of primary pulmonary hypertension associated with the use of TENUATE® (see WARNINGS).

Valvular heart disease has been very rarely reported with TENUATE® but the causal relationship remains uncertain (see WARNINGS).

Gastrointestinal:

Diarrhea, constipation, nausea, vomiting, abdominal discomfort, unpleasant taste, dryness of the mouth, and other gastrointestinal disturbances.

Allergic:

Urticaria, rash, ecchymosis and erythema.

Endocrine:

Impotence, changes in libido, dysmenorrhea, menstrual upset and gynecomastia.

Drug Abuse and Dependence:

There have been reports of subjects becoming psychologically dependent on diethylpropion.

Other:

Dyspnea, hair loss, muscle pain, dysuria, polyuria, bone marrow depression, leukopenia, agranulocytosis and increased sweating.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Clinical manifestations of diethylpropion hydrochloride intoxication are as follows: restlessness, tremor, hyperreflexia, nervousness and irritability, insomnia, rapid respiration, confusion, assaultiveness, hallucinations, and panic states. Mydriasis has been observed. Convulsions and tachycardia are frequently present. Exhaustion, drowsiness, fatigue or depression usually follow central stimulation, and coma may occur. Cardiovascular effects may include arrhythmias, changes in blood pressure (hypertension or hypotension) and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps. Overdose has resulted in death.

Management of acute intoxication is largely symptomatic. It includes gastric lavage if possible, and sedation with a barbiturate may be desirable. Experience with peritoneal dialysis or hemodialysis is not sufficient to permit a recommendation at this time.

DOSAGE AND ADMINISTRATION

Adults: One 25 mg tablet of TENUATE® (diethylpropion hydrochloride) may be administered three times daily, one hour before meals. Alternatively, one 75 mg sustained release tablet may be given once daily, in midmorning. Administration should not be extended beyond a period of four weeks. The least amount feasible should be prescribed or dispensed at one time (not to exceed a two-week supply) in order to minimize the possibility of abuse.

TENUATE® should be used for a duration of no more than a few weeks (see WARNINGS).

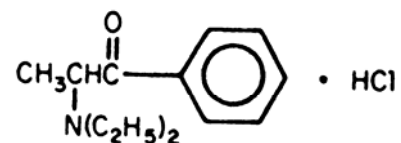
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name: diethylpropion hydrochloride

Chemical name: C₁₃H₁₉NO.HCl

Structural formula:



Molecular weight: 241.76

Physical characteristics: White to off-white crystalline powder

Composition:

Each TENUATE® Tablet contains 25 mg diethylpropion hydrochloride. Each tablet also contains as non-medicinal ingredients: lactose, magnesium stearate, talc, tartaric acid and corn starch.

Each TENUATE® DOSPAN® Tablet contains 75 mg diethylpropion hydrochloride. Each tablet also contains as non-medicinal ingredients: carboxypolymethylene, mannitol, povidone, tartaric acid, and zinc stearate.

Stability and Storage Recommendations:

Store between 15° and 30°C.

AVAILABILITY OF DOSAGE FORMS

TENUATE® Tablets 25 mg: White compressed round tablet debossed with **TENUATE 25** on one side. Other side of tablet is plain. Bottles of 100.

TENUATE® DOSPAN® Tablets 75 mg: White compressed capsule-shaped tablet debossed with **TENUATE 75** on one side. Other side of tablet is plain. Bottles of 100.

TENUATE® is a controlled (Schedule G) drug.

PHARMACOLOGY

TENUATE® (diethylpropion hydrochloride) is a psychomotor stimulant, 2-(diethylamino) propiophenone hydrochloride. Intravenous infusion of diethylpropion hydrochloride in unanesthetized dogs produces dose-dependent mydriasis, tachycardia and increase in blood pressure at a minimal dose of 3 mg/kg. Intravenous doses of 5 and 15 mg/kg produce T-wave elevation and extrasystoles, respectively. After administration of 10 mg/kg, intravenous, symptoms of central nervous system stimulation are observed.

TOXICOLOGY

Acute Toxicity:

The minimum lethal intravenous dose observed in dogs was 60 mg/kg, death occurring after convulsions and respiratory arrest.

Chronic Toxicity:

Daily oral administration of 10 mg/kg of diethylpropion hydrochloride to dogs during six months did not result in clinical nor pathological alterations.

A six month oral toxicity study in rats, at dose levels of 25, 50 and 100 mg/kg, resulted in a decrease in food consumption and in body weight gain in all dose groups. The high dose group had slightly enlarged livers, though all tissues were within normal limits on histopathologic examination. Low hemoglobin and erythrocytic values also occurred in the high dose group.

TERATOLOGY

After administration of average daily dose levels of 7 to 18 mg/kg to pregnant rats throughout gestation, the effect of diethylpropion hydrochloride appeared to be minimal. Litter size, weight and survival were comparable to those for controls. Such data, based on studies in animals, should not be considered conclusive for projection to human clinical situations.

Dependence Liability Potential: Self-Administration Studies:

Rhesus monkeys were initially trained to intravenously self-administer cocaine, 0.2 mg/kg, and after responding became stable, saline or different doses of diethylpropion were substituted for the cocaine solution. For all three animals tested responding was maintained above saline levels by doses ranging from 0.05 mg/kg to 1.0 mg/kg of diethylpropion. The shape of the dose-response curve was similar to those of other stimulants.

Choice Procedure Test:

Monkeys equipped with double lumen intravenous catheters were first trained to press a lever to receive a drug injection. Then the animals were presented with the opportunity to choose between various doses of cocaine or diethylpropion and saline. In all cases the animals chose the drug rather than the saline, high doses rather than low doses. Three out of four monkeys preferred cocaine over diethylpropion; the fourth monkey chose diethylpropion (1.0 mg/kg) over cocaine (0.1 mg/kg).

Unlimited Access:

Naive monkeys equipped with intravenous catheters were given unlimited access to a series of stimulant drugs at doses within a range previously shown to maintain response rates above saline operant levels. The drugs were available to the monkeys for 30 days. Doses were as follows: cocaine (0.2 mg/kg), l-amphetamine (0.05 mg/kg), d-amphetamine (0.05 mg/kg), d-methamphetamine (0.025) and diethylpropion (0.5 mg/kg). One of the two animals given access to l-amphetamine and two of the five given access to diethylpropion died before the 30-day period terminated. A cyclic pattern of intake similar to that reported in the literature for stimulant drugs, was observed in all animals and for all drugs in this study. For most animals, food intake was initially suppressed and became highly variable for the remainder of the experiment. There was no systematic relationship between food and drug intake.

REFERENCES

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