CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-907

Generic Name: Hydrochlorothiazide Capsules, 12.5mg

Sponsor: Vintage Pharmaceuticals, Inc.

Approval Date: September 17, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-907

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Reviews / Information Included in this ANDA Review.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-907

APPROVAL LETTER

ANDA 75-907

SEP 17 2002

Vintage Pharmaceuticals, Inc.
Attention: Christopher J. Nascone
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 16, 2000, 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 July 3, 2001 and May 13, 2002.

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 that 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 FDA 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 FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 9/17/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-907

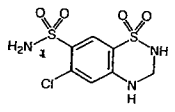
FINAL PRINTED LABELING

HYDROCHLOROTHIAZIDE CAPSULES

Rx only

DESCRIPTION

Hydrochlorothiazide 12.5 mg is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$; its molecular weight is 297.72; 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 is supplied as 12.5 mg capsules for oral use. Each capsule contains the following inactive ingredients: Docusate Sodium, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Pregelatinized Starch.

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 toxicities associated with excessive electrolyte changes caused by hydrochlorothiazide have been shown to be dose-related.

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 is 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 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 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 is 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 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 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**).

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 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 (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

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 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 angiitis (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.

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 LD_{50} 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 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.

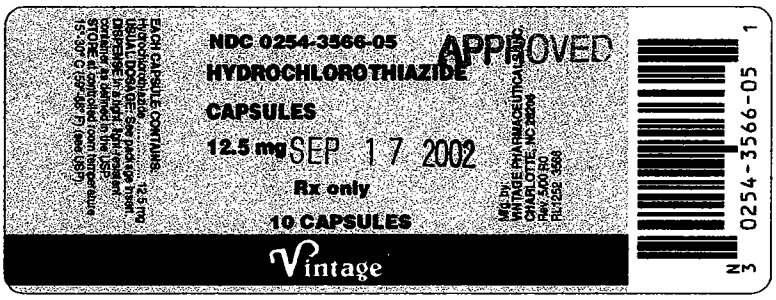
HOW SUPPLIED

Hydrochlorothiazide capsules are Opaque Teal two piece hard gelatin capsules imprinted with "V" and "3566". They are supplied in bottles of 10, 100, 500, 1000 and in unit-dose cartons of 100.

Storage: Keep container tightly closed. Protect from light, moisture, freezing, -20°C (-4°F) and store at controlled room temperature, 15–30°C (59–86°F) (see USP).

Manufactured by:
VINTAGE PHARMACEUTICALS, INC.
Charlotte, NC 28206

IN-177
Rev. 5/00
R0



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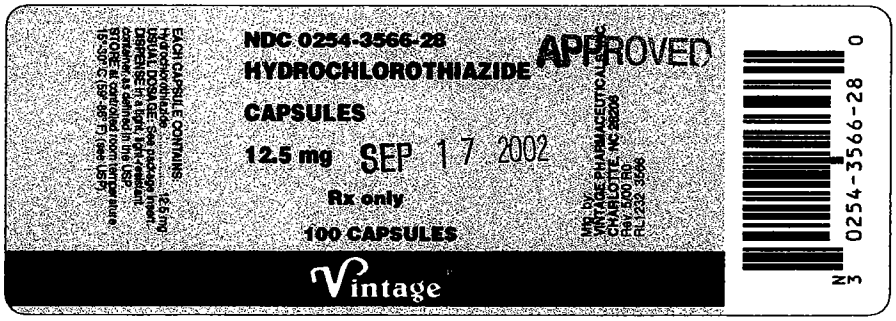

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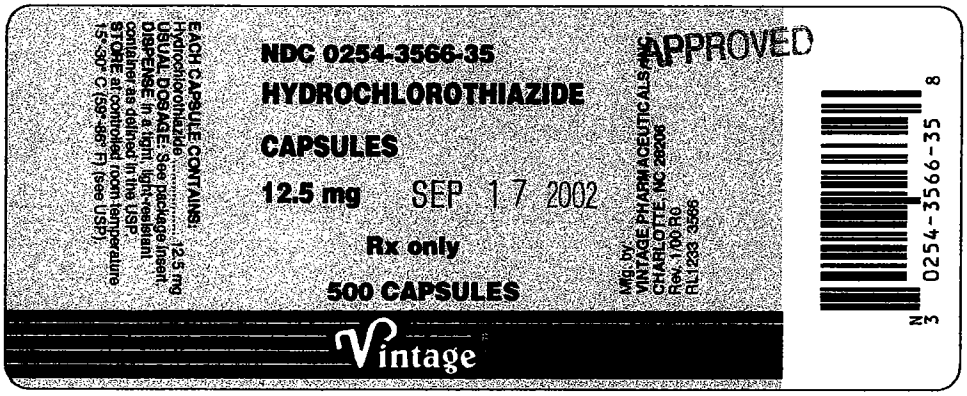

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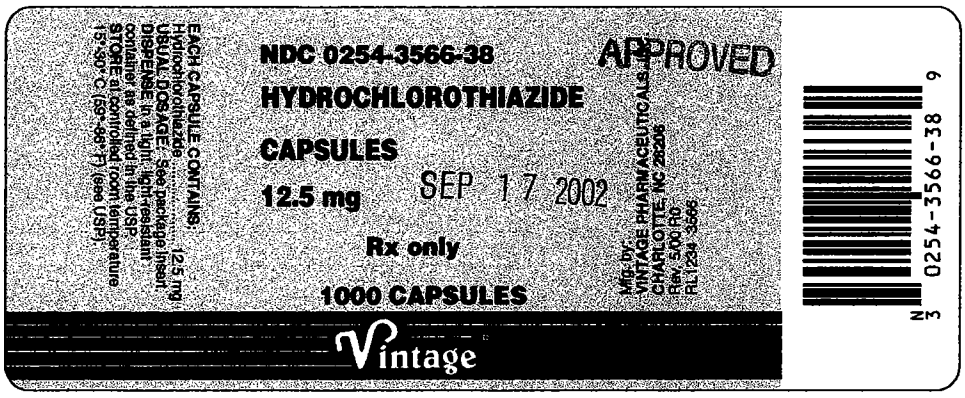

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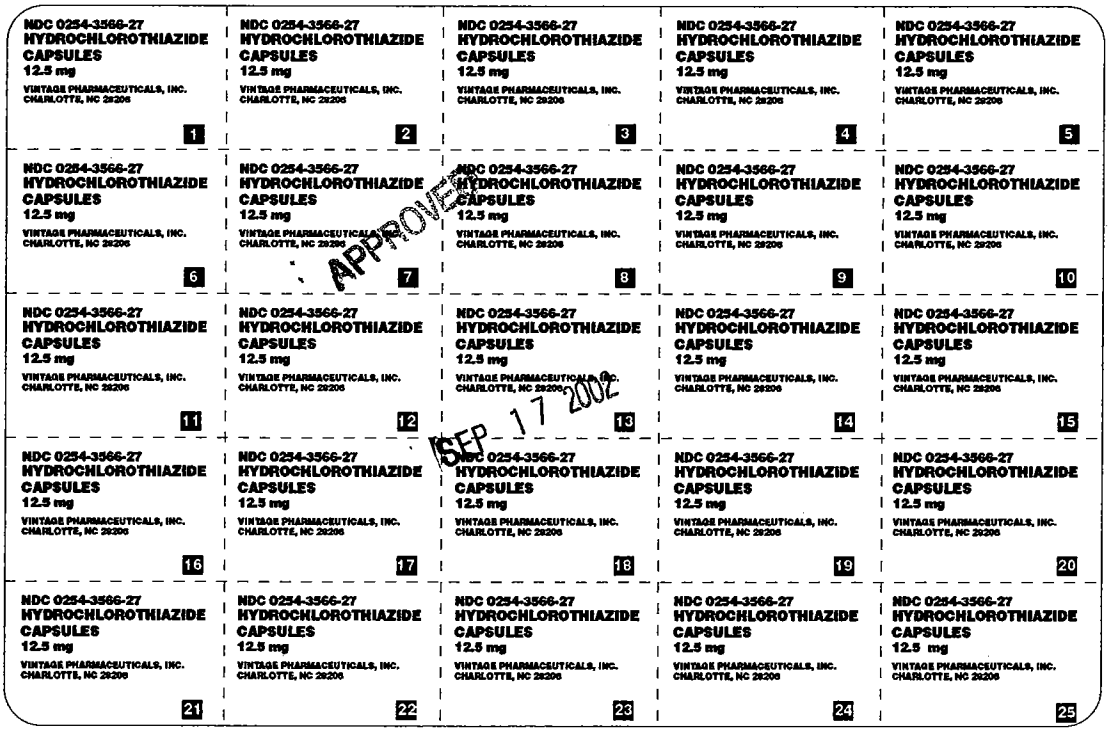


CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-907

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO**: No. 1

2. **ANDA**: 75-907

3. **NAME AND ADDRESS OF APPLICANT**:
Vintage Pharmaceuticals, Inc.,
Attention: Christopher J. Nascone,
3241 Woodpark Blvd.,
Charlotte, NC 28206.
Phone: 704-596-0516
Fax: 704-598-6237

4. **LEGAL BASIS for ANDA SUBMISSION**: 505 (j) F F D & C Act
MICROZIDE, N-20504 (Holder is Watson Labs.). No patent or other exclusivity is applicable to this product.

