5.3 Valvular Heart Disease

Presence of pulmonary hypertension should be evaluated for patients who develop new, unexplained symptoms of dyspnea, lower extremity edema. Patients should be advised that symptoms may include angina pectoris, syncope or other symptoms of cardiovascular disease.

5.2 Primary Pulmonary Hypertension

Primary pulmonary hypertension (PPH) – a rare, often fatal disease of the lungs – has been reported to occur in patients receiving a combination of phentermine with fenfluramine or dexfenfluramine. The possibility of an association between PPH and the use of ADIPEX-P® alone cannot be ruled out; there have been rare cases of PPH in patients who reportedly have taken phentermine alone. The initial symptom of PPH is usually dyspnea. Other initial symptoms may include angina pectoris, syncope or lower extremity edema. Patients should be advised to report immediately any deterioration in exercise tolerance. Treatment should be discontinued in patients who develop new, unexplained symptoms of dyspnea, angina pectoris, syncope or lower extremity edema, and patients should be evaluated for the possible presence of pulmonary hypertension.

5.5 Valvular Heart Disease

Serious regurgitant cardiac valvular disease, primarily affecting the mitral, aortic and/or tricuspid valves, has been reported in otherwise healthy persons who had taken a combination of phentermine with fenfluramine or dexfenfluramine for weight loss. The possible role of phentermine in the etiology of these valvulopathies has not been established and their course in individuals after the drugs are stopped is not known. The possibility of an association between valvular heart disease and the use of ADIPEX-P® alone cannot be ruled out; there have been rare cases of valvular heart disease in patients who reportedly have taken phentermine alone.

5.4 Development of Tolerance, Discontinuation in Case of Tolerance

When tolerance to the anorectic effect develops, the recommended dosage increase should not be made in an attempt to increase the effect; rather, the drug should be discontinued.

5.5 Effect on the Ability to Engage in Potentially Hazardous Tasks

ADIPEX-P® 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.

5.6 Risk of Abuse and Dependence

ADIPEX-P® is related chemically and pharmacologically to amphetamine (d- and dl-amphetamine) and to other related stimulant drugs that have been extensively abused. The possibility of abuse of ADIPEX-P® should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. See Drug Abuse and Dependence (9) and Overdose (10). The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose.

5.7 Usage With Alcohol

Concomitant use of alcohol with ADIPEX-P® may result in an adverse drug reaction.

5.8 Use in Patients With Hypertension

Use caution in prescribing ADIPEX-P® for patients with even mild hypertension (risk of increase in blood pressure).

5.9 Use in Patients on Insulin or Oral Hypoglycemic Medications for Diabetes Mellitus

A reduction in insulin or oral hypoglycemic medications in patients with diabetes mellitus may be required.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

• Primary pulmonary hypertension [see Warnings and Precautions (5.2)]
• Valvular heart disease [see Warnings and Precautions (5.3)]
• Effect on the ability to engage in potentially hazardous tasks [see Warnings and Precautions (5.5)]

Withdrawal effects following prolonged high dosage administration [see Drug Abuse and Dependence (9.3)]

The following adverse reactions have been identified:

Cardiovascular

Primary pulmonary hypertension and/or regurgitant cardiac valvular disease, palpitation, tachycardia, elevation of blood pressure, ischemic events.

Central Nervous System

Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis.

Gastrointestinal

Dryness of the mouth, unpleasant taste, diarrhoea, constipation, other gastrointestinal disturbances.

Allergic

Urticaria.

Endocrine

Impotence, changes in libido.

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors

Use of ADIPEX-P® is contraindicated during or within 14 days following the administration of monoamine oxidase inhibitors because of the risk of hypertensive crisis.

7.2 Alcohol

Concomitant use of alcohol with ADIPEX-P® may result in an adverse drug reaction.

7.3 Insulin and Oral Hypoglycemic Medications

Requirements may be altered [see Warnings and Precautions (5.9)].

7.4 Adrenergic Neuron Blocking Drugs

ADIPEX-P® may decrease the hypotensive effect of adrenergic neuron blocking drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

ADIPEX-P® is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to obligatory weight gain that occurs in maternal tissues during pregnancy. Phentermine has pharmacologic activity similar to amphetamine (d- and dl-amphetamine) [see Clinical Pharmacology (12.1)]. Animal reproduction studies have not been conducted with phentermine. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

It is not known if ADIPEX-P® is excreted in human milk; however, other amphetamines are present in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because pediatric obesity is a chronic condition requiring long-term treatment, the use of this product, approved for short-term therapy, is not recommended.

8.5 Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually 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. 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.

8.6 Renal Impairment

Based on the reported excretion of phentermine in urine, exposure increases can be expected in patients with renal impairment [see Clinical Pharmacology (12.9)].

Use caution when administering ADIPEX-P® to patients with renal impairment. In patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²), limit the dosage of ADIPEX-P® to 15 mg daily [see Dosage and Administration (2.2)]. ADIPEX-P® has not been studied in patients with eGFR less than 15 mL/min/1.73 m² including end-stage renal disease requiring dialysis; avoid use in these populations.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Phentermine is a Schedule IV controlled substance.

9.2 Abuse

Phentermine is related chemically and pharmacologically to the amphetamines. Amphetamines and other stimulant drugs have been extensively abused and the possibility of abuse of phentermine should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program.

