

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

75-640

Generic Name: Hydrochlorothiazide Capsules, 12.5mg

Sponsor: Mylan Pharmaceuticals Inc.

Approval Date: January 28, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-640

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-640

APPROVAL LETTER

ANDA 75-640

JAN 28 2000

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated May 27, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Hydrochlorothiazide Capsules, 12.5 mg.

Reference is also made to your amendments dated June 25, November 16, 1999 (2 submissions), and January 5, 2000.

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 Hydrochlorothiazide Capsules, 12.5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Microzide® Capsules, 12.5 mg, of Watson Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

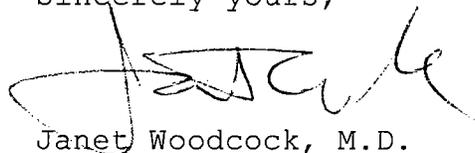
Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Janet Woodcock", written over a horizontal line.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-640

FINAL PRINTED LABELING

HCTZ:R1



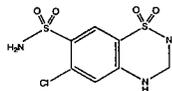
12.5 mg

**HYDROCHLOROTHIAZIDE
CAPSULES**

12.5 mg

Rx only

DESCRIPTION: Hydrochlorothiazide is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_2O_4S_2$; its molecular weight is 297.75; and its structural formula is:



It is a white, or practically white, crystalline powder, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Hydrochlorothiazide capsules, for oral administration, are available containing 12.5 mg of hydrochlorothiazide, USP. In addition, each capsule also contains the following inactive ingredients: colloidal silicon dioxide, D&C yellow No. 10 aluminum lake, FD&C blue No. 1 aluminum lake, FD&C blue No. 2 aluminum lake, FD&C red No. 40 aluminum lake, gelatin, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, pharmaceutical glaze, pregelatinized (corn) starch, propylene glycol, SDA-3A alcohol, silicon dioxide, sodium lauryl sulfate, synthetic black iron oxide and titanium dioxide.

CLINICAL PHARMACOLOGY: Hydrochlorothiazide blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen and chloride ions. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. Metabolic toxicity

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Pharmacokinetics and Metabolism: Hydrochlorothiazide is well absorbed (65% to 75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure.

Peak plasma concentrations are observed within 1 to 5 hours of dosing, and range from 70 to 490 ng/mL following oral doses of 12.5 to 100 mg. Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6 to 1.8 times higher in whole blood than in plasma. Binding to serum proteins has been reported to be approximately 40% to 68%. The plasma elimination half-life has been reported to be 6 to 15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5 to 100 mg, 55% to 77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged.

When hydrochlorothiazide capsules are administered with food, its bioavailability is reduced by 10%, the maximum plasma concentration is reduced by 20%, and the time to maximum concentration increases from 1.6 to 2.9 hours.

Pharmacodynamics: Acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

Thiazides do not affect normal blood pressure. Onset of action occurs within 2

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Thiazides do not affect normal blood pressure. Onset of action occurs within 2 hours of dosing, peak effect is observed at about 4 hours, and activity persists for up to 24 hours.

Clinical Studies: In an 87 patient 4-week double-blind, placebo controlled, parallel group trial, patients who received hydrochlorothiazide capsules had reductions in seated systolic and diastolic blood pressure that were significantly greater than those seen in patients who received placebo. In published placebo-controlled trials comparing 12.5 mg of hydrochlorothiazide to 25 mg, the 12.5 mg dose preserved most of the placebo-corrected blood pressure reduction seen with 25 mg.

INDICATIONS AND USAGE: Hydrochlorothiazide capsules are indicated in the management of hypertension either as the sole therapeutic agent, or in combination with other antihypertensives. Unlike potassium sparing combination diuretic products, hydrochlorothiazide may be used in those patients in whom the development of hyperkalemia cannot be risked, including patients taking ACE inhibitors.

Usage in Pregnancy: The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Diuretics are indicated in pro-

cannot be risked, including patients taking ACE inhibitors.

Usage in Pregnancy: The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Diuretics are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy. Dependent edema in pregnancy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances this edema may cause extreme discomfort which is not relieved by rest. In these cases a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS: Hydrochlorothiazide is contraindicated in patients with anuria. Hypersensitivity to this product or other sulfonamide derived drugs is also contraindicated.

WARNINGS: Diabetes and Hypoglycemia: Latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose.

Renal Disease: Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia.

PRECAUTIONS: Electrolyte and Fluid Balance Status: In published studies, clinically significant hypokalemia has been consistently less common in patients who received 12.5 mg of hydrochlorothiazide than in patients who received higher doses. Nevertheless, periodic determination of serum electrolytes should be performed in patients who may be at risk for the development of hypokalemia. Patients should be observed for signs of fluid or electrolyte disturbances, i.e., hyponatremia, hypochloremic alkalosis, and hypokalemia and hypomagnesemia.

Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis when severe cirrhosis is present, during concomitant use of corticosteroid or adrenocorticotrophic hormone (ACTH) or after prolonged therapy. Interference with adrenergic

of diuretics may provide relief and may be appropriate.

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Hypokalemia may develop, especially with brisk diuresis when severe cirrhosis is present, during concomitant use of corticosteroid or adrenocorticotropic hormone (ACTH) or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia and hypomagnesemia can provoke ventricular arrhythmias or sensitize or exaggerate the response of the heart to the toxic effects of digitalis. Hypokalemia may be avoided or treated by potassium supplementation or increased intake of potassium rich foods.

Dilutional hyponatremia is life-threatening and may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia: Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics.

Impaired Hepatic Function: Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver disease.

Parathyroid Disease: Calcium excretion is decreased by thiazides, and pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have

been observed in a few patients on prolonged thiazide therapy.

Drug Interactions: When given concurrently the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs: (Oral agents and insulin) dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive effect or potentiation.

Cholestyramine and Colestipol Resins: Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroid, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., Norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., Tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with hydrochlorothiazide.

Non-steroidal Anti-inflammatory Drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. When hydrochlorothiazide and non-steroidal anti-inflammatory agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

Drug/Laboratory Test Interactions: Thiazides should be discontinued before carrying out tests for parathyroid function (see PRECAUTIONS: Parathyroid Disease).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clasto-

discontinue before carrying out tests for parathyroid function (see PRECAUTIONS: Parathyroid Disease).

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Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

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.

Nonteratogenic Effects: Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers: Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Elderly Use: A greater blood pressure reduction and an increase in side effects may be observed in the elderly (i.e., >65 years) with hydrochlorothiazide. Starting treatment with the lowest available dose of hydrochlorothiazide (12.5 mg) is therefore recommended. If further titration is required, 12.5 mg in-

should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Elderly Use: A greater blood pressure reduction and an increase in side effects may be observed in the elderly (i.e., >65 years) with hydrochlorothiazide. Starting treatment when the lowest available dose of hydrochlorothiazide (12.5 mg) is therefore recommended. If further titration is required, 12.5 mg increments should be utilized.

