CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040227

Trade Name : PHENTERMINE HYDROCHLORIDE CAPSULES USP 30MG

Generic Name: Phentermine Hydrochloride Capsules USP 30mg

Sponsor : Amide Pharmaceutical, Inc.

Approval Date: June 18, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040227

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040227

APPROVAL LETTER

ANDA 40-227

JUN 18 1997

Amide Pharmaceuticals, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

Dear Sir:

This is in reference to your abbreviated new drug application dated December 11, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Phentermine Hydrochloride Capsules USP, 30 mg.

Reference is also made to your amendments dated April 24 and May 12, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Phentermine Hydrochloride Capsules USP, 30 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Fastin® Capsules, 30 mg of SmithKline Beecham Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 6/18/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040227

FINAL PRINTED LABELING

Amide
PHARMACEUTICAL, INC.

NDC 52152-160-02

PHENTERMINE HYDROCHLORIDE CAPSULES, USP
30 mg

C IV

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

Each Capsule Contains:
Phentermine hydrochloride 30 mg
(equivalent to 24 mg of Phentermine)

Usual Dose: 1 capsule at approximately 2 hours after breakfast. See accompanying prescribing information.

Dispense in a tight container as defined in the USP/NF.

Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Store at controlled room temperature 15°-30°C (59°-86°F).

JUN 18 1997

N 3 52152-160-02 7

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424

Conrol No.:
Exp. Date:

7862-00

Amide
PHARMACEUTICAL, INC.

NDC 52152-160-05

PHENTERMINE HYDROCHLORIDE CAPSULES, USP
30 mg

C IV

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

Each Capsule Contains:
Phentermine hydrochloride 30 mg
(equivalent to 24 mg of Phentermine)

Usual Dose: 1 capsule at approximately 2 hours after breakfast. See accompanying prescribing information.

Dispense in a tight container as defined in the USP/NF.

Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Store at controlled room temperature 15°-30°C (59°-86°F).

N 3 52152-160-05 8

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424

JUN 18 1997

Conrol No.:
Exp. Date:

7863-00

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. Fatal poisoning usually terminates in convulsions and coma.

Management of acute phentermine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard. Acidification of the urine increases phentermine excretion. Intravenous phentolamine has been suggested for possible acute, severe hypertension, if this complicates phentermine overdosage.

DOSAGE AND ADMINISTRATION
Dosage should be individualized to obtain an adequate response with the lowest effective dose.

Usual Adult Dosage:
Exogenous Obesity: One Capsule at approximately 2 hours after breakfast for appetite control. Administration of one capsule (30 mg) daily has been found to be adequate in depression of the appetite for 12 to 14 hours.

Late evening medication should be avoided because of the possibility of resulting insomnia.

Phentermine hydrochloride is NOT recommended for use in children under 12 years of age.

HOW SUPPLIED
Phentermine hydrochloride capsules USP, 30 mg (equivalent to 24 mg phentermine base) are size 3 Rich Yellow Opaque capsules with imprint "A160" on cap and body and are available in bottles of 100 (NDC 52152-160-02) and 1000 (NDC 52152-160-05).

Dispense in a tight container as defined in the USP/NF.

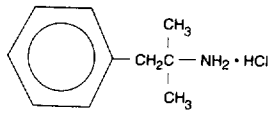
Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

4/97

MANUFACTURED BY:
AMIDE PHARMACEUTICAL, INC.
LITTLE FALLS, NJ 07424

DESCRIPTION
Phentermine hydrochloride, USP has the chemical name of α, α-Dimethylphenethylamine hydrochloride. The structural formula is as follows:



$C_{10}H_{15}N \cdot HCl$ 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.

7861-00

PHENTERMINE HYDROCHLORIDE CAPSULES, USP 30 mg

Phentermine hydrochloride, an anorectic agent for oral administration, is available as a capsule containing 30 mg of phentermine hydrochloride (equivalent to 24 mg of phentermine base).

Phentermine hydrochloride capsules contain the inactive ingredients D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #3, FD&C Red #40 Aluminum Lake, Gelatin, Lactose Monohydrate, Magnesium Stearate, Pharmaceutical Glaze, Propylene Glycol, Silicon Dioxide, Sodium Lauryl Sulfate, Synthetic Black Iron Oxide, Talc and Titanium Dioxide.

CLINICAL PHARMACOLOGY
Phentermine hydrochloride is a sympathomimetic amine with pharmacologic 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 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, for example.

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 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 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.

INDICATIONS AND USAGE
Phentermine hydrochloride capsules 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. The limited usefulness of agents of this class (see CLINICAL PHARMACOLOGY) should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS
Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

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.

Phentermine hydrochloride 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.

Usage in Pregnancy: Safe use in pregnancy has not been established. Use of phentermine hydrochloride by women who are or who may become pregnant, and those in the first trimester of pregnancy, requires that the potential benefit be weighed against the possible hazard to mother and infant.

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

Usage with Alcohol: Concomitant use of alcohol with phentermine hydrochloride may result in an adverse drug interaction.

PRECAUTIONS
Caution is to be exercised in prescribing phentermine hydrochloride for patients with even mild hypertension.

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

Phentermine hydrochloride may decrease the hypotensive effect of guanethidine.

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

ADVERSE REACTIONS
Cardiovascular: Palpitation, tachycardia, elevation of blood pressure.

