Diethylpropion HCl USP
25 mg Tablets

DESCRIPTION
Diethylpropion hydrochloride is available for oral administration in immediate-release tablets containing 25 mg diethylpropion hydrochloride. The inactive ingredients in each immediate-release tablet are: crospovidone, lactose, magnesium stearate, starch pregelatinized and tarteric acid. Diethylpropion hydrochloride is a sympathomimetic agent.

The name for diethylpropion hydrochloride is 1-phenyl-2-diethylamino-1-propanone hydrochloride.

Its chemical structure is:

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\text{H} \quad \text{O} \\
\text{C} \quad \text{H} \\
\text{N} \quad \text{H} \\
\text{C} \quad \text{H} \\
\text{C} \quad \text{H}
\]

CLINICAL PHARMACOLOGY
Diethylpropion hydrochloride is a sympathomimetic amine with some pharmacologic activity similar to that of other prototype drugs of this class used in obesity, the amphetamines. Actions include some central nervous system stimulation and elevation of blood pressure. Tolerance has been demonstrated with all drugs of this class in which these phenomena have been looked for.

Drugs of this class used in common are known as "anorexics" or "anorexigenics." It has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. For example, other central nervous system actions or metabolic effects may be involved. Adulthood subjects instructed in dietary treatment and managed with "anorexics" lose more weight on 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 averages some fraction of a pound a week. However, individual weight loss may vary substantially from patient to patient. The rate of weight loss is greatest in the first week of therapy for both drug and placebo subjects, and tends to decrease in succeeding weeks. The possible origins of the increased weight loss due to the various drug effects are not established. The amount of weight loss and 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 relationship, the population treated, and the diet prescribed. Studies do not provide a basis for assigning relative importance of the drug and non-drug factors on weight loss.

The natural history of obesity is measured in years, whereas most studies cited are restricted to a few weeks or months. Thus, the total impact of induced weight loss over that of diet alone is unknown. Diethylpropion is rapidly absorbed from the GI tract after oral administration and is extensively metabolized through a complex pathway of biotransformation involving N-dealkylation and reduction. Many of these metabolites are biologically active and may participate in the therapeutic action of diethylpropion hydrochloride. Due to the varying lipid solubility of these metabolites, their circulating levels are affected by urinary pH. Diethylpropion and/or its active metabolites are believed to cross the blood/brain barrier and the placenta.

Diethylpropion and its metabolites are excreted mainly by the kidney. It has been reported that between 75-100% of the dose is recovered in the urine within 48 hours after dosing. Using a phosphorescence assay that is specific for basic compounds containing a benzyl group, the plasma half-life of the amine metabolite is estimated to be between 4 to 6 hours.

The extended-release characteristics of the diethylpropion hydrochloride 75 mg formulation have been demonstrated in studies in humans in which plasma levels of diethylpropion-related materials were measured by phosphorescence analysis. Plasma levels obtained with the 75 mg diethylpropion hydrochloride formulation administered once daily indicated a more gradual release than an immediate-release formulation (three 25 mg tablets given in a single dose).

The diethylpropion hydrochloride 75 mg extended-release formulation has not shown superiority in effectiveness to the immediate-release formulation in terms of weight loss or improved metabolic parameters such as insulin resistance.

INDICATIONS AND USAGE
Diethylpropion hydrochloride is indicated in the management of exogenous obesity as a short-term (up to 12 weeks) adjunct to dieting or low calorie diet for weight reduction regimen in calorie-restricted patients with an initial body mass index (BMI) of 30 kg/m² or higher and who have not responded to appropriate diet and exercise alone. A diet is a balanced diet of 1200 to 1500 calories per day and exercise is at least 20 minutes per day at least 5 days per week. Ineffective patients should be discontinued after 4 weeks.

In a case-controlled epidemiological study, the use of anorectic agents, including diethylpropion, was associated with an increased risk of developing pulmonary hypertension, a rare, but often fatal disorder. The use of anorectic agents for longer than 2 months was associated with a 23-fold increase in the risk of developing pulmonary hypertension. Increased risk of pulmonary hypertension with repeated courses of therapy cannot be excluded. 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, diethylpropion hydrochloride should be immediately discontinued, and the patient should be evaluated for the possible presence of pulmonary hypertension.

Valvular heart disease associated with the use of anorectic agents such as fenfluramine and dexfenfluramine has been reported. Possible contributing factors include use for extended periods of time, higher than recommended doses, and/or use in combination with other anorectic drugs. Valvulopathy has been very rarely reported with diethylpropion hydrochloride. Monotherapy, but the causal relationship remains uncertain. The potential risk of possible serious adverse effects such as valvular heart disease and pulmonary hypertension should be considered against the potential benefit of weight loss. Baseline cardiovascular evaluation should be considered to detect preexisting valvular heart diseases or pulmonary hypertension prior to initiation of diethylpropion hydrochloride treatment. Diethylpropion hydrochloride is not recommended in patients with known heart murmur or valvular heart disease. Echocardiogram during and after treatment could be useful for detecting any valvular disorders which may occur.