ADVERSE REACTIONS: The adverse reactions associated with hydrochlorothiazide have been shown to be dose related. In controlled clinical trials, the adverse events reported with doses of 12.5 mg hydrochlorothiazide once daily were comparable to placebo. The following adverse reactions have been reported for doses of hydrochlorothiazide 25 mg and greater and, within each category, are listed in the order of decreasing severity.

Body as a Whole: Weakness.

Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Anaphylactic reactions, necrotizing angitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura.

Metabolic: Electrolyte imbalance (see PRECAUTIONS), hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Vertigo, paresthesia, dizziness, headache, restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis. (See WARNINGS.)

Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSSAGE: The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or arti-

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OVERDOSAGE: The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

The oral LD₅₀ of hydrochlorothiazide is greater than 10 g/kg in the mouse and rat.

DOSAGE AND ADMINISTRATION: For Control of Hypertension: The adult initial dose of hydrochlorothiazide capsules is one capsule given once daily whether given alone or in combination with other antihypertensives. Total daily doses greater than 50 mg are not recommended.

HOW SUPPLIED: Hydrochlorothiazide Capsules, 12.5 mg have a white opaque cap and a white opaque body that are axially printed with **MYLAN** over **810** in black ink on both the cap and body. They are available as follows:

NDC 0378-0810-01
bottles of 100 capsules
NDC 0378-0810-05
bottles of 500 capsules

**STORE AT ROOM
TEMPERATURE**

15° TO 30°C (59° TO 86°F).

**PROTECT FROM LIGHT,
MOISTURE AND FREEZING.**

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.



Mylan Pharmaceuticals, Inc.
Morgantown, WV 26505

REVISED NOVEMBER 1989
HCTZ-R1

SPECIM

**CENTER FOR DRUG
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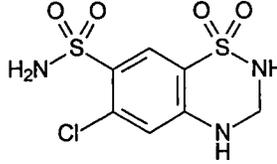
APPLICATION NUMBER:

75-640

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1 (one)
2. ANDA # 75-640
3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc
Attention: Frank R Sisto
781 Chestnut Ridge Road
P.O. Box 4310, Morgantown, WV 26504-4310
4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Microzide™ (hydrochlorothiazide) capsules, 12.5 mg.
Pursuant to Section 505(j)(2)(a)(vii) of the Fereal FD&CA, Mylan certifies that in its opinion and to the best of its knowledge, according to the patent information published by the FDA in that document entitled "Approved Drug Products With Therapeutic Equivalence Evaluations" (19th Edition through Cumulative Supplement 1), there are no patents that claim the listed drug referred to in this application. Mylan further certifies that the referenced product is covered by an exclusivity provision which expires December 27, 1999.
Mylan will market its Hydrochlorothiazide Capsules, 12.5 mg upon approval of this application, and expiration of the December 27, 1999 exclusivity.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Hydrochlorothiazide Capsules, 12.5mg
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Date of submission: May 27, 1999
10. PHARMACOLOGICAL CATEGORY
Diuretic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
Capsules
14. POTENCY
12.5 mg
15. CHEMICAL NAME AND STRUCTURE

Hydrochlorothiazide. 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide. C₇H₈ClN₃O₄S₂. 297.75. 58-93-5. Diuretic.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application is not approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is not approvable.

19. REVIEWER: DATE COMPLETED:
Liang-Lii Huang, Ph.D. October 14, 1999
Endorsed by Paul Schwartz, Ph.D./ 10/14/99

cc:

ANDA 75-640
ANDA DUP 75-640
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/ Liang-Lii Huang, Ph.D./10/14/99
HFD-627/ Paul Schwartz, Ph.D./ 10/14/99
HFD-617/Joseph Buccine/10/20/99

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October 20, 1999

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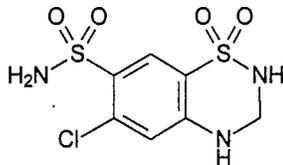
information

1. CHEMISTRY REVIEW NO. 2 (two)
2. ANDA # 75-640
3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc
Attention: Frank R Sisto
781 Chestnut Ridge Road
P.O. Box 4310, Morgantown, WV 26504-4310
4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Microzide™ (hydrochlorothiazide) capsules, 12.5 mg.
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8. SUPPLEMENT (s) PROVIDE (s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Date of submission: May 27, 1999
Amendment: November 16, 1999
Telephone amendment: January 5, 2000
10. PHARMACOLOGICAL CATEGORY
Diuretic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF (s)
DMF# _____

13. DOSAGE FORM
Capsules

14. POTENCY
12.5 mg

15. CHEMICAL NAME AND STRUCTURE
Hydrochlorothiazide. 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide. C₇H₈ClN₃O₄S₂. 297.75. 58-93-5.
Diuretic.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application is approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is approvable.

19. REVIEWER: Liang-Lii Huang, Ph.D. DATE COMPLETED: December 20, 1999
Endorsed by Paul Schwartz, Ph.D./ 12/21/99

cc:

ANDA 75-640
ANDA DUP 75-640
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Endorsements (Draft and Final with Dates):

HFD-627/ Liang-Lii Huang, Ph.D./12/20/99 *LLHuang 1/6/2000*
HFD-627/ Paul Schwartz, Ph.D./ 12/21/99 *PS 1/6/00*

V:\FIRMSAM\MYLAN\LTRS&REV\75640S00RV2.DOC
Date: January 6, 2000

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-640

**BIOEQUIVALENCE
REVIEW(S)**

Prabhon 2

2.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-640

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Hydrochlorothiazide 12.5-mg capsules,

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

You should incorporate the dissolution testing into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.01N Hydrochloric acid at 37°C using USP XXIII apparatus I (basket) at 100 rpm. The test drug should meet the following specifications:

Not less than $\frac{1}{Q}$ of the labeled amount of the Drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-640
ANDA DUPLICATE
DIVISION FILE
S.Pradhan

Endorsements: (Final with Dates)

HFD-652/ S Pradhan *SP*

HFD-650/ Y. Huang *YH 7/29/99*

HFD-617/ E. Hu *EH 8/4/99*

HFD-650/ D. Conner *DC 8/4/99*

V:\FIRMSAM\ Mylan \LTRS&REV\75640S2D.599

Printed in final on 7/27/99

BIOEQUIVALENCY -

Submission date: 5/27/99

1. Fasting Study (STF) *etc*

Strength: 12.5 mg
Outcome: AC

2. Fed Study (STP) *etc*

Strength: 12.5 mg
Outcome: AC

3. Study Amendment (STA) *etc*
(Attachment 1: Firm's
declaration regarding study data)

Submission date: 6/25/99

Outcome: AC

Outcome Decisions: AC - Acceptable

**APPEARS THIS WAY
ON ORIGINAL**

Hydrochlorothiazide 12.5 mg Capsules
ANDA #75-640
Reviewer: Sikta Pradhan
V:\firmsam\Mylan\lt&rev\75640S2D.599

Mylan Pharmaceuticals Inc.
Morgantown, WV
Submission Date:
May 27, 1999
June 25, 1999

REVIEW OF TWO IN-VIVO BIOEQUIVALENCE STUDIES AND DISSOLUTION DATA

BACKGROUND:

Hydrochlorothiazide blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted.