Central Nervous System: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, rarely psychotic episodes at recommended doses.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE: Phentermine hydrochloride is a schedule IV controlled substance. Phentermine hydrochloride is related chemically and pharmacologically to the amphetamines. Amphetamines and related stimulant drugs have been extensively abused, and the possibility of abuse of phentermine hydrochloride 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 intoxications is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSAGE
Manifestations of acute overdosage with phentermine include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040227

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-227

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceuticals, Inc.
Attention: Jasmine Shah, M.S., R.Ph.
101 E. Main St.
Little Falls, NJ 07424

4. LEGAL BASIS FOR SUBMISSION
Conditions of use, active ingredients, route of administration, dosage form and strength of the proposed product is the same as Fastin Capsules manufactured by King Pharmaceuticals, Inc. for SmithKline Beecham Pharmaceuticals.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Phentermine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission	12/11/96
Ack. Letter	01/27/97
NA Letter	04/09/97
Amendment	04/24/97
New Correspondence	05/12/97

10. PHARMACOLOGICAL CATEGORY
Anorexiant

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM
Capsule

14. POTENCY
30 mg

15. CHEMICAL NAME AND STRUCTURE

NAME:	Phentermine HCl
CHEMICAL NAME:	Benzeneethanamine, 1,1 di-methyl, HCl
MOLECULAR WEIGHT:	185.70
CHEMICAL FORMULA:	$C^{10}H_{15}N.HCl$

16. RECORDS AND REPORTS
N/A

17. COMMENTS
See text of review.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
5/07/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040227

BIOEQUIVALENCE REVIEW(S)

ANDA 40-227

Amide Pharmaceuticals, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls NJ 07424

MAY 2 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Phentermine Hydrochloride Capsules USP, 30 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 30 1997

Phentermine Hydrochloride Capsules
30.0 mg
ANDA # 40-227
Reviewer: Jahnavi S. Kharidia
x:\wpfile\biofinal\40227w.497

Amide Pharmaceutical, Inc.
Little Falls, NJ 07424
Submission Date:
December 11, 1996

Review of a Waiver and Dissolution Data

Introduction:

Phentermine hydrochloride is a sympathomimetic amine. The drug is used as an "Anorectic" in the treatment of obesity. The weight loss is achieved by appetite control and dietary management.

Objective:

The firm is requesting a waiver of *in vivo* bioequivalence requirements for its phentermine hydrochloride capsules based on the fact that phentermine capsules, USP are rated AA in the orange book. The reference listed product is Fastin capsule, 30.0 mg manufactured by SmithKline Beecham Pharmaceutical, Inc. The firm has conducted dissolution testing on its test product and compared it to reference listed product.

Comments:

1. The drug product is classified AA in the list of the "Approved Drug Products With Therapeutic Equivalence Evaluations". Only an *in vitro* testing is required for bioequivalence.

2. The composition of test product is given in Attachment I.

3. The firm has submitted *in vitro* dissolution data at 20, 30 and 45 minutes comparing its Phentermine HCL capsules (30.0 mg) with the listed reference product, Fastin capsules (30.0 mg). The firm has used the following USP dissolution methodology.

Method:	USP XXIII, 2 (paddle) at 50 RPM
Medium:	900 mL Water
Number of Capsules:	12
Specifications:	NLT (b)4 Q) in 45 minutes
Test Product:	Phentermine Hydrochloride 30.0 mg Capsules

	lot # 6222A
Reference Product:	Fastin Capsules 30.0 mg
	lot #DM07

Time	Test		Reference	
(min)	Mean	CV (%)	Mean	CV (%)
20	98.1	1.0	92.0	2.4
30	100.6	0.9	95.6	2.3
45	102.6	0.8	100.9	1.2

4. The *in vitro* dissolution data conducted by Amide Pharmaceuticals, Inc. on its test product and reference product have been found acceptable.

Recommendations:

1. The Division of Bioequivalence agrees that the information submitted by Amide Pharmaceuticals, Inc. demonstrates that phentermine hydrochloride, USP 30.0 mg capsule falls under 21 CFR Section 320.22(d) of the Bioavailability / Bioequivalence Regulations. The waiver of the *in vivo* bioequivalence study for the test phentermine hydrochloride 30.0 mg capsules is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test capsule formulation to be bioequivalent to Fastin 30.0 mg capsules, manufactured by SmithKline Beecham Pharmaceutical, Inc.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water using USP XXIII Apparatus II (Paddle) at 50 RPM. The test should meet the following specification:

   Not less than (b)4 of phentermine hydrochloride is dissolved in 45 minutes.

3. The firm should be informed of the recommendations.

(b)4 - Confidential

Jahnavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE (b)4 - e 4/25/97
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur: (b)4 - Confidentiale 4/30/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc:ANDA # 40228 (original, duplicate), Kharidia, HFD-658HFD-630, Drug File, Division File

Attachment I

Comparative Formulation :
(Not to be released under FOI)

Ingredient	Test Product Amide's Phentermine HCL mg/capsule	Reference Product SmithKline Beecham's Fastin mg/capsule
Phentermine HCL, USP	30.0	30.0
Lactose Anhydrous, NF	(b)4 - Confidential Business	
Starch, Corn		
Magnesium Stearate		
Gelatin		
Talc		
Methylcellulose		
Polyethylene Glycol		
Shellac		
Titanium Dioxide		
Dye FDC Blue #1		
Sucrose		
Invert Sugar		
Propylene Glycol		