To limit unwanted exposure and risks, treatment with diethylpropion hydrochloride should be continued only if the patient has satisfactory weight loss within the first 4 weeks of treatment (e.g., weight loss of at least 4 pounds, or as determined by the physician and patient).

Diethylpropion hydrochloride is not recommended for patients who used any anorectic agents within the prior year.

If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Diethylpropion hydrochloride should be used with caution in patients who are pregnant or lactating. Women who may become pregnant should be advised of the potential hazard to the fetus due to diethylpropion hydrochloride. 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.

Information for Patient
The patient should be cautioned about concomitant use of other CNS-active drugs and diethylpropion hydrochloride. (See WARNINGS.) The patient should be advised to observe caution when driving or engaging in any potentially hazardous activity.

Laboratory Tests
None.

Drug Interactions
Because diethylpropion hydrochloride is a monoamine, hypertension may result when this agent is used with monoamine oxidase (MAO) inhibitors (see CONTRAINDICATIONS). Efficacy of diethylpropion with other anorectic agents has not been studied and the combined use may have the potential for serious cardiac problems; therefore, the concomitant use with other anorectic agents is contraindicated.

Antibiotic drug requirements (i.e., insulin) may be altered. Concomitant use with general anesthetics may result in arrhythmias. The pressor effects of diethylpropion and those of other drugs may be additive when the drugs are used concomitantly; conversely, diethylpropion may interfere with antihypertensive drugs (e.g., quinidine, α-methyldopa). Concomitant use of phenothiazines may antagonize the anorectic effect of diethylpropion.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
There are no long-term animal studies of diethylpropion hydrochloride. Reproduction studies have been done in rats at doses up to 1.6 times the human dose (based on mg/m²) and have revealed no evidence of impaired fertility or harm to the fetus due to diethylpropion hydrochloride. 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. Spontaneous reports of congenital malformations have been recorded in humans, but no causal relationship to diethylpropion hydrochloride has been established.

Nonteratogenic Effects
Abuse with diethylpropion hydrochloride during pregnancy may result in withdrawal symptoms in the human neonate.

Nursing Mothers
Since diethylpropion hydrochloride and/or its metabolites have been shown to be excreted in human milk, caution should be exercised when diethylpropion hydrochloride is administered to a nursing woman.

Geriatric Use
Clinical studies of diethylpropion hydrochloride did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. For elderly patients, it may be necessary to have decreased renal function, care should be taken in dose selection, and it may be necessary to monitor renal function.

Pediatric Use
Since safety and effectiveness in pediatric patients below the age of 16 have not been established, diethylpropion hydrochloride is not recommended for use in pediatric patients 16 years of age and under.

ADVERSE REACTIONS
Cardiovascular: Precordial pain, arrhythmia (including ventricular), ECG changes, tachycardia, elevation of blood pressure, palpitation and rare reports of pulmonary hypertension. Valvular heart disease associated with the use of amphetamines has been reported; however, it is not clear whether this effect is independent or especially when used in combination, have been reported. Valvulopathy has been
very rarely reported with diethylpropion hydrochloride monotherapy, but the causal relationship remains uncertain.

Central Nervous System: In a few epileptics an increase in convulsive episodes has been reported; rarely psychotic episodes at recommended doses; dyskinesia, blurred vision, overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, mydriasis, drowsiness, malaise, headache, and cerebrovascular accident

Gastrointestinal: Vomiting, diarrhea, abdominal discomfort, dryness of the mouth, unpleasant taste, nausea, constipation, other gastrointestinal disturbances

Allergic: Urticaria, rash, ecchymosis, erythema

Endocrine: Impotence, changes in libido, gynecomastia, menstrual upset

Hematopoietic System: Bone marrow depression, agranulocytosis, leukopenia

Miscellaneous: A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dysuria, dyspnea, hair loss, muscle pain, increased sweating, and polyuria.

DRUG ABUSE AND DEPENDENCE

Diethylpropion hydrochloride is a Schedule IV controlled substance. Diethylpropion hydrochloride has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse 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 varying degrees of psychological dependence and social dysfunction which, in the case of certain drugs, may be severe. 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.

OVERDOSAGE

Manifestations of acute overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, and mydriasis. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include tachycardia, arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in convulsions, coma and death. The reported oral LD50 for mice is 600 mg/kg, for rats is 250 mg/kg and for dogs is 225 mg/kg. Management of acute diethylpropion hydrochloride 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. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates diethylpropion hydrochloride overdose.

DOSEAGE AND ADMINISTRATION

Diethylpropion hydrochloride immediate-release: One immediate-release 25 mg tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger.

Geriatric Use: This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See PRECAUTIONS, Geriatric Use.)

HOW SUPPLIED

25 mg immediate-release tablets in bottles of 30, 60 and 100.

Bottles of 30, NDC 10702-044-03

Bottles of 60, NDC 10702-044-06

Bottles of 100, NDC 10702-044-01

Each white to off-white, round flat tablets debossed “K 44” on one side and plain on the other side. Keep tightly closed. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Rx only

Manufactured by: KVK-TECH, INC.

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Item ID # 6129-03 01/11

Manufacturer’s Code: 10702

KVK

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