Hydrochlorothiazide is well absorbed (65%-75%) following oral administration of Microzide™. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure. Peak plasma concentrations are observed within 1 to 5 hours of dosing, and range from 70 to 490 ng/mL following oral doses of 12.5 to 100 mg. Plasma concentrations of hydrochlorothiazide are 1.6 or 1.8 times higher in whole blood than in plasma. Binding to serum proteins has been reported to be approximately 40% to 68%. The plasma elimination half-life has been reported to be 6 to 15 hours.

Hydrochlorothiazide is eliminated primarily by renal pathways. In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged.

When Microzide™ is administered with food, both its bioavailability and the maximum plasma concentration are reduced, and the time to maximum concentration is increased.

Hydrochlorothiazide is indicated in the management of hypertension either as the sole therapeutic agent, or in combination with other antihypertensives. Hydrochlorothiazide is contraindicated in the patients with anuria.

The adult initial dose of hydrochlorothiazide is one capsule given once daily whether given alone or in combination with other antihypertensives. Total daily dose greater than 50 mg is not recommended.

FASTING IN-VIVO BIOEQUIVALENCE STUDY #: HCTZ-98103

STUDY INVESTIGATORS AND CONTRACT LABORATORY: This bioequivalence study was conducted at _____
_____ The study medical directors were _____

INFORMED CONSENT AND IRB APPROVAL: The clinical portion of this study was conducted in compliance with the Institutional Review Board regulations.

STUDY OBJECTIVE

The objective of this study is to investigate the relative bioavailability of Mylan hydrochlorothiazide capsules to Microzide™ (Watson Laboratories) capsules following a single, oral 25-mg (2 x 12.5 mg) dose under fasting conditions.

STUDY DESIGN

This study was designed as a randomized, one-enrollment, two-period, two-treatment, two-sequence crossover study in 24 healthy subjects.

SUBJECT SELECTION CRITERIA

Sufficient healthy, non-smoking, adult, male volunteers were enrolled from the general population with the intent to complete twenty-four (24) subjects. Subjects who failed to complete the study ("Drop-outs") were not replaced without written authorization from Mylan.

Non-smoking, adult male volunteers aged 18-45 years and within 10% of their ideal body weight were selected for the study after physical examination, laboratory evaluation. The subjects had no history of significant chronic diseases, hepatitis or drug/alcohol abuse. Each subject signed a written informed consent.

STUDY SCHEDULE

Subjects were dosed in one enrollment. Subjects were housed on the evening prior to dosing until after the 24 hour blood draw. After a supervised overnight fast of at least

10 hours, subjects received a single, oral 25-mg (2 x 12.5 mg) dose of Mylan hydrochlorothiazide 12.5 mg capsules or Watson Microzide™ 12.5 mg capsules with 240 mL of water at ambient temperature.

Water was not permitted for 1 hour before and until 1 hour after dosing, but was allowed at all other times. Subjects received a standard meal 5 hours post-dose followed by an evening meal 10 hours after dosing and snacks at appropriate times thereafter. Subjects were released after the 24-hour blood draw, but were required to return to the clinic for the 28-hour blood draw.

Period 1 was dosed on January 17, 1999.

Period 2 was dosed on January 24, 1999.

Washout Period: Seven days

DRUG TREATMENTS

Treatment A = Watson Microzide™ Capsules (12.5 mg), Fasting
Administration 2 x 12.5 mg, Lot #827801, Exp. 8/00
Assay Potency: 101.7%

Treatment B = Mylan Hydrochlorothiazide Capsules (12.5 mg), Fasting
Administration 2 x 12.5 mg, Lot #2E005N, Exp. Not available
Theoretical Lot Size: _____ Capsules, Manufacturing Date: 12/2/98,
Assay Potency: 99.9%

For safety, blood pressure, pulse and respiration rates were measured before dosing and hourly for the first eight hours after dosing and at 12, 16, 24 and 28 hours after dosing.

Serial blood samples (1 x 10 mL) were collected at 0 hour (pre-dose) and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 16, 24 and 28 hours post-dose. Plasma was stored in suitably labeled tubes at $-70^{\circ}\text{C} \pm 15^{\circ}\text{C}$ until analysis.

ANALYTICAL METHODS

Samples were assayed in the Pharmacokinetics Laboratory of Mylan Pharmaceuticals Inc. from the period of January 26, 1999 to February 10, 1999.

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Results:

Of the twenty-eight (28) subjects who began the study, twenty-seven subjects completed both periods of the study. Subject #25 was discontinued from the study prior to dosing Period 2 due to an elevated blood pressure reading. A total of 5 post-dose adverse events (3 for reference drug and 2 for test drug) were experienced in 5 subjects during the study. All five of the adverse events were listed as possibly drug related. In addition, there were two pre-dose adverse events listed for this study. All events were listed mild in intensity.

The mean plasma concentrations of the reference and the test products are presented in Table 2.

Table 2. MEAN HYDROCHLOROTHIAZIDE PLASMA LEVELS
(27 SUBJECTS)

TIME (HR)	REFERENCE TREATMENT A (ng/mL)		TEST TREATMENT B (ng/mL)		REFERENCE / TEST A/B
	Mean	CV%	Mean	CV%	
0.00	0.00	-	0.00	-	----
0.33	0.63	387	1.55	253	0.41
0.67	42.65	71	41.85	65	1.02
1.00	95.40	52	96.75	46	0.99
1.33	119.33	41	137.27	38	0.87
1.67	131.49	31	151.93	30	0.86
2.00	135.36	25	149.87	24	0.93
2.50	125.37	22	133.73	19	0.94
3.00	115.26	21	118.73	14	0.97
4.00	89.66	23	92.05	16	0.97
6.00	48.97	22	51.15	19	0.96
8.00	31.75	24	33.19	21	0.96
12.00	18.37	25	19.05	24	0.96
16.00	12.94	26	13.18	28	0.98
24.00	8.56	39	8.80	26	0.97
28.00	6.01	57	5.98	56	1.00

The mean plasma concentrations versus time profiles (Table 2) are illustrated graphically in Figure 1 (attached).