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**: Hydrochlorothiazide Capsules

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

9. **AMENDMENTS AND OTHER DATES**:
06/16/00 Submission of ANDA
08/02/00 New Correspondence
FDA:
06/19/00 Accepted for filing

10. **PHARMACOLOGICAL CATEGORY**: Hypertensive

11. **HOW DISPENSED**: Rx

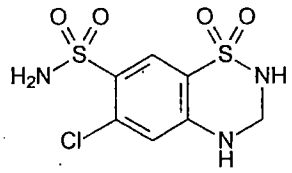
12. **RELATED IND/NDA/DMF(s)**:
MICROZIDE, N-20504 (Holder is Watson Labs.)
See Item 37 for a complete list of DMFs.

13. **DOSAGE FORM**: Oral Capsules

14. **Strength**: 12.5mg

15. **CHEMICAL NAMES AND STRUCTURE:**

Generic name: Hydrochlorothiazide
Chemical name: 2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide
Formula: $C_7H_8ClN_3O_4S_2$
Molecular weight: 297.75
CAS registry number(s): 58-93-5
Hypertensive



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:** The drug product is not listed in the USP monograph, therefore, the analytical methods used to characterize the drug product have to be validated by the District Laboratory.

18. **CONCLUSIONS AND RECOMMENDATIONS:** Not Approvable - MAJOR

19. **REVIEWER:** RD'Costa

DATE COMPLETED: 11/16/00

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Page(s) of trade secret and /or confidential commercial information

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO**: No. 2

2. **ANDA**: 75-907

3. **NAME AND ADDRESS OF APPLICANT**:
Vintage Pharmaceuticals, Inc.,
Attention: Christopher J. Nascone,
3241 Woodpark Blvd.,
Charlotte, NC 28206.

4. **LEGAL BASIS for ANDA SUBMISSION**: 505 (j) F F D & C Act
MICROZIDE, N-20504 (Holder is Watson Labs.). No patent or other exclusivity is applicable to this product.

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**: Hydrochlorothiazide Capsules

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

9. **AMENDMENTS AND OTHER DATES**:
06/05/01 Major Amendment
06/16/00 Submission of ANDA
08/02/00 New Correspondence
FDA:
06/19/00 Accepted for filing

10. **PHARMACOLOGICAL CATEGORY**: Hypertensive

11. **HOW DISPENSED**: Rx

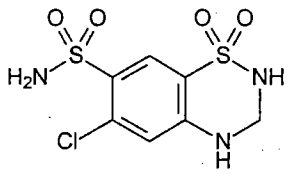
12. **RELATED IND/NDA/DMF(s)**:
MICROZIDE, N-20504 (Holder is Watson Labs.)
See Item 37 for a complete list of DMFs.

13. **DOSAGE FORM**: Oral Capsules

14. **Strength**: 12.5mg

15. **CHEMICAL NAMES AND STRUCTURE:**

Generic name: Hydrochlorothiazide
Chemical name: 2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide
Formula: $C_7H_8ClN_3O_4S_2$
Molecular weight: 297.75
CAS registry number(s): 58-93-5
Hypertensive



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:** 1. The drug product is not listed in the USP monograph, therefore, the analytical methods used to characterize the drug product have to be validated by the District Laboratory. The firm will have samples available to FDA district laboratory to conduct methods validation.
2. The firm recognizes that all firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs at the time of approval.

18. **CONCLUSIONS AND RECOMMENDATIONS:** Not Approvable - FAX

19. **REVIEWER:** RD'Costa

DATE COMPLETED: 09/10/01

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Page(s) of trade secret and /or confidential commercial information

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO**: No. 3

2. **ANDA**: 75-907

3. **NAME AND ADDRESS OF APPLICANT**:
Vintage Pharmaceuticals, Inc.,
Attention: Christopher J. Nascone,
3241 Woodpark Blvd.,
Charlotte, NC 28206.

4. **LEGAL BASIS for ANDA SUBMISSION**: 505 (j) F F D & C Act
MICROZIDE, N-20504 (Holder is Watson Labs.). No patent or other exclusivity is applicable to this product.

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**: Hydrochlorothiazide Capsules

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

9. **AMENDMENTS AND OTHER DATES**:
01/29/02 Telephone Amendment
12/21/01 Telephone Amendment
11/16/01 Telephone Amendment
10/26/01 Minor Amendment
06/05/01 Major Amendment
06/16/00 Submission of ANDA
08/02/00 New Correspondence
FDA:
06/19/00 Accepted for filing

10. **PHARMACOLOGICAL CATEGORY**: Hypertensive

11. **HOW DISPENSED**: Rx

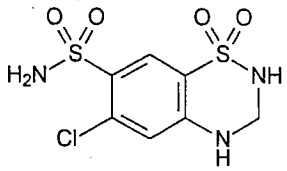
12. **RELATED IND/NDA/DMF(s)**:
MICROZIDE, N-20504 (Holder is Watson Labs.)
See Item 37 for a complete list of DMFs.

13. **DOSAGE FORM**: Oral Capsules

14. **Strength**: 12.5mg

15. **CHEMICAL NAMES AND STRUCTURE:**

Generic name: Hydrochlorothiazide
Chemical name: 2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide
Formula: $C_7H_8ClN_3O_4S_2$
Molecular weight: 297.75
CAS registry number(s): 58-93-5
Hypertensive



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:** Based on the satisfactory results obtained by Denver District Laboratory dated December 19, 2001, the analytical methods used to characterize the drug product are suitable for regulatory purposes.

18. **CONCLUSIONS AND RECOMMENDATIONS: Not Approvable**

19. **REVIEWER:** RD'Costa

DATE COMPLETED: 05/01/02

APPEARS THIS WAY
ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO**: No. 4

2. **ANDA**: 75-907

3. **NAME AND ADDRESS OF APPLICANT**:
Vintage Pharmaceuticals, Inc.,
Attention: Christopher J. Nascone,
3241 Woodpark Blvd.,
Charlotte, NC 28206.

4. **LEGAL BASIS for ANDA SUBMISSION**: 505 (j) F F D & C Act
MICROZIDE, N-20504 (Holder is Watson Labs.). No patent or other exclusivity is applicable to this product.

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**: Hydrochlorothiazide Capsules

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

9. **AMENDMENTS AND OTHER DATES**:
05/13/02 Minor Amendment
01/29/02 Telephone Amendment
12/21/01 Telephone Amendment
11/16/01 Telephone Amendment
10/26/01 Minor Amendment
06/05/01 Major Amendment
06/16/00 Submission of ANDA
08/02/00 New Correspondence
FDA:
06/19/00 Accepted for filing

10. **PHARMACOLOGICAL CATEGORY**: Hypertensive

11. **HOW DISPENSED**: Rx

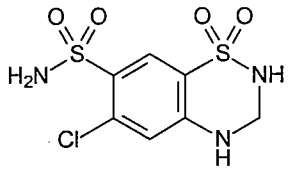
12. **RELATED IND/NDA/DMF(s)**:
MICROZIDE, N-20504 (Holder is Watson Labs.)
See Item 37 for a complete list of DMFs.

13. **DOSAGE FORM**: Oral Capsules

14. **Strength**: 12.5mg

15. **CHEMICAL NAMES AND STRUCTURE:**

Generic name: Hydrochlorothiazide
Chemical name: 2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide
Formula: $C_7H_8ClN_3O_4S_2$
Molecular weight: 297.75
CAS registry number(s): 58-93-5
Hypertensive



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:** Based on the satisfactory results obtained by Denver District Laboratory dated December 19, 2001, the analytical methods used to characterize the drug product are suitable for regulatory purposes.