9.3 Dependence

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 of these drugs to many times that recommended. Abrupt cessation following prolonged high dosage administration results in a syndrome of 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. A severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

10 OVERDOSAGE

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

10.1 Acute Overdose

Manifestations of acute overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, and panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include tachycardia, arrhythmia, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning usually terminates in convulsions and coma. Management of acute phentermine hydrochloride intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with monoaminergic drugs suggests that the least amount of feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose.

10.2 Chronic Intoxication

Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. See Drug Abuse and Dependence (9.3).

11 DESCRIPTION

Phentermine hydrochloride USP is a sympathomimetic amine of the phenylalanine series. It has the chemical name of α-phenyl-1-methyl-2-propanol. Dimethylphenethylamine hydrochloride, the structural formula is as follows:

- CH₃
- C₆H₅-NH₂ + HCl
- M.W. 185.7

Phentermine hydrochloride is a white, odorless, hygroscopic, crystalline powder which is soluble in water and lower alcohols, slightly soluble in chloroform and insoluble in ether.

ADIPEX-P®, an anorectic agent for oral administration, is available as a capsule or tablet containing 37.5 mg of phentermine hydrochloride (equivalent to 30 mg of phentermine base).

ADIPEX-P® Capsules contain the inactive ingredients Black Iron Oxide, Corn Starch, D&C Red #33, FD&C Yellow 6, and Magnesium Stearate.
ADIPEX-P® Tablets contain the inactive ingredients Corn Starch, Lactose (Anhydrous), Magnesium Stearate, Microcrystalline Cellulose, pregelatinized Starch, Sucrose, and FD&C Blue #1.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
ADIPEX-P® is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class used in obesity, amphetamine (d- and dl-amphetamine). Drugs of this class used in obesity are commonly known as “anorectics” or “anorexigenics.” It has not been established that the primary action of such drugs in treating obesity is one of appetite suppression since other central nervous system actions, or metabolic effects, may also be involved.

12.2 Pharmacodynamics
Typical actions of amphetamines 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.

12.3 Pharmacokinetics
Following the administration of phentermine, phentermine reaches peak concentrations (Cmax) after 3.0 to 4.4 hours. Drug Interactions

In a single-dose study comparing the exposures after oral administration of a combination capsule of 15 mg phentermine and 92 mg topiramate to the exposures after oral administration of a 15 mg phentermine capsule or a 92 mg topiramate capsule, there is no significant topiramate exposure change in the presence of phentermine. However, in the presence of topiramate, phentermine Cmax and AUC increase 13% and 42%, respectively.

Specific Populations
Renal Impairment
Cumulative urinary excretion of phentermine under uncontrolled urinary pH conditions was 62% to 85%. Systemic exposure to phentermine may increase up to 91%, 45%, and 22% in patients with severe, moderate, and mild renal impairment, respectively [see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies have not been performed with phentermine to determine the potential for carcinogenesis, mutagenesis or impairment of fertility.

14 CLINICAL STUDIES

In relatively short-term clinical trials, adult obese subjects instructed in dietary management and treated with “anorectic” drugs lost more weight on the average than those treated with placebo and diet. 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 origins of the increased weight loss due to the various drug effects are 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 drugs 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 over several 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.

16 HOW SUPPLIED/STORAGE AND HANDLING
Available in tablets and capsules containing 37.5 mg phentermine hydrochloride (equivalent to 30 mg phentermine base). Each blue and white, oblong, speckled, scored tablet is debossed with “ADIPEX-P®” and “9”-“9”. The #3 capsule has an opaque white body and an opaque bright blue cap. Each capsule is imprinted with “ADIPEX-P®” - “37.5” on the cap and two stripes on the body using dark blue ink.

Tablets are packaged in bottles of 30 (NDC 57844-009-56); 100 (NDC 57844-009-01); and 1000 (NDC 57844-009-10).

Capsules are packaged in bottles of 100 (NDC 57844-019-01).

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

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

17 PATIENT COUNSELING INFORMATION

Patients must be informed that ADIPEX-P® is a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and, if necessary, restrictions in the management of exogenous obesity, and that coadministration of phentermine with other drugs for weight loss is not recommended [see Indications and Usage (1) and Warnings and Precautions (5)].

Patients must be instructed on how much ADIPEX-P® to take, and when and how to take it [see Dosage and Administration (2)].

Advise pregnant women and nursing mothers not to use ADIPEX-P® [see Use in Specific Populations (8.1, 8.3)].

The patients must also be informed about

• the risk of dependence and the potential consequences if they suspect development of tolerance [see Warnings and Precautions (5.4) and Drug Interactions (7)];
• the risk of interactions [see Contraindications (4), Warnings and Precautions (5) and Drug Interactions (7)];
• the risk of an increase in blood pressure [see Warnings and Precautions (5.8) and Adverse Reactions (6)];
• the risk of serious cardiovascular heart disease [see Warnings and Precautions (5.3)];
• the potential for developing tolerance and actions if they suspect development of tolerance [see Warnings and Precautions (5.4) and Contraindications (4)];
• the risk of dependence and the potential consequences of abuse [see Warnings and Precautions (5.8), Drug Abuse and Dependence (9), and Overdosage (10)];

Tell patients to keep ADIPEX-P® in a safe place to prevent theft, accidental overdose, misuse or abuse. Selling or giving away ADIPEX-P® may harm others and is against the law.

All trademarks are the property of their respective owners. Manufactured In Croatia By: Pliva Hrvatska d.o.o. Zagreb, Croatia

Manufactured For: Teva Select Brands, Horsham, PA 19044 Division of Teva Pharmaceuticals USA, Inc. Rev. Z 3/2017