TABLE 3. MEAN (%CV) HYDROCHLOROTHIAZIDE PHARMACOKINETIC PARAMETERS IN TWENTY-SEVEN *Subjects*

Parameter	Arithmetic Mean A = Microzide™	Arithmetic Mean B = Mylan	LSMEANS Ratio (B/A)*	90% Confidence Interval**
AUCL (ng x hr/mL)	873 (21.0)	919 (17.9)	1.06	101% - 110%
AUCI (ng x hr/mL)	1018 (22.8)	1053 (18.2)	1.04	100% - 109%
CPEAK (ng/mL)	148 (25.2)	162 (23.2)	1.09	102% - 117%
KEL (hr ⁻¹)	0.0571 (37.7)	0.0555 (15.3)	-----	-----
HALF (hr)	13.2 (25.6)	12.8 (17.0)	-----	-----
TPEAK (hr)	1.96 (25.3)	1.86 (25.3)	-----	-----

*Ratio (B/A) = e [LSMEAN of LNB - LSMEAN of LNA]

**Used natural Log Transformed Parameter

Mean of test (AUC_T/AUC_{inf}) = 0.873 (range: 0.794 - 0.913)

Mean of Ref. (AUC_T/AUC_{inf}) = 0.861 (range: 0.763 - 0.923)

The pharmacokinetic and statistical analyses (using SAS-GLM procedure for analysis of variance) were conducted on data obtained from 27 subjects. The mean pharmacokinetic parameters are shown in Table 3. The test and reference formulations demonstrated similar mean pharmacokinetic parameters and variability.

The 90% confidence intervals fall within 80-125% for the test to reference ratio for the natural log transformed parameters: LNAUCL, LNAUCI and LNCPEAK. This study demonstrates that Mylan's hydrochlorothiazide 12.5-mg capsules are bioequivalent to Watson Microzide™ 12.5 mg capsules following a single, oral 25 mg (2 x 12.5 mg) dose under fasting conditions.

II. IN-VIVO FOOD EFFECTS STUDY CONDUCTED UNDER FASTING AND NON FASTING CONDITIONS

PROTOCOL #:HCTZ-98104

A. Study Investigators and Contract Laboratory:

This bioequivalence study was conducted at

study medical directors were
M.D.

The

B. Informed Consent and RIB Approval:

The clinical portion of this study was conducted in compliance with the Institutional Review Board regulations and Informed Consent regulations.

Study Objective:

The objective of this study is to investigate the relative bioavailability of Mylan hydrochlorothiazide capsules to Microzide™ (Watson Laboratories) capsules following a single, oral 25-mg (2 x 12.5 mg) dose under fed conditions.

Study Design:

This study was designed as a randomized, one-enrollment, three-period, three-treatment, six-sequence crossover study in healthy subjects.

Subject Selection Criteria: As mentioned in the fasting study.

Study Schedule:

Period 1 was dosed on January 23, 1999, Period 2 was dosed on January 30, 1999 and Period 3 was dosed on February 6, 1999. The study subjects were healthy males between the ages of 18 to 44.

Drug Treatments:

Treatment A = Watson Microzide™ Capsules (12.5 mg)
2 x 12.5 mg, Administered with Food
Lot# 827801, Exp. 8/00
Commerical Lot
Assay Potency - 101.7%

Treatment B = Mylan Hydrochlorothiazide Capsules (12.5 mg)
2 x 12.5 mg, Administered with Food
Lot# 2E005N, Exp. TBE
Theoretical Lot Size - _____ Capsules
Manufacturing Date - 12/2/98
Assay Potency - 99.9%

Treatment C = Mylan Hydrochlorothiazide Capsules (12.5 mg)
2 x 12.5 mg, Fasting Administration
Lot #2E005N, Exp. TBE
Theoretical Lot Size - _____ Capsules
Manufacturing Date - 12/2/98
Assay Potency - 99.9%

Washout Period: Seven days

For safety, blood pressure, pulse and respiration rates were measured before dosing and for the first eight hours after dosing and at 12, 16, 24 and 28 hours. When the time of vital signs monitoring coincided with a blood draw, vital signs were taken approximately 10 minutes before the scheduled blood draw. Serial blood samples (1 x 10 mL) were collected at predose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 16, 24 and 28 hours post-dose. Plasma was stored in suitability labeled tubes at $-70^{\circ}\text{C} \pm 15^{\circ}\text{C}$ until analysis.

ANALYTICAL METHODOLOGY

Samples were assayed in the Pharmacokinetics Laboratory of Mylan Pharmaceuticals Inc. from the period of February 10, 1999 to February 22, 1999.

Method Validation: The analytical method used for the fed study was same as that was used in the fasting study. Furthermore, as the fasting and fed study samples were analyzed at the same time continuously, the assay validation of the fed study is the same as that of the fasting study.

In brief, the assay was _____ and had a limit of quantification of _____. During the course of the study, the between-day precision of the assay was _____ or less. Detailed information about stability can be found in Table 1.

RESULTS OF FOOD BIOEQUIVALENCE STUDY

Of the twenty-four subjects who began this study, twenty-one subjects completed all periods. Therefore, the statistical and pharmacokinetic analyses were conducted on plasma data of 21 subjects. Subject #8 failed to report for Period 2 due to personal reasons that were not study related. Subject #11 failed to report for Period 2 due to an adverse experience. Subject #20 was discontinued after Period 3 due to an adverse event for which he was given acetaminophen. There were 14 post-dose adverse events in 6 subjects (4 subjects due to test drug and 2 subjects due to reference drug) reported for this study. Of those, four were listed as possibly drug related. In addition, there was 1 predose adverse event reported for this study. Eleven of the events were listed as mild in severity and four were listed as moderate.

The mean plasma concentrations versus time points are presented in Table 4. The mean concentration profile is illustrated graphically in Figure 2 (attached). Mean plasma profiles are similar between Mylan hydrochlorothiazide capsules and Watson Microzide™ capsules under fed conditions. A summary of the pharmacokinetic parameters is shown in Table 5 below.

