DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 12427/S-026 **SUPPLEMENT APPROVAL**

Pharmacia & Upjohn Company
c/o Pfizer, Inc., Agent
Attention: Carol J. Haley
Director, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Ms. Haley:

Please refer to your supplemental new drug application dated and received August 28, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Didrex (benzphetamine hydrochloride) Tablets, 50 mg.

This "Changes Being Effected" supplemental new drug application provides for the following changes in the labeling so as to furnish adequate information for the safe and effective use of the drug.

New information is underlined for clarity only and should not be underlined in the package insert. New information that utilizes **bolded** font should be **bolded** in the package insert.

- **To the INDICATIONS AND USAGE section:**

  DIDREX Tablets are indicated in the management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial body mass index (BMI) of 30 kg/m^2 or higher who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone. 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 (kg), divided by the patient's height, in meters (m), squared. Metric conversions are as follows: pounds ÷2.2 =kg; inches ×0.0254 = meters. The limited usefulness of agents of this class (See CLINICAL PHARMACOLOGY) should be weighed against possible risks inherent in their use such as those described below.

BODY MASS INDEX (BMI), kg/m^2
Height (feet, inches)

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

DIDREX Tablets are indicated for use as monotherapy only.

- **To the WARNINGS section**

DIDREX Tablets should not be used in combination with other anorectic agents, including prescribed drugs, over-the-counter preparations and herbal products.

In a case-control epidemiological study, the use of anorectic agents was associated with an increased risk of developing pulmonary hypertension, a rare, but often fatal disorder. The use of anorectic agents for longer than three 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. It should be noted that benzphetamine was not specifically studied in this case-control study.

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, DIDREX Tablets 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 some anorectic agents such as fenfluramine and dexfenfluramine has been reported. Possible contributing factors include use for extended periods of time, higher than recommended dose, and/or use in combination with other anorectic drugs. However, no cases of this valvulopathy have been reported when benzphetamine has been used alone.

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 pre-existing valvular heart diseases or pulmonary hypertension prior to initiation of benzphetamine treatment. DIDREX Tablets are 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 unwarranted exposure and risks, treatment with DIDREX Tablets should be continued only if the patient has satisfactory weight loss within the first 4 weeks of treatment (i.e., weight loss of at least 4 pounds, or as determined by the physician and patient).

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

DIDREX Tablets are not recommended for severely hypertensive patients or for patients with symptomatic cardiovascular disease including arrhythmias.

DIDREX Tablets are not recommended for patients who used any anorectic agents within the prior year.

- **To the PRECAUTIONS section, Drug Interactions subsection:**

Drug Interactions: Efficacy of DIDREX Tablets in combination with other anorectic agents has not been studied and the combined use may have the potential for serious cardiac problems.

Hypertensive crises have resulted when sympathomimetic amines have been used concomitantly or within 14 days following use of monoamine oxidase inhibitors. DIDREX should not be used concomitantly with other CNS stimulants.

Amphetamines may decrease the hypotensive effect of antihypertensives. Amphetamines may enhance the effects of tricyclic antidepressants.

Urinary alkalinizing agents increase blood levels and decrease excretion of amphetamines. Urinary acidifying agents decrease blood levels and increase excretion of amphetamines.

- **To the PRECAUTIONS section, Pediatric Use subsection:**

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Use of benzphetamine hydrochloride is not recommended in individuals under 12 years of age.

- **To the ADVERSE REACTIONS section, Cardiovascular subsection:**

Cardiovascular
Palpitation, tachycardia, elevation of blood pressure.

There have been isolated reports of cardiomyopathy and ischemic cardiac events associated with chronic amphetamine use.

Valvular heart disease associated with the use of some anorectic agents such as fenfluramine and dexfenfluramine, both independently and especially when used in combination with other anorectic drugs, have been reported. However, no cases of this valvulopathy have been reported when DIDREX Tablets have been used alone.

We have completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below:

- **To the PRECAUTIONS section, Geriatric Use subsection:**

  Clinical studies of DIDREX Tablets did not include sufficient numbers of subjects aged 65 and over to establish safety and efficacy in this population. ~~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, 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.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed text for the package insert. These revisions are terms of the NDA approval. For administrative purposes, please designate this submission, "SPL for approved NDA 12427/S-026.

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-12427	SUPPL-26	PHARMACIA AND UPJOHN CO	DIDREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC C COLMAN
02/05/2010