18. **CONCLUSIONS AND RECOMMENDATIONS: Approvable pending EER**

19. **REVIEWER:** RD'Costa

DATE COMPLETED: 05/20/02

Redacted 14

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-907

BIOEQUIVALENCE REVIEW(S)

Hydrochlorothiazide Capsules 12.5 mg	Vintage Pharmaceuticals, Inc. Charlotte, NC
ANDA #75-907	Submission Date:
Reviewer: Moheb H. Makary	July 3, 2001
W 758907S.701	

Review of an Amendment

I. Objective:

In response to the Agency's letter dated August 29, 2000, the firm has submitted a post-prandial bioequivalence study on its Hydrochlorothiazide Capsule, 12.5 mg, comparing the test product to the RLD Microzide^{R} Capsule, 12.5 mg (Watson Laboratories, Inc).

The firm has previously submitted an acceptable single-dose study under fasting conditions on its Hydrochlorothiazide Capsule, 12.5 mg (submission dated June 16, 2000).

In this study, the firm used the same lots of the test and reference products that were used in the fasting study.

II. Post-Prandial Bioequivalence Study #10027011 for Hydrochlorothiazide Capsule, 12.5 mg

Clinical site: [redacted]

Analytical site: [redacted]

Study design: A randomized, single oral dose, three-treatment, three-period, six-sequence crossover study.

Dosing date: Period I 9/30/2000
Period II 10/07/2000
Period III 10/14/2000

Washout period: One week

Analytical date: From October 18 to November 09, 2000

Subjects selection: Eighteen (18) male subjects enrolled and completed the study.

Selection criteria: Selection criteria listed in Vol. 3.1, page 4.

Demographic profile of subjects in Study #10027011

CRO : [redacted]

Age

Mean:	26 years
SD:	8.9
Range:	18-44 years

Groups	
< 18	0 %
18 - 40	88.9%
40 - 64	11.1%
65 - 75	0%
> 75	0%
Gender	
Male	100%
Female	0%

Race	
Asian	5.6%
African American	44.4%
Hispanic	5.6%
Caucasian	38.9%
Other	5.6%

Dose and Treatment: A. Test product:
4 x 12.5 mg Hydrochlorothiazide Capsules, manufactured by Vintage Pharmaceuticals, Inc., lot #005069B, lot size [redacted] Capsules, potency 98.1%, content uniformity 99.7%, administered after a high fat breakfast preceded by an overnight fast.

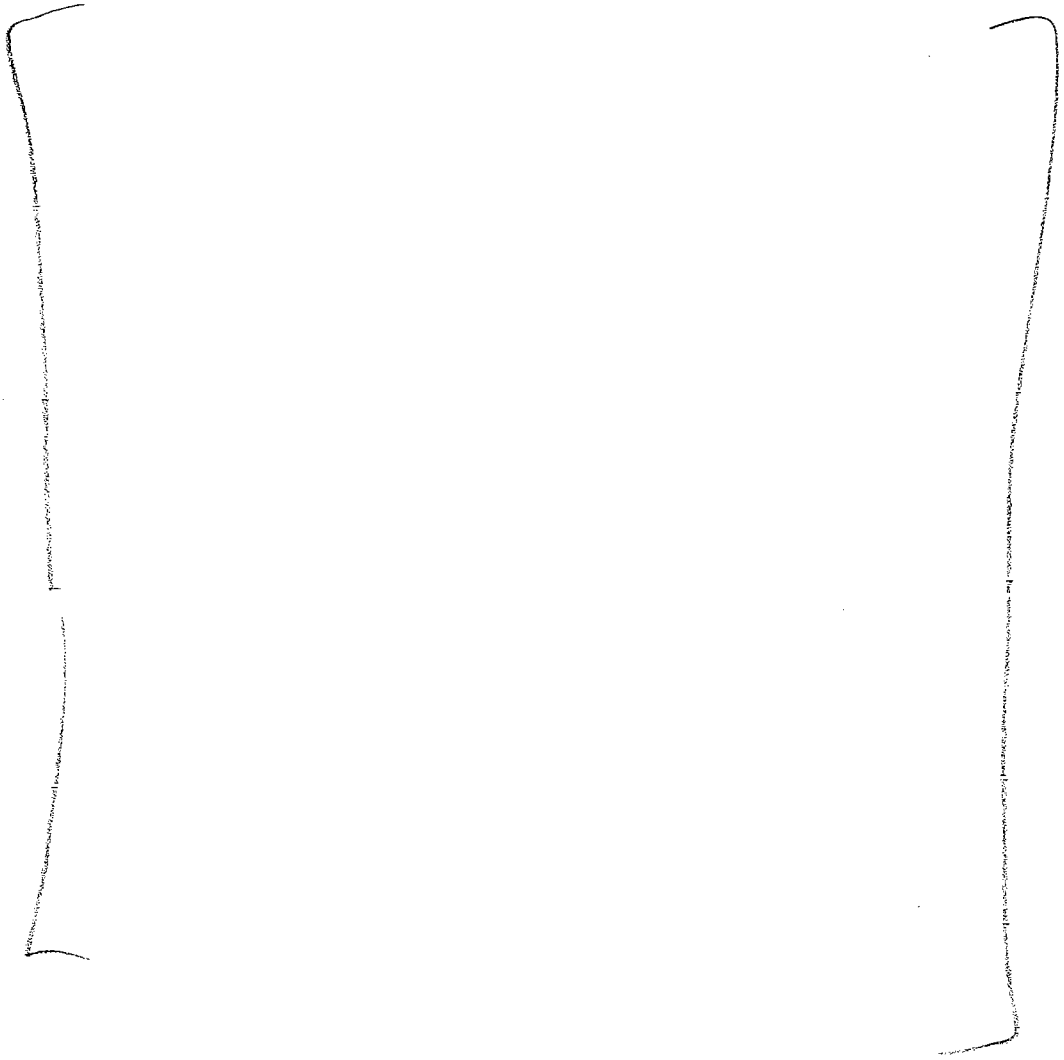
B. 4 x 12.5 mg Hydrochlorothiazide Capsules, manufactured by Vintage Pharmaceuticals, Inc., lot #005069B, lot size [redacted]

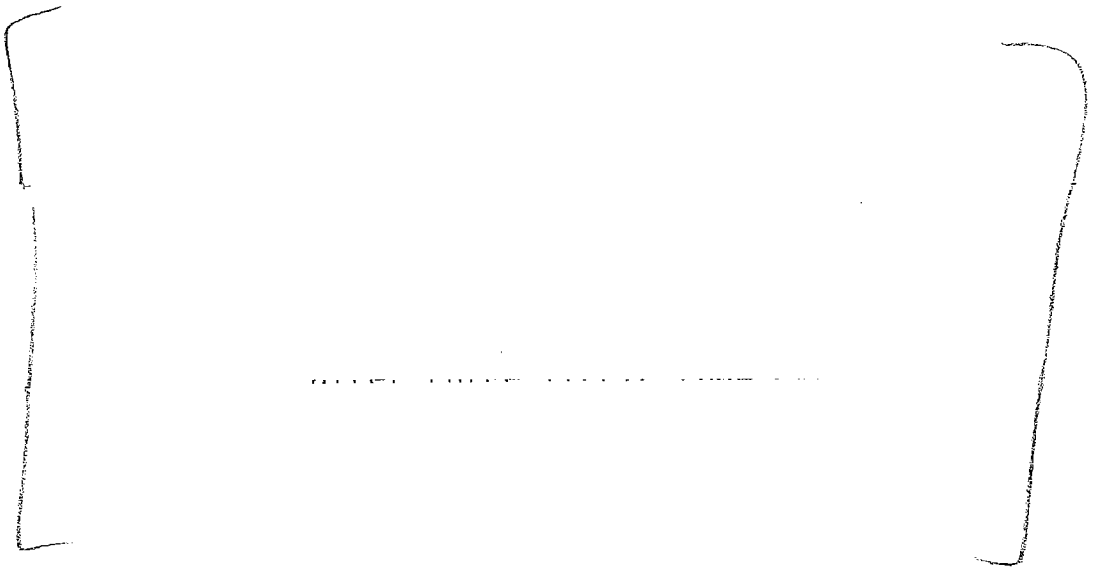
Capsules, potency 98.1%, content uniformity 99.7%, following an overnight fast.

C. Reference product:
4 x 12.5 mg Microzide™ Capsules, manufactured by Watson Laboratories, Inc., lot #928061, Exp. 9/2001, potency 101.8%, administered after a high fat breakfast preceded by an overnight fast.

Blood samples: Blood samples were collected at 0 (pre-dose) 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24 and 36 hours after dosing. Plasma samples were immediately frozen.

Analytical Methodology





Statistical Analysis:

Statistical analysis was performed on Hydrochlorothiazide data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects.