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 4. MEAN HYDROCHLOROTHIAZIDE PLASMA CONCENTRATIONS OF POST-PRANDIAL SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY (21 SUBJECTS)

TIME (HR)	REFERENCE TREATMENT A = Microzide ^R (Fed) (ng/mL)		TEST TREATMENT B = Mylan (Fed) (ng/mL)		RATIO (B/A)	TEST TREATMENT C = Mylan (Fasting) (ng/mL)	
	Mean	CV%	Mean	CV%		Mean	CV%
0.00	0.00	-	0.00	-	-----	0.00	----
0.33	0.83	458	0.76	458	0.92	6.19	141
0.67	2.56	244	7.38	144	2.88	63.02	68
1.00	19.31	103	26.82	93	1.39	125.88	45
1.33	40.40	68	51.87	57	1.28	144.54	32
1.67	67.96	39	78.89	39	1.16	152.08	28
2.00	93.18	30	102.87	28	1.10	148.35	27
2.50	112.54	24	112.76	24	1.00	134.54	27
3.00	124.32	21	118.11	20	0.95	121.01	26
4.00	113.58	20	101.21	18	0.89	92.73	24
6.00	64.62	20	61.89	26	0.96	50.41	24
8.00	37.43	22	36.27	24	0.97	32.8	27
12.00	20.22	23	20.16	24	1.00	19.14	26
16.00	13.78	35	13.94	26	1.01	13.71	28
24.00	8.99	36	8.93	30	0.99	8.88	31
28.00	7.23	38	7.24	36	1.00	7.07	48

Test to reference ratios for the two fed treatments (A and B) are within 0.80 and 1.20 for the natural log transformed parameters LNAUCL, LNAUCI and LNCPEAK. This study demonstrates that Mylan's 12.5 mg hydrochlorothiazide capsules are bioequivalent to Watson MicrozideTM 12.5 mg capsules following a single, oral 25 mg (2 x 12.5 mg) dose under fed conditions.

TABLE 5. PHARMACOKINETIC PARAMETERS IN TWENTY-ONE HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 25 MG (2 X 12.5 MG) DOSE OF HYDROCHLOROTHIAZIDE CAPSULES IN A FOOD STUDY

Parameter	Arithmetic Mean A = Microzide ^R (Fed)	Arithmetic Mean B = Mylan (Fed)	Arithmetic Mean C = Mylan (Fasting)	LSMEANS* Ratio (B/A)
AUCL (ng x hr/mL)	874 (16.8)	859 (16.5)	947 (22.6)	0.97
AUCI (ng x hr/mL)	1031 (19.7)	1014 (19.4)	1093 (25.4)	0.97
CPEAK (ng/mL)	131 (15.3)	124 (18.7)	167 (27.7)	0.89
KEL (hr ⁻¹)	0.0589 (37.7)	0.0533 (23.8)	0.0557 (22.2)	-----
HALF (hr)	13.4 (43.0)	13.8 (26.7)	13.0 (21.9)	-----
TPEAK (hr)	2.99 (21.8)	2.81 (24.8)	1.72 (34.1)	-----

* Ratio (B/A) = e^[LSMEAN of LNB - LSMEAN of LNA]

PRODUCT FORMULATION:

The formulation of the test product, as supplied by the manufacturer, is given in Table 6 below.

APPEARS THIS WAY
ON ORIGINAL

TABLE 6. QUANTITATIVE COMPOSITION HYDROCHLOROTHIAZIDE CAPSULES, 12.5MG

COMPONENTS	Amounts (mg/capsule)
A. <u>ACTIVE COMPONENT</u> Hydrochlorothiazide, USP	12.5
B. <u>INACTIVE COMPONENTS</u>	
<u>Colloidal Silicon Dioxide, NF</u>	
<u>Magnesium Stearate/Sodium Lauryl Sulfate ()</u>	
<u>Microcrystalline Cellulose, NF</u>	
<u>Pregelatinized Starch, NF</u>	
TOTAL THEORETICAL WEIGHT	100.0

EMPTY GELATIN CAPSULE

— White Opaque () cap/ White Opaque () body imprinted MYLAN 810 in black ink on cap and body.

Each Empty Gelatin Capsule consists of:

Gelatin, NF²

¹Based upon a capsule weight of 37mg. Capsule weights may vary by ± 3mg.

²Silicon Dioxide, NF and Sodium Lauryl Sulfate, NF are added as ()

Synthetic Black Iron Oxide, SDA-3A Alcohol, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake, n-Butyl Alcohol, and propylene glycol. This information was provided by the supplier. Further information regarding the composition of the _____ may be obtained by referencing DMF _____ as provided for in this application.

Note: The manufacturing process for Hydrochlorothiazide Capsules, 12.5mg utilizes _____ which is manufactured with a separate batch record. The above quantitative composition includes the quantities of those ingredients supplied to the capsules via the _____

IN-VITRO DISSOLUTION TESTING RESULTS:

The results of the dissolution testing and the method used are given in Table 7.

TABLE 7. HYDROCHLOROTHIAZIDE CAPSULES, 12.5MG DISSOLUTION PROFILE SUMMARY

	10 MINUTES	20 MINUTES	30 MINUTES
Mylan Lot 2E005N (12.5mg) Mean Range RSD	94% - 101%	97% - 103%	98% - 106%
Microzide™ Lot 827801 (12.5mg) Mean Range RSD	54% - 86%	93% - 102%	95% - 103%

CONDITIONS: (FDA Dissolution method)

Dissolution Medium: 0.01 N Hydrochloric acid, 900mL @ 37°C ± 0.5°C
Apparatus: 1 (Basket)
Speed: 100 rpm
Sample Times: @ 10, 20 and 30 minutes
Limits: NLT — (Q) in 30 minutes
Number of capsules tested: 12

The dissolution data are acceptable.

N.B. See P.2509 & 2512 in Volume 1.5 for Individual capsule's dissolution data.

COMMENTS:

1. The results of the single-dose bioequivalence studies conducted under fasting and fed conditions demonstrated that Mylan's hydrochlorothiazide 12.5-mg capsules are bioequivalent to Watson Microzide™ 12.5 mg capsules following a single, oral 25 mg (2 x 12.5 mg) dose.
2. The dissolution data indicate that Mylan's hydrochlorothiazide 12.5-mg capsules and Watson Microzide™ 12.5 mg capsules had comparable dissolution profiles and both met the USP dissolution specifications.

RECOMMENDATIONS:

1. The single dose bioequivalence studies conducted under fasting and fed conditions on the test product, Mylan's Hydrochlorothiazide 12.5-mg capsules, lot # 2E005N, comparing it to the reference product, Microzide™ 12.5 mg capsules, lot # 827801 of Watson, have been found acceptable by the Division of Bioequivalence. These studies demonstrated that Hydrochlorothiazide 12.5-mg capsules, lot # 2E005N manufactured by Mylan are bioequivalent to the reference listed drug, Microzide™ 12.5 mg capsules.

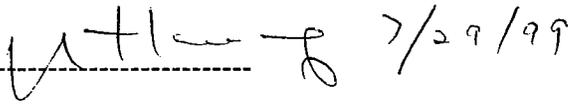
2. The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals Inc. on its Hydrochlorothiazide 12.5-mg capsules, lot # 2E005N, and Microzide™ 12.5 mg capsules, lot # 827801 of Watson, using FDA dissolution method, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.01N Hydrochloric acid at 37°C using USP XXIII apparatus I (basket) at 100 rpm. The test drug should meet the following specifications:

Not less than % of the labeled amount of the Drug in the dosage form is dissolved in 30 minutes.



Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

 7/29/99

Concur: 

Date: 8/4/99

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-640S2D.599 (original, duplicate), HFD-652 (Huang, Pradhan),
HFD-650 (Director), Drug File, Division File

Draft: SP/7-26-99/ V:\firmsam\Mylan\ltrs&rev\75640S2D.599

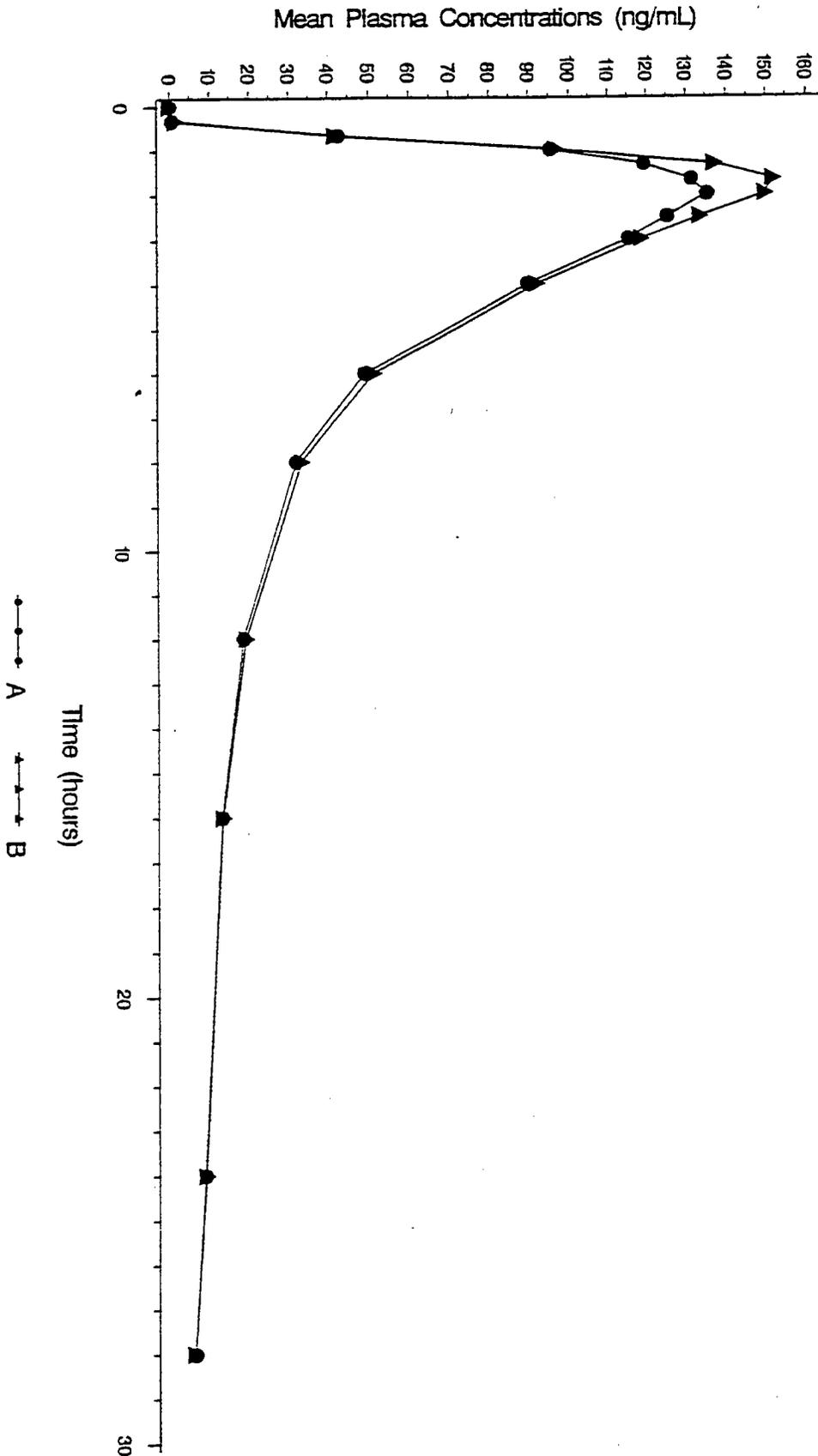
**APPEARS THIS WAY
ON ORIGINAL**

HYDROCHLOROTHIAZIDE (HCTZ-98103)