IV. In Vivo Results:

Seven (7) adverse events were reported by seven of the eighteen subjects dosed over the course of the study. No serious adverse events occurred during the study. A summary of adverse events is reported on page 1, Section 3, Vol.3.1.

The plasma concentrations and pharmacokinetic parameters for hydrochlorothiazide are summarized in Table I.

Table I
Mean Hydrochlorothiazide Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 4x12.5 mg Hydrochlorothiazide Capsules Under Nonfasting Conditions
(N=18)

Time hr	A Vintage Test Product Lot # 005069B	B Vintage Test Product Lot # 005069B	C Watson Reference Product Lot #928601	A/C

	Nonfasting ng/mL (CV%)	Fasting ng/mL (CV%)	Nonfasting ng/mL (CV%)	
0	0.00 (.)	0.00 (.)	0.00 (.)	.
0.5	3.18 (222)	6.74 (117)	4.46 (338)	0.71
1	27.47 (144)	97.84 (72.2)	48.52 (83.6)	0.57
1.5	81.11 (71.5)	168.97 (39.6)	122.73 (59.0)	0.66
2	139.57 (41.9)	205.34 (38.5)	169.56 (29.0)	0.82
2.5	162.46 (29.2)	212.81 (32.6)	200.39 (20.6)	0.81
3	187.72 (21.0)	218.39 (29.6)	214.61 (18.5)	0.83
3.5	198.00 (20.4)	210.44 (26.2)	207.00 (17.8)	0.96
4	200.89 (18.9)	195.22 (24.4)	205.28 (23.6)	0.98
5	193.06 (24.3)	169.11 (22.0)	174.11 (20.4)	1.10
6	140.27 (24.0)	119.19 (24.5)	133.18 (21.2)	1.05
8	90.51 (25.2)	97.36 (21.0)	86.94 (17.1)	1.04
10	64.69 (21.7)	58.64 (17.3)	63.14 (20.6)	1.02
12	48.92 (22.0)	43.21 (20.6)	46.11 (22.0)	1.06
24	17.38 (53.0)	16.28 (26.0)	15.04 (44.0)	1.15
36	6.77 (52.8)	7.00 (58.6)	5.86 (79.1)	1.16

AUC(0-t) (ng.hr/mL)	1851.7(19)	1851.3(19)	1849.1 (19)
AUCinf (ng.hr/mL)	1962.7(19)	1981.1(20)	1982.0 (18)
Cmax (ng/mL)	225.8(16)	244.3(25)	236.6 (18)
Tmax(hr)	3.70	2.97	3.25
Kel(1/hr)	0.087	0.076	0.087
t1/2 (hr)	8.23	9.48	8.56

	A/C Geometric Mean
AUCT	1.00
AUCI	1.03
CMAX	0.96

1. The mean hydrochlorothiazide plasma levels peaked at 3 and 4 hours for the reference and the test products, respectively, following their administration under nonfasting conditions.

2. For Vintage's hydrochlorothiazide, the mean AUCinf, Cmax and AUC(0-t) values were 0.97%, 4.6% and 0.14%, lower and higher, respectively, than those for the reference product

values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.25 for AUC(0-t), AUCinf and Cmax.

V. Comments:

1. The firm's single-dose bioequivalence study #10027011 under nonfasting conditions, conducted on its 12.5 mg hydrochlorothiazide capsule is acceptable. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.25 for AUC(0-t), AUCinf and Cmax.

2. The firm has previously submitted an acceptable single-dose study under fasting conditions and dissolution data on its Hydrochlorothiazide Capsule, 12.5 mg (submission dated June 12, 2000).

VI. Recommendations:

1. The bioequivalence study under nonfasting conditions conducted by Vintage Pharmaceuticals, Inc., on its Hydrochlorothiazide Capsule, 12.5 mg, lot #005069B, comparing it to Microzide™ Capsule, 12.5 mg, manufactured by Watson Laboratories, Inc., has been found acceptable by the Division of Bioequivalence.

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 0.1N HCl at 37°C using USP 24 apparatus I (basket) at 100 rpm. The test product should meet the following specification:

> Not less than — (Q) of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

moheb H. Mak

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT
for FT INITIALLED BDAVIT Zakaria Wahba Date: 7/19/01

Concur Dale P. Conner Date: 7/30/01
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/7-12-01, 7-19-01, 75907S.701
cc: ANDA #75-907, original, HFD-658 (Makary), Drug File, Division File.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-907 APPLICANT: Vintage Pharmaceuticals, Inc.

DRUG PRODUCT: Hydrochlorothiazide Capsules, 12.5 mg

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

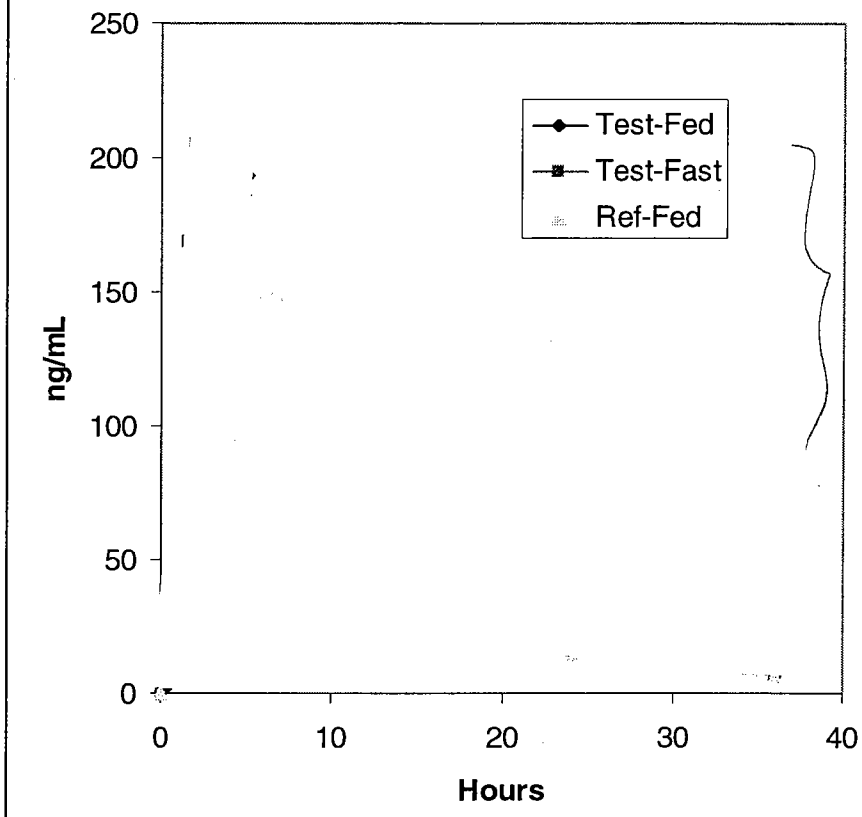
The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 24 apparatus I (basket) at 100 rpm. The test product should meet the following specification:

> Not less than — (Q) of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

Sincerely yours,

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

Fig I



CC: ANDA #75-907
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V:\FIRMSNZ\VINTAGE\LTRS&REV\75907S.701
Printed in final on 7/19/01

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM
for HFD-658/ Bio team Leader B. Davit ZZW 7/19/01
HFD-650/ D. Conner 7/30/01

BIOEQUIVALENCY - ACCEPTABLE submission date: 7-3-01

BIOEQUIVALENCY - DEFICIENCIES

1. Food Study (STP) Strengths: 12.5 mg
Clinical: [redacted] Outcome: AC
Analytical: [redacted]

Outcome Decisions:
AC - Acceptable

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-907 SPONSOR : Vintage Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM : Hydrochlorothiazide Capsules

STRENGTH(S) : 12.5 mg

TYPES OF STUDIES : Two bioequivalence studies under fasting and nonfasting conditions

CLINICAL STUDY SITE(S): [redacted]

ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY : The studies are acceptable

DISSOLUTION : Dissolution testing is acceptable.

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 7/12/01

for TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 7/19/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : [signature] **DATE :** 7/30/01

Hydrochlorothiazide Capsules 12.5 mg	Vintage Pharmaceuticals, Inc. Charlotte, NC
ANDA # 75-907	Submission Date:
Reviewer: Moheb H. Makary	June 16, 2000
W 758907SD.600	

Review of a Bioequivalence Study and Dissolution Data

I. Objective:

The firm submitted a bioequivalence study under fasting conditions to assess the bioequivalence of its Hydrochlorothiazide Capsule, 12.5 mg, to Watson's Microzide™ Capsule, 12.5 mg.

II. 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.

III. Fasting In-Vivo Bioequivalence Study #997010 for Hydrochlorothiazide Capsule, 12.5 mg

Clinical site: [redacted]

Analytical site: [redacted]

Study design: A randomized, single oral dose, two-treatment, two-period, two-sequence crossover study.

Dosing date: Period I 1/29/2000
Period II 2/05/2000

Washout period: One week

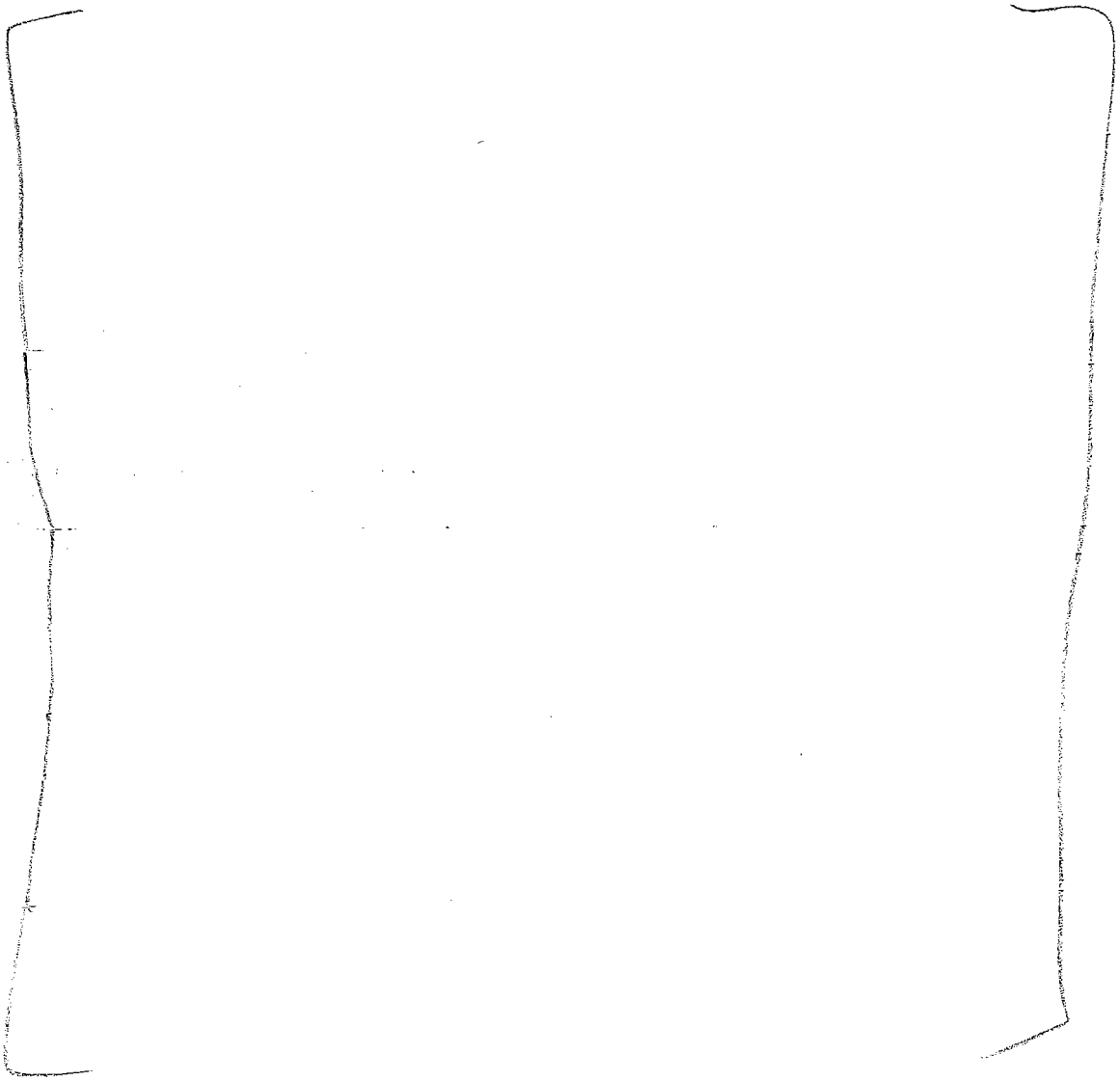
Analytical date: From February 10 to February 26, 2000

Subjects selection: Twenty-four (24) male and female subjects enrolled and twenty-three (23) subjects completed the study. Subject #23 voluntarily withdrew from study participation on 2/4/00 (period II, check-in) due to personal reasons. Statistical and pharmacokinetic analyses for hydrochlorothiazide were performed on data from the 23 subjects who completed both periods of the study.

Dose and Treatment:
A. Test product:
4 x 12.5 mg Hydrochlorothiazide Capsules, manufactured by Vintage Pharmaceuticals, Inc., lot #005069B, lot size [redacted] Capsules, potency 98.1%, content uniformity 99.7%, following an overnight fast.
B. Reference product:
4 x 12.5 mg Microzide™ Capsules, manufactured by Watson Laboratories, Inc., lot #928061, Exp. 9/2001, potency 101.8%, following an overnight fast.

Food and fluid intake: Subjects were required to fast overnight prior to and 4.5 hours after drug administration. No fluid was allowed from two hours prior to dose administration until 1 hour after dosing. Standard meals were served during the study.

Analytical Methodology



Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for

hydrochlorothiazide. Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure.

IV. In Vivo Results:

Twelve (12) adverse events were reported by eight of the twenty-four subjects dosed over the course of the study. No serious adverse events occurred during the study. A summary of adverse events is reported on page 000193, Vol.1.2.

The plasma concentrations and pharmacokinetic parameters for hydrochlorothiazide are summarized in Table I.

Table I
Mean Hydrochlorothiazide Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 4x12.5 mg Hydrochlorothiazide Capsules Under Fasting Conditions
(N=23)

Time hr	Vintage Test Product Lot # 005069B ng/mL (CV%)	Watson Reference Product Lot #928601 ng/mL (CV%)
0	0.00 (.)	0.00 (.)
0.5	21.57 (100)	30.04 (96.4)
1	160.90 (78.9)	239.00 (74.7)
1.5	226.29 (49.5)	303.87 (46.0)
2	246.97 (34.2)	300.87 (39.1)
2.5	242.04 (33.1)	279.83 (35.7)
3	229.26 (31.6)	253.79 (34.4)
3.5	233.00 (32.4)	232.23 (30.5)
4	230.83 (33.7)	215.48 (31.8)
5	193.17 (34.5)	176.80 (31.7)
6	139.13 (32.8)	133.04 (35.4)
8	92.81 (31.4)	91.00 (37.1)
10	68.99 (29.0)	68.02 (34.3)
12	52.06 (31.1)	52.00 (35.1)
24	19.77 (36.0)	20.83 (33.6)
36	9.65 (87.9)	9.01 (53.1)

Pharmacokinetic Parameters

	Test	Reference	T/R
AUC(0-t) (ng.hr/mL)	2236.2(28)	2337.7(32)	0.96

AUCinf (ng.hr/mL)	2453.5(29)	2480.4(32)	0.99
Cmax (ng/mL)	291.2(31)	349.1(38)	0.83
Tmax (hr)	2.72	1.93	
Kel(1/hr)	0.077	0.070	
t1/2 (hr)	9.1	10.1	

	90% CI
LnAUC(0-t)	92-102%
LnAUCinf	91-103%
LnCmax	80-92%

1. For Vintage's hydrochlorothiazide, the mean AUC(0-t), AUCinf and Cmax values were 4.3%, 1.1% and 16.6% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax.

2. The hydrochlorothiazide plasma levels peaked at 1.5 and 2 hours for the reference and the test products, respectively, following the administration of hydrochlorothiazide under fasting conditions.

V. Formulation:

The formulation of hydrochlorothiazide capsule , 12.5 mg, is shown below:

Ingredient	mg/Capsule
Hydrochlorothiazide, USP	12.5 mg
Microcrystalline Cellulose NF	[redacted]
Lactose Monohydrate, NF	[redacted]
Pregelatinized [redacted] Starch, NF	[redacted]
Docusate Sodium, USP	[redacted]
Magnesium Stearate, NF	[redacted]
Total	150.0 mg

Each capsule shell contains:

	Composition
[redacted]	[redacted]

VI. Dissolution Testing: (FDA method)

Method:	USP 24 apparatus I (basket) at 100 rpm
Medium:	900 mL of 0.1N HCl
Number of Tablets:	12
Test products:	Vintage's Hydrochlorothiazide Capsules 12.5 mg, lot #005069
Reference Products:	Watson's Microzide™ Capsules 12.5 mg, lot #928601
Specifications:	NLT — (Q) in 30 minutes

The dissolution testing results are shown in Table II.

VII. Comments:

1. The firm's single-dose bioequivalence study #9927010 under fasting conditions, conducted on its 12.5 mg hydrochlorothiazide capsule is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% for hydrochlorothiazide.

2. The *in vitro* dissolution testing submitted by the firm on its hydrochlorothiazide capsules, 12.5 mg, is acceptable.

3. The firm's financial disclosure statements submitted with the bioequivalence section in support of this application did not indicate any conflict of interests between the CRO's investigators and the firm. The reviewer agrees with that conclusion.

VIII. Deficiency Comment:

The labeling states that "When Microzide™ is 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". Since a food effect is mentioned in the drug product labeling, the firm should conduct a single-dose post-prandial bioequivalence study on its hydrochlorothiazide capsule, 12.5 mg, to demonstrate that its product is bioequivalent to the reference product under nonfasting conditions..

IX. Recommendations:

1. The bioequivalence study under fasting conditions conducted by Vintage Pharmaceuticals, Inc., on its Hydrochlorothiazide Capsule, 12.5 mg, lot #005069B, comparing it to Microzide™ Capsule, 12.5 mg, manufactured by Watson Laboratories, Inc., has been found acceptable by the Division of Bioequivalence. However, the application is incomplete for the reason given in deficiency comment.

2. The dissolution testing conducted by the firm on its Hydrochlorothiazide Capsules, 12.5 mg, lot #005069, is acceptable.

3. 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 0.1N HCl at 37°C using USP 24 apparatus I (basket) at 100 rpm. The test product should meet the following specification:

> Not less than — (Q) of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

The firm should be informed of the deficiency comment and recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

BMD 8/11/00

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Barbara M David Date: 8/14/00

Concur Dale P. Conner Date: 8/21/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/8-10-00, 8-14-00, 75907SD.600
cc: ANDA #75-907, original, HFD-658 (Makary), Drug File, Division File.

Table II

Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Vintage Lot #005069 Capsule Strength(mg) 12.5			Reference Product Microzide Lot #928601 Capsule Strength(mg) 12.5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	60.7		8.4	93.4		5.5
30	84.8		7.3	101.2		3.2
45	96.0		5.1	102.4		2.7
60	100.7		4.0	102.1		2.4

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #75-907
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-658 /Reviewer M. Makary MHM
HFD-658 /Bio Team Leader B. Davit BMD
HFD-617/Project Manager JF 8/23/00
HFD-650/Dale Conner DRC 8/21/00

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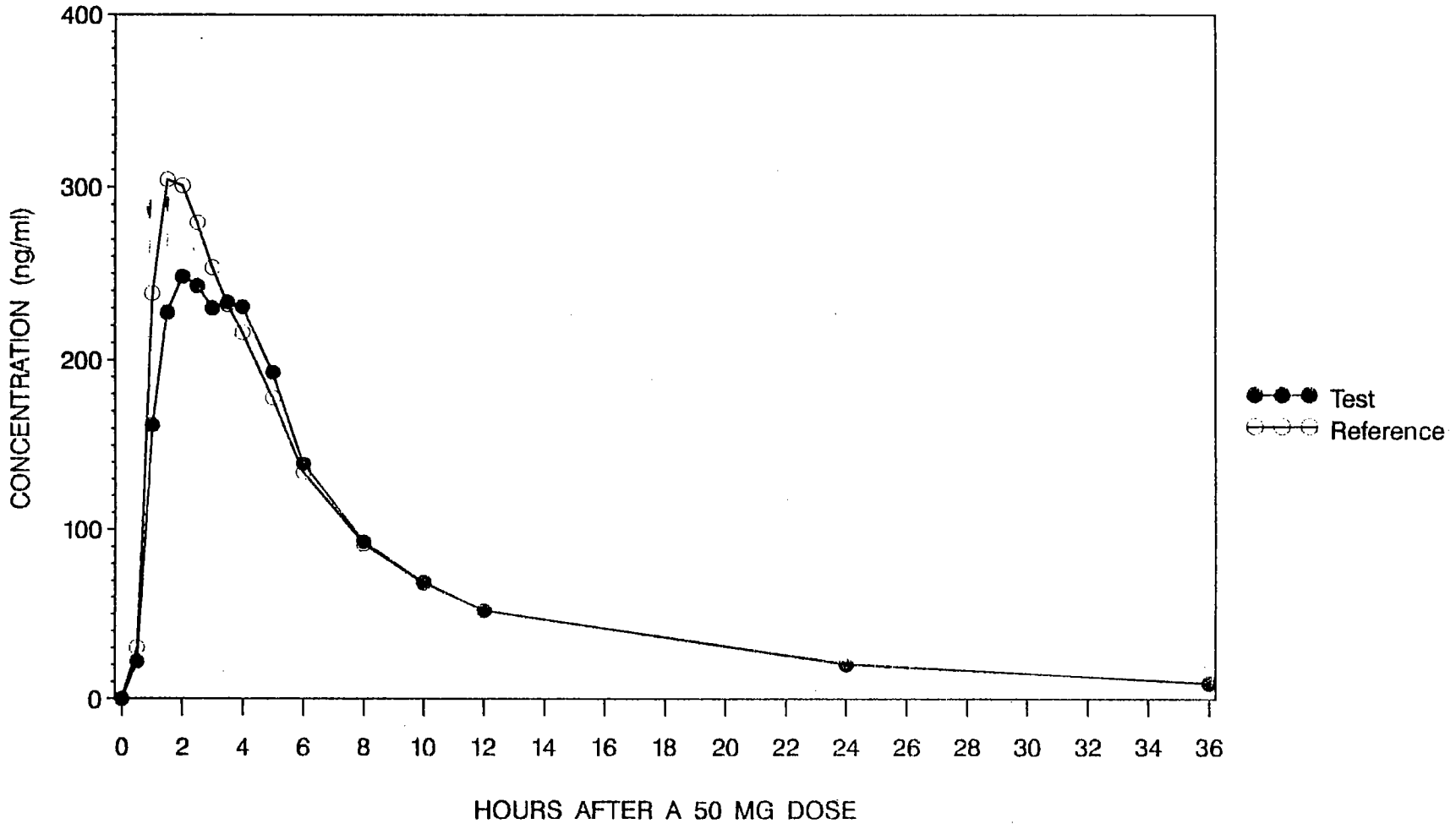
BIOEQUIVALENCY - DEFICIENCIES Submission Date: 6/16/2000

ok 1. **FASTING STUDY** (STF) Strengths: 12.5 mg
Clinical: Outcome: ~~IC~~ IN
Analytical:

Outcome Decisions:
~~IC~~ - Incomplete
IN

APPEARS THIS WAY
ON ORIGINAL

HYDROCHLOROTHIAZIDE STUDY NO. 9927010
LEAST – SQUARES MEAN PLASMA CONCENTRATIONS (N = 23)



1.1 AUG 29

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-907 APPLICANT: Vintage Pharmaceuticals, Inc.

DRUG PRODUCT: Hydrochlorothiazide Capsules, 12.5 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please submit a post-prandial bioequivalence study on your hydrochlorothiazide capsule, 12.5 mg.

2. We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 24 apparatus I (basket) at 100 rpm. The test product should meet the following specification:

> Not less than —— (Q) of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

Sincerely yours,

Dale P. Conner

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-907 SPONSOR : Vintage Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM : Hydrochlorothiazide Capsules

STRENGTH(S) : 12.5 mg

TYPES OF STUDIES : Two bioequivalence studies under fasting and nonfasting conditions

CLINICAL STUDY SITE(S): ———

ANALYTICAL SITE(S) : ———

STUDY SUMMARY : The studies are acceptable

DISSOLUTION : Dissolution testing is acceptable.

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 7/12/01

for TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 7/19/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : [illegible] **DATE :** 7/30/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-907

ADMINISTRATIVE DOCUMENTS

301 - 594 - 0180
FAX #:

Vintage
Pharmaceuticals, Inc.

3241 Woodpark Blvd.
Charlotte, NC 28206

(704) 596-0516

DATE: 1/29/02

ORIG AMENDMENT
N/FA

TO: Mr. Tim Ames

COMPANY: FDA

FROM: Fran Hutchins

COMPANY: Vintage Pharmaceuticals

Telephone: (704) 596-0516 Fax (704) 598-6237

NUMBER OF PAGES INCLUDING COVER PAGE: 4

Mr. Ames,

Please find attached the revised product specifications for ANDA applications #40412 and #75907.

If you have any questions, please feel free to contact me.

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

FINISHED PRODUCT SPECIFICATIONS

Product:	Hydrochlorothiazide Tablets, USP (Hydrochlorothiazide 25 mg)
Manufacturing Site:	Vintage Pharmaceuticals Inc. 3241 Wood Park Blvd. Charlotte, NC 28206
Product Code:	H06
Description:	Peach, flat faced, beveled edge, debossed "3571/V".
Reference:	Current USP

In-house Specifications:	Limits:
Appearance	Meets above description
Avg. Tablet Weight	104.5 - 115.5 mg
Avg. Tablet Hardness	
Tablet Friability	Loses NMT
Avg. Tablet Thickness	2.4 - 2.6 mm
Related Substances/Impurities	
	NMT
	NMT
	No individual impurity exceeds
	NMT
Identification	
A)	Compares to Standard
B)	Compares to Standard
Dissolution	Meets USP Specifications
Hydrochlorothiazide	NLT (Q) in 60 minutes
Uniformity of Dosage - Content Uniformity	Meets USP Specifications
Hydrochlorothiazide	Range:
	RSD NMT
Assay	
Hydrochlorothiazide	

Approvals:

Quality Control	Date:	1/28/02
Quality Control	Date:	1/28/02
Production	Date	01/29/02

Effective Date: 01/25/02 Supersedes: 04/17/01

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

FINISHED PRODUCT SPECIFICATIONS

Product:	Hydrochlorothiazide Tablets, USP (Hydrochlorothiazide 50 mg)
Manufacturing Site:	Vintage Pharmaceuticals Inc. 3241 Wood Park Blvd. Charlotte, NC 28206
Product Code:	H05
Description:	Peach, flat faced, beveled edge, debossed "3572/V".
Reference:	Current USP

In-house Specifications:	Limits:
Appearance	Meets above description
Avg. Tablet Weight	209.0 - 231.0 mg
Avg. Tablet Hardness	[redacted]
Tablet Friability	Loses NMT [redacted]
Avg. Tablet Thickness	3.1 - 3.6 mm
Related Substances/Impurities	
[redacted]	NMT [redacted]
	NMT [redacted] No individual impurity exceeds [redacted]
	NMT [redacted]
Identification	
A) [redacted]	Compares to Standard
B) [redacted]	Compares to Standard
Dissolution [redacted] Hydrochlorothiazide	Meets USP Specifications NLT [redacted], (Q) in 60 minutes
Uniformity of Dosage - Content Uniformity Hydrochlorothiazide	Meets USP Specifications Range: [redacted] RSD NMT [redacted]
Assay [redacted] Hydrochlorothiazide	[redacted]

Approvals:

[signature] Quality Control	Date:	1/29/02
[signature] Quality Control	Date:	1/29/02
[signature] Production	Date:	01/29/02

Effective Date: 01/25/02 Supersedes: 04/17/01

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

FINISHED PRODUCT SPECIFICATIONS

Product:	Hydrochlorothiazide Capsules (Hydrochlorothiazide 12.5 mg)
Manufacturing Site:	Vintage Pharmaceuticals Inc. 3241 Wood Park Blvd. Charlotte, NC 28206
Product Code:	H08
Description:	Capsules - Opaque Teal, Body/Cap - imprinted Cap - Teal, Body - Teal, printed.
Reference:	Current USP

In-house Specifications:	Limits:
Appearance	Meets above description
Avg. Capsule Weight	182.5 - 191.5 mg
Avg. Fill Weight	145.5 - 154.5 mg
Related Substances/Impurities	
[redacted]	NMT [redacted]
[redacted]	NMT [redacted] No individual impurity exceeds [redacted]
[redacted]	NMT [redacted]
Identification	
A) [redacted]	Compares to Standard
B) [redacted]	Compares to Standard
Dissolution ([redacted] Hydrochlorothiazide	Meets USP Specifications NLT [redacted] (Q) in 30 minutes
Uniformity of Dosage - Content Uniformity Hydrochlorothiazide	Meets USP Specifications Range: RSD NMT [redacted]
Assay [redacted] Hydrochlorothiazide	[redacted]

Approvals:

[signature] Quality Control	Date:	1/25/02
[signature] Quality Control	Date:	1/28/02
[signature] Production	Date:	01/29/02

Effective Date: 01/25/02 Supersedes: 04/17/01

Telephone Conversation Memorandum

ANDA: 75-907

DRUG: Hydrochlorothiazide Capsules 12.5 mg

FIRM: Vintage Pharmaceuticals, Inc.

PERSONS INVOLVED: Christopher Nascone, Vintage
Tim Ames, FDA

PHONE NUMBER: 256-859-2222

DATE: December 17, 2001

Called firm at CMC reviewer's request to ask for a tightening of the individual unknown impurities spec for the drug product. CMC reviewer felt that it was [redacted], and that the firm's data supported a lower spec in the neighborhood of [redacted]

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem. I, Team 1, OGD

cc: ANDA 75-907
Division file (1)

File: V:\firmsnz\vintage\telecons\75907tc2.doc

APPEARS THIS WAY
ON ORIGINAL

West, Robert L

'om: Alcock, Patricia L
ent: Monday, April 01, 2002 8:41 AM
To: West, Robert L
Cc: Hartman, Bruce W
Subject: FW: NEED INSPECTION REPORT FOR ANDA 75-907 FOR VINTAGE'S HYDROCHLOROTHIAZIDE CAPSULES

Bob - The inspection report is still pending at the district level. We will follow our procedures when we receive the report. Since the recommendation was made only last week - the EIR is expected within the next 30 days. The inspection occurred in March.

Shirnette - Please call district and try to get estimated time of arrival (ETA) on the inspection report.

Pat

-----Original Message-----
From: Alcock, Patricia L
Sent: Monday, April 01, 2002 8:10 AM
To: West, Robert L
Cc: Hartman, Bruce W
Subject: RE: NEED INSPECTION REPORT FOR ANDA 75-907 FOR VINTAGE'S HYDROCHLOROTHIAZIDE CAPSULES

We will need to see if we have received the report and/or have reviewed the EIR. Please keep in mind that this office is well aware of "review chemist" issues and always refers the EIRs accordingly. Sounds like this is another example where the firm has told you all before the inspection report has followed suit to this office for review. So, let's take a look and see where the EIR is first and then determine if, based on the issues described in the EIR - are indeed chemistry and/or chemistry and CGMP.

We will forward any memo etc. per our usual procedure - to Tim Ames. I don't want the entire package to be lost.

Bruce - Please look into this -

Pat

-----Original Message-----
From: West, Robert L
Sent: Friday, March 29, 2002 10:10 AM
To: Alcock, Patricia L
Cc: McNeal, Elizabeth T; D Costa, Rosario; Mueller, Albert J; Ames, Timothy W; Rickman, William P
Subject: NEED INSPECTION REPORT FOR ANDA 75-907 FOR VINTAGE'S HYDROCHLOROTHIAZIDE CAPSULES

Pat:

I understand that the PAI for the above ANDA was been completed and the investigator continues to recommend withhold. The firm's representative told me that the investigator took issue with the dissolution data. Since dissolution data is generally considered a review issue, please forward a copy of the inspection report to Dr. D'Costa in OGD. We would like to know the nature of the deficiencies before we take an action.

Thank you,

Bob

Telephone Conversation Memorandum

ANDA: 75-907

DRUG: Hydrochlorothiazide Capsules 12.5 mg

FIRM: Vintage Pharmaceuticals, Inc.

PERSONS INVOLVED: Christopher Nascone, Vintage
Tim Ames, FDA

PHONE NUMBER: 256-859-2222

DATE: November 13, 2001

Telephone Request:

Please explain the fluctuation in stability test results for impurity Chlorothiazide in going from 12 months (0%) to 18 months [redacted] and back to 0% in 24 months (Attachment A.2, pages 2-4).

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem. I, Team 1, OGD

cc: ANDA 75-907
Division file (1)

File: V:\firmsnz\vintage\telecons\75907tc1.doc

Telephone Conversation Memorandum

ANDA: 75-907

DRUG: Hydrochlorothiazide Capsules, 12.5 mg

FIRM: Vintage Pharmaceuticals, Inc.

PERSONS INVOLVED: Christopher Nascone, Vintage
Tim Ames, FDA

PHONE NUMBER: 704-596-2222

DATE: November 13, 2001

Called firm to request explanation of the fluctuations in the stability test results for the impurity, [redacted], where at 12 months the result equals 0%, at 18 months [redacted] and at 24 months back to 0%. Mr. Nascone was instructed to reply with a telephone amendment faxed in with hard copy to the ANDA, which he agreed to do.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem. I, Team 1, OGD

cc: ANDA 75-907
Division file (1)

File: V:\firmsnz\vintage\telecons\75907tc1.doc

RECORD OF TELEPHONE CONVERSATION/MEETING

We attempted to call Mr. Christopher Nascone, Regulatory Affairs, but he was out of the office and the call was taken by Fran Hutchins who also included Pam Proxler into our conversation. Both Ms. Hutchins and Proxler were familiar with these applications.

We reviewed the related impurities specifications for release and stability of both the tablet and capsule drug products, indicating that we would like Vintage to reduce the total impurities and unknown impurities specifications to values consistent to those reported in the applications. Current values for Total Impurities are nmt —. and for any unknown impurities, nmt —. The USP specification for the target impurity, . —— of nmt — is acceptable.

We also noted that Mr. Nascone had been informed of our request in December, 2001 and that they responded that they would still would want to keep the higher values. I indicated that we are still requesting to lower these values and that these applications would be sent to the divisional level for approval if they would lower these impurity specifications.

Both Ms. Hutchins and Proxler understood our request and would communicate our conversation to Mr. Nascone, who was out of the office. They requested our Fax number.

We indicated that we would await their response to our request.

(End of memo)

DATE:
January 17, 2002

ANDA NUMBERS:
40-412; 75-907

IND NUMBER:
N/A

TELECON

INITIATED BY:
- ☐ APPLICANT/SPONSOR
- ■ FDA

MADE:
- ■ BY TELEPHONE
- ☐ IN PERSON

PRODUCT NAME:
HCTZ Tablets/Capsules

FIRM NAME:
Vintage Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Fran Hutchins, Plt. Mgr.
Pam Proxler, Lab. Mgr.

TELEPHONE NUMBER:
704-596-0516

SIGNATURE:
A. Mueller
B. R. D'Costa 3/19/02

V:\FIRMSNZ\VINTAGE\TELECONS\76044MEM.DOC

cc: ANDA 75-907
DFJ File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-907

CORRESPONDENCE

Vintage
Pharmaceuticals, Inc.

3241 Woodpark Boulevard
Charlotte, NC 28206

Phone (704) 596-0516
Fax (704) 598-6237

January 30, 2002

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/FA

RE: ANDA # 75-907
Hydrochlorothiazide Capsules
12.5 mg
Fax Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to our Abbreviated New Drug Application for the above product.

This amendment is in response to a telephone request from Tim Ames of FDA on January 17, 2002.

The archival copy of the ANDA consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

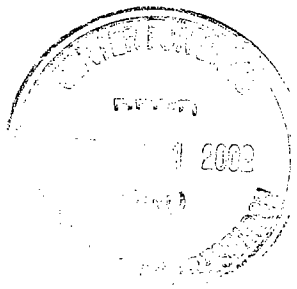
-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Ms Fran Hutchins, Plant Manager, at Tel. (704)596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

C J Nascone

Christopher J. Nascone
Regulatory Affairs



Vintage
Pharmaceuticals, Inc.

3241 Woodpark Boulevard
Charlotte, NC 28206

Phone (704) 596-0516
Fax (704) 598-6237

May 13, 2002

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

RE: ANDA # 75-907
Hydrochlorothiazide Capsules
12.5 mg
Minor Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to our Abbreviated New Drug Application for the above product.

This amendment is in response to a minor deficiency letter dated May 6, 2002. In response to Item B.1, Vintage acknowledges that all firms referenced in the application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

The archival copy of the ANDA consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Ms Fran Hutchins, Plant Manager, at Tel. (704)596-0516.

phone (256) 859 4011 Huntsville Alabama facility
FAX (256) 859-2903

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

C J Nascone

Christopher J. Nascone
Regulatory Affairs

RECEIVED
MAY 14 2002
OGD / CDER

5/14/02

Vintage
Pharmaceuticals, Inc.

3241 Woodpark Boulevard
Charlotte, NC 28206

Phone (704) 596-0516
Fax (704) 598-6237

12/31/01 Tcon Amend recd to CMC Reviewer for review.

December 21, 2001

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

FA

RE: ANDA# 75-907
Hydrochlorothiazide Capsules
12.5 mg
Telephone Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to the Abbreviated New Drug Application for the above product in response to a telephone request on December 17, 2001 from Tim Ames of FDA.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one separately bound, orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this amendment, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

256-859-4011

C J Nascone

Christopher J. Nascone
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 26 2001

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

November 16, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

N/FA

ORIG AMENDMENT

RE: ANDA # 75-907
Hydrochlorothiazide Capsules
12.5 mg
Telephone Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to our Abbreviated New Drug Application for the above product.

This amendment is in response to a telephone request by Mr. Tim Ames of FDA on November 13, 2001.

The archival copy of the ANDA consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Ms Fran Hutchins, Plant Manager, at Tel. (704)596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

Christopher J. Nascone
Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

BIOAVAILABILITY

FA noted,
To CMC Review for
review.
10/30/01

October 26, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

FA

RE: ANDA #75-907
Hydrochlorothiazide Capsules
12.5mg
Fax Amendment

Dear Sir:

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to our Abbreviated New Drug Application for the above product.

This amendment is in response to a Fax deficiency letter dated October 24, 2001.

The archival copy of the Amendment consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

CENTER FOR DRUG
OCT 29 2001
EVALUATION AND RESEARCH

C J Nascone

Christopher J. Nascone
Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

ORIG AMENDMENT
N/AB

July 3, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA # 75-907
Hydrochlorothiazide Capsules
12.5 mg
Bioequivalence Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to our Abbreviated New Drug Application for the above product.

This amendment is in response to a bioequivalence deficiency letter dated August 29, 2000. The requested post-prandial bioequivalence study on our Hydrochlorothiazide Capsules, 12.5 mg, is attached.

The archival copy of the ANDA consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Ms Fran Hutchins, Plant Manager, at Tel. (704)596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

C J Nascone

Christopher J. Nascone
Regulatory Affairs

CENTER FOR DRUG
JUL 0 9 2001
OGD
EVALUATION AND RESEARCH

Vintage
Pharmaceuticals, Inc.

3241 Woodpark Boulevard
Charlotte, NC 28206

Phone (704) 596-0516
Fax (704) 598-6237

June 5, 2001

ORIG AMENDMENT
N/AC

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA # 75-907
Hydrochlorothiazide Capsules
12.5 mg
Major Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to our Abbreviated New Drug Application for the above product.

This amendment is in response to a major deficiency letter dated December 7, 2000.

The archival copy of the ANDA consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Ms Fran Hutchins, Plant Manager, at Tel. (704)596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

CJ Nascone

Christopher J. Nascone
Regulatory Affairs

ANDA 75-907

Vintage Pharmaceuticals, Inc.
Attention: Christopher J. Nascone
3241 Woodpark Blvd.
Charlotte, NC 28206

AUG 3 2000

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated July 31, 2000 and your amendment dated August 2, 2000

NAME OF DRUG: Hydrochlorothiazide Capsules, 12.5 mg

DATE OF APPLICATION: June 16, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 19, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Bonnie McNeal
Project Manager
(301) 827-5848

Sincerely yours,

for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

August 2, 2000

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

NEW CORRESP
NC BIO

Re: ANDA # 75-907
Hydrochlorothiazide Capsules
12.5 mg
Telephone Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to our Abbreviated New Drug Application for the above product.

This amendment is in response to a telephone request made on July 31, 2000 by Saundra Middleton of FDA. We have included the following requested item:

1. A revised Form 3454.

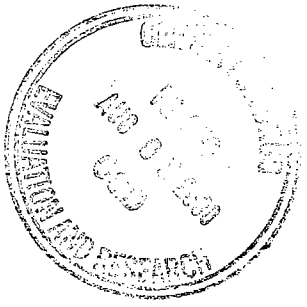
The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed chemistry volume and one orange-jacketed bioequivalence volume.

We look forward to your early response. If you have any questions regarding this amendment, please contact the undersigned, or Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

C J Nascone

Christopher J. Nascone
Regulatory Affairs



3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

ack for filing 5 Middleton 75-907
8/3/00 505(j)

June 16, 2000

Mr. Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Rm. 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Dear Mr. Buehler:

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an original Abbreviated New Drug Application for:

Hydrochlorothiazide Capsules
12.5 mg

In-vivo and *in-vitro* bioequivalence studies are included in Section VI.

Vintage commits to resolve any post approval issues identified which concern the methods validation process.

The archival copy of the amendment consists of five volumes. The review copy consists of six red-jacketed chemistry & manufacturing volumes and three separately bound, orange-jacketed bioequivalence volumes. All volumes contain a complete Table of Contents.

We look forward to your early response. If you have any questions or comments regarding this amendment, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

CJ Nascone

Christopher J. Nascone
Regulatory Affairs