Total Dose: 25mg (2x12.5mg Capsules), Study Type: Fasting

Mean Hydrochlorothiazide Plasma Concentrations

N = 27



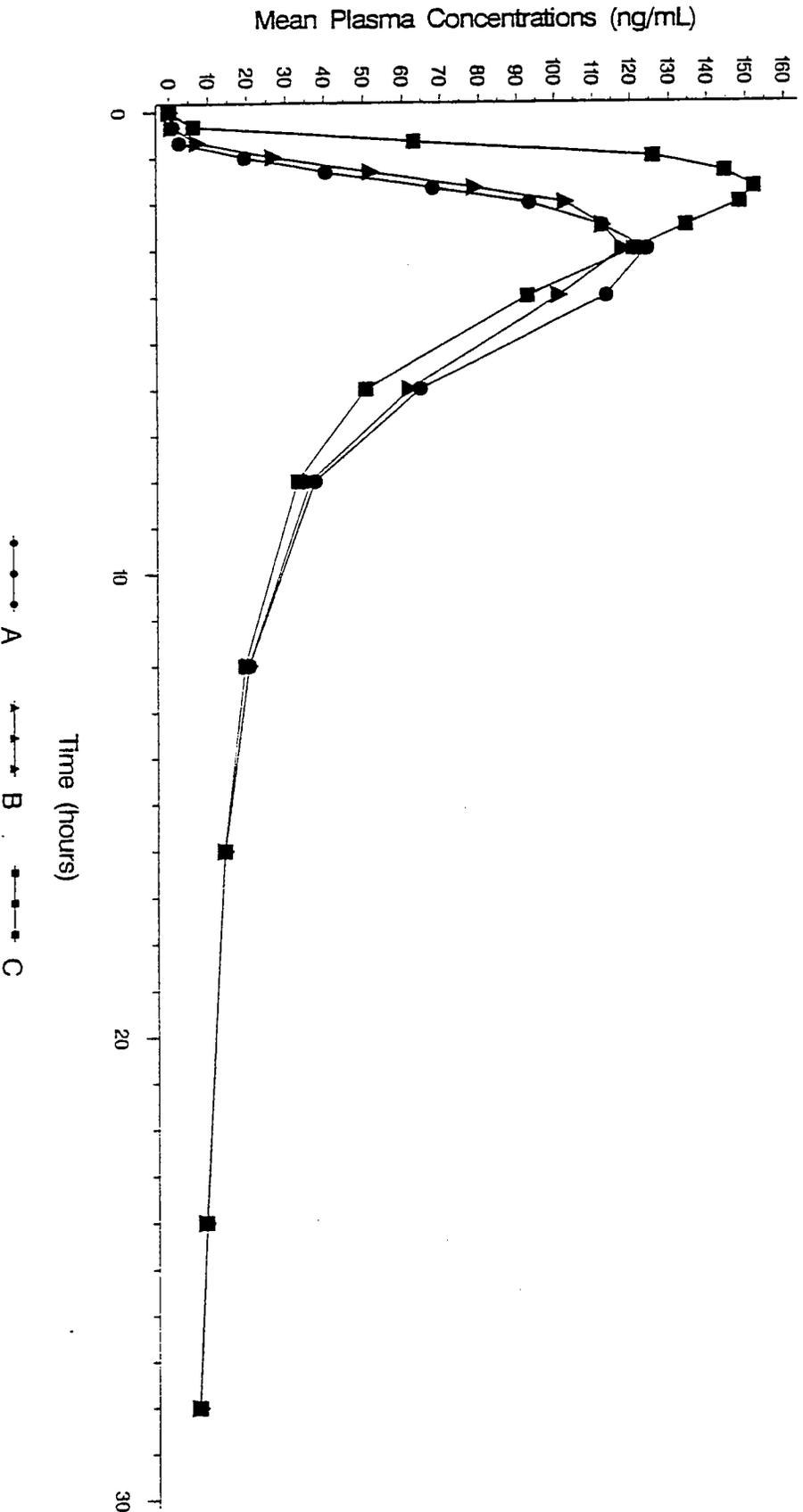
Treatment A is A (Microzide #827801)
Treatment B is B (Hydrochlorothiazide #2E005N)

HYDROCHLOROTHIAZIDE (HCTZ-98104)

Total Dose: 25mg (2x12.5mg Capsules), Study Type: Fed

Mean Hydrochlorothiazide Plasma Concentrations

N=21



①

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA #: 75-640 SPONSOR: Mylan Pharmaceuticals Inc.

DRUG AND DOSAGE FORM: Hydrochlorothiazide Capsules

STRENGTH(S): 12.5 mg

TYPES OF STUDIES: Bioequivalence studies under fasting and fed conditions.

CLINICAL STUDY SITE(S): _____

ANALYTICAL SITE(S): Same as above

STUDY SUMMARY: Bioequivalence studies ^{conducted} under fasting and fed conditions are acceptable.

DISSOLUTION: Dissolution (using FDA-Method) is also acceptable.

DSI INSPECTION STATUS

Inspection needed: <u>YES</u> / NO	Inspection status:	Inspection results:
First Generic <input checked="" type="checkbox"/>	Inspection requested: (date)	
New facility <input type="checkbox"/>	Inspection completed: (date)	
For cause <input type="checkbox"/>		
other <input type="checkbox"/>		

PRIMARY REVIEWER: (NAME) BRANCH:
INITIAL: SP DATE: 7/26/99

TEAM LEADER: (NAME) BRANCH:
INITIAL: [Signature] DATE: 7/29/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.
INITIAL: DP DATE: 8/4/99

v: / division / bio / signoff.doc

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-640

**ADMINISTRATIVE
DOCUMENTS**

ANDA APPROVAL SUMMARY

ANDA: 75-640

DRUG PRODUCT: Hydrochlorothiazide Capsules

FIRM: Mylan Pharmaceuticals Inc.

DOSAGE FORM: Capsules **STRENGTH:** 12.5 mg

CGMP: Statement/EIR Update Status:

EER is acceptable (OC recommendation, 9/02/99)

BIO: The bioequivalence studies was found to be acceptable by the Division of Bioequivalence. (reviewed by S Pradhan, 8/4/99).

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Method validation has not been completed by the Philadelphia District Laboratories in Philadelphia, PA.

STABILITY: (Are containers used in study identical to those in container section?)

The containers used in the stability study are identical to those described in the container section.

LABELING:

Container, carton and insert labeling have been found satisfactory (Labeling approval summary 11/24/99, reviewed by J Barlow)

STERILIZATION VALIDATION (IF APPLICABLE):

Not applicable

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

The _____ capsules (equivalent to _____ of the exhibit batch (bio batch) of the Hydrochlorothiazide Capsules, 12.5 mg (lot#2E005N) were manufactured. DMF _____ (Hydrochlorothiazide USP drug substance) was found adequate (7/30/99, reviewed by LCT)

SIZE OF STABILITY BATCHES- (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The exhibit batch (lot#2E005N) was the stability batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

The proposed production batch is _____ capsules of the Hydrochlorothiazide Capsules, 12.5 mg. The manufacturing process will be the same as was used for the exhibit batch.

CHEMIST: Liang-Lii Huang, Ph.D. *LL Huang 1/6/2000* DATE: January 6, 2000
SUPERVISOR: Paul Schwartz, Ph.D. DATE: January 6, 2000

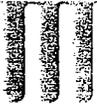
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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-640

CORRESPONDENCE



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

JAN 5 2000

TELEPHONE AMENDMENT
N/FA

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT (CMC INFORMATION ENCLOSED)

RE: HYDROCHLOROTHIAZIDE CAPSULES, 12.5MG
ANDA #75-640
RESPONSE TO AGENCY TELEPHONE CALL OF JANUARY 5, 2000

Dear Mr. Sporn:

Reference is made to the pending abbreviated new drug application identified above and to a January 5, 2000 telephone conversation with Mr. Robert West of your Office with regard to re-evaluating the need to include ~~_____~~ in the application as a contract ~~_____~~

~~_____~~ was referenced in the original application as a potential contract ~~_____~~ for the elemental analysis of drug substance intended for use as a house standard should the USP reference standard be unavailable. It should be noted that it has not been necessary to utilize ~~_____~~ in support of this application. Therefore, Mylan has re-evaluated the need to include ~~_____~~ as a contract ~~_____~~. With this letter, Mylan hereby withdraws ~~_____~~ as a contract ~~_____~~ in support of ANDA 75-640.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This correspondence is submitted in duplicate. Should you require additional information or have any questions regarding this correspondence, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures



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MYLAN PHARMACEUTICALS INC

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NOV 16 1999

NEW CORRESP
NC to Bio E

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT

RE: HYDROCHLOROTHIAZIDE CAPSULES, 12.5MG
ANDA #75-640
RESPONSE TO AGENCY CORRESPONDENCE DATED NOVEMBER 1, 1999

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently under review, and to the comments from the Division of Bioequivalence pertaining to this application which were included in the Agency's facsimile correspondence that was forwarded to Mylan on November 1, 1999. In response to the November 1st correspondence from the Division of Bioequivalence, Mylan wishes to amend the application as follows:

1. REGARDING BIOEQUIVALENCE ISSUES:

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

You should incorporate the dissolution testing into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.01 N Hydrochloric acid at 37°C using USP XXIII apparatus I (basket) at 100 rpm. The test drug should meet the following specifications:

Not less than $\frac{1}{2}$ (Q) of the labeled amount of the Drug in the dosage form is dissolved in 30 minutes.



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Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

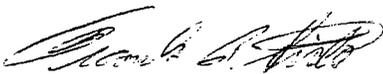
MYLAN RESPONSE: As requested, the dissolution testing for Hydrochlorothiazide Capsules, 12.5mg has already been incorporated into Mylan's stability and quality control programs. This testing was proposed in the original ANDA for the above referenced product which was submitted on May 27, 1999.

It is acknowledged and understood that the bioequivalency comments expressed in the correspondence dated November 1, 1999 are preliminary and may be revised after review of the entire application. It is also understood that the reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

For your reference, a copy of the November 1, 1999 Agency correspondence is provided in Attachment A. Responses to the chemistry comments contained in the November 1st correspondence along with revised labeling, also requested in the Agency's correspondence of November 1, 1999, will be forwarded simultaneously in a separate amendment to this application.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

NOV 16 1999

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIS AMENDMENT
N/FA

FACSIMILE AMENDMENT (CMC AND LABELING INFORMATION ENCLOSED)

RE: HYDROCHLOROTHIAZIDE CAPSULES, 12.5MG
ANDA #75-640
RESPONSE TO AGENCY CORRESPONDENCE DATED NOVEMBER 1, 1999

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments from the Agency pertaining to this application which were provided to Mylan in a facsimile dated November 1, 1999. In response to the Agency's November 1 comments, Mylan wishes to amend this application as follows.

A. REGARDING CHEMISTRY ISSUES

FDA COMMENT 1.

MYLAN RESPONSE:

[Redacted content]

this component.

It is understood that the computation of the expiration dating period for this drug product begins at the time the active ingredient is initially blended and mixed, as currently recommended in the FDA's stability guidelines.

FDA COMMENT 2.

In the exhibit batch of the subject product, ~~_____~~ of hydrochlorothiazide (HCTZ) ~~_____~~ was prepared (lot# R&D-1566). Only a small portion of the HCTZ ~~_____~~ was used for the manufacture of the HCTZ capsules (lot# 2E005N). Please reconcile the difference.

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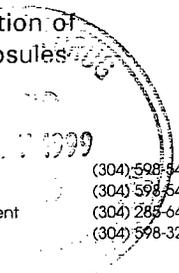
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FDA COMMENT 2. The FDA district office will be performing method validation on the finished drug product. Please submit samples promptly when so requested.

MYLAN RESPONSE: Method validation samples were requested by FDA on November 4, 1999. Samples were submitted to the FDA Laboratory, Philadelphia Branch on November 10, 1999.

FDA COMMENT 3. Please provide all available long-term stability data.

MYLAN RESPONSE: As requested, provided in Attachment I is the current room temperature stability data through nine months for Mylan's Hydrochlorothiazide Capsules, 12.5mg (lot 2E005N). The specifications listed on the stability data sheets have been revised to incorporate the changes within this amendment.

C. REGARDING LABELING ISSUES

MYLAN RESPONSE: Attachment M contains twelve (12) copies of the following final printed bottle labels and outsert for Hydrochlorothiazide Capsules, 12.5mg:

BOTTLE LABELS

Code RM0810A - Bottles of 100 Capsules
Code RM0810B - Bottles of 500 Capsules

OUTSERT

Code HCTZ:R1, Revised November 1999

A copy of the Agency's November 1, 1999 correspondence is provided in Attachment J for the reviewer's convenience.

Although no changes were made to the labeling pursuant to the Agency's comment, Mylan did make minor editorial changes in the labeling. These revisions are described in the side-by-side comparison of the bottle labeling in Attachment K and in the side-by-side comparison of the outsert in Attachment L. It is noted that prior to approval of this application, the Agency reserves the right to request further changes in the Mylan labeling based upon the changes in the approved labeling of the listed drug or upon further review of the application.

Douglas L. Sporn
Page 5 of 5

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

A handwritten signature in black ink, appearing to read "Frank R. Sisto for". The signature is written in a cursive style.

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures

**APPEARS THIS WAY
ON ORIGINAL**



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

MAY 27 1999

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OK Paras Patel
6/23/99

**ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED**

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: HYDROCHLOROTHIAZIDE CAPSULES, 12.5MG

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None

Established Name: Hydrochlorothiazide Capsules

This application consists of a total of 15 volumes.

Archival Copy - 6 volumes.

Review Copy - 7 volumes.

Technical Section For Chemistry - 2 volumes.

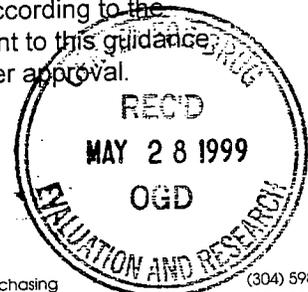
Technical Section For Pharmacokinetics - 5 volumes.

Analytical Methods - 2 extra copies; 1 volume each.

NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application. In addition, the diskettes providing the Bioequivalence Electronic Submission ESD (BA/BE) EVA will be forwarded to the Agency within the 30 day grace period.

This application provides for the manufacture of Hydrochlorothiazide Capsules, 12.5mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.



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Douglas L. Sporn
Page 2 of 2

As required by 21 CFR 314.94(d)(5) we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

A handwritten signature in black ink, appearing to read "Frank R. Sisto". The signature is written in a cursive style with a large initial "F" and "S".

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr