

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **74970**

Trade Name **Triamterene and Hydrochlorthiazide**
Capsules USP 37.5mg/25mg

Generic Name **Triamterene and Hydrochlorthiazide**
Capsules USP 37.5mg/25mg

Sponsor Barr Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74970

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74970

APPROVAL LETTER

JAN 6 1998

Barr Laboratories, Inc.
Attention: Christine A. Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated September 30, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg.

Reference is also made to your amendments dated October 21, 1997 and November 6, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug [Dyazide® Capsules, 37.5 mg/25 mg of SmithKline Beecham Pharmaceuticals]. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

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

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

Sincerely yours,

1-5-98
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74970

FINAL PRINTED LABELING

Each capsule contains 37.5mg triamterene and 25mg hydrochlorothiazide. This product meets USP Dissolution Test 3.

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

Usual Dosage: 1 or 2 capsules once daily. See package brochure.

Dispense in a tight, light-resistant container as defined in the USP/NF. Store at controlled room temperature 15°-30°C (59°-86°F).

BARR LABORATORIES, INC.
Pomona, NY 10970
R4-97
1120875020101



BARR LABORATORIES, INC.



Triamterene and Hydrochlorothiazide Capsules, USP

37.5mg/25mg

Caution: Federal law prohibits dispensing without prescription.

100 Capsules

NDC 0555-0875-02



Exp. Date:

Lot No.:

SAMPLE

Each capsule contains 37.5mg triamterene and 25mg hydrochlorothiazide. This product meets USP Dissolution Test 3.

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

Usual Dosage: 1 or 2 capsules once daily. See package brochure.

Dispense in a tight, light-resistant container as defined in the USP/NF.

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

BARR LABORATORIES, INC.
Pomona, NY 10970

R4-97
1120875050101



BARR LABORATORIES, INC.



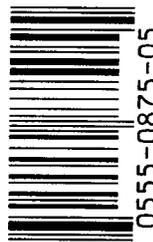
Triamterene and Hydrochlorothiazide Capsules, USP

37.5mg/25mg

Caution: Federal law prohibits dispensing without prescription.

1000 Capsules

NDC 0555-0875-05



N 3

0555-0875-05

Exp. Date:

Lot No.:

SAMPLE

**TRIAMTERENE AND
HYDROCHLOROTHIAZIDE
CAPSULES, USP**



Revised APRIL 1997
1008750101

6 1998

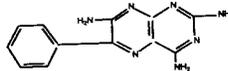
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DESCRIPTION:

Triamterene is an antihypertensive agent and hydrochlorothiazide is a diuretic/antihypertensive agent.

At 50°C, triamterene is practically insoluble in water (less than 0.1%). It is soluble in formic acid, sparingly soluble in methoxyethanol and very slightly soluble in alcohol.

Triamterene is 2,4,7-Triamino-6-phenylpteridine and its structural formula is:

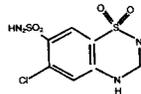


C₁₂H₁₁N₇

Molecular Weight: 253.27

Hydrochlorothiazide is slightly soluble in water. It is soluble in dilute ammonia, dilute aqueous sodium hydroxide and dimethylformamide. It is sparingly soluble in methanol.

Hydrochlorothiazide is 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxide and its structural formula is:



C₇H₈ClN₃O₄S₂

Molecular Weight: 297.75

Each capsule, for oral administration, contains 37.5 mg triamterene and 25 mg hydrochlorothiazide. In addition, inactive ingredients include citric acid, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, poloxamer, povidone, sodium starch glycolate and stearic acid.

The capsule shell contains benzyl alcohol, butyl paraben, carboxymethylcellulose, edetate calcium disodium, gelatin, iron oxide red, iron oxide yellow, methyl paraben, propyl paraben, sodium lauryl sulfate, sodium propionate and titanium dioxide.

The imprinting ink contains black iron oxide, 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, pharmaceutical glaze, propylene glycol and synthetic black iron oxide.

Triamterene and Hydrochlorothiazide Capsules meet USP Dissolution Test 3.

CLINICAL PHARMACOLOGY:

Triamterene and hydrochlorothiazide is a diuretic/antihypertensive drug product that combines natriuretic and antihypertensive effects.

Each component complements the action of the other.

The triamterene component of triamterene and hydrochlorothiazide exerts its diuretic effect on the distal renal tubule to inhibit the reabsorption of sodium in exchange for potassium and hydrogen ions. Its natriuretic activity is limited by the amount of sodium reaching its site of action. Although it blocks the increase in this exchange that is stimulated by mineralocorticoids (chiefly aldosterone) it is not a competitive antagonist of aldosterone and its activity can be demonstrated in adrenalectomized rats and patients with Addison's disease. As a result, the dose of triamterene required is not proportionally related to the level of mineralocorticoid activity, but is dictated by the response of the individual patients, and the kaliuretic effect of concomitantly administered

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The hydrochlorothiazide component blocks the reabsorption of sodium and chloride ions, and 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. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

Duration of diuretic activity and effective dosage range of the triamterene and hydrochlorothiazide components of triamterene and hydrochlorothiazide are similar. Onset of diuresis with triamterene and hydrochlorothiazide takes place within 1 hour, peaks at 2 to 3 hours and tapers off during the subsequent 7 to 9 hours.

Triamterene and hydrochlorothiazide capsule is well absorbed.

It has been reported that upon administration of a single oral dose to fasted normal male volunteers, the following mean pharmacokinetic parameters were determined:

	AUC(0-48) ng hr/mL (±SD)	C _{max} ng/mL (±SD)	Median T _{max} hrs	A _e mg (±SD)
triamterene	1487 (69.9)	46.4 (29.4)	1.1	27 (4)
p-hydroxytriamterene	1885 (47.1)	720 (364)	1.3	19.7 (6.1)
sulfate	834 (177)	135.7 (35.7)	2.0	14.3 (3.8)

where AUC(0-48), C_{max}, T_{max} and A_e represent area under the plasma concentration versus time plot, maximum plasma concentration, time to reach C_{max} and amount excreted in urine over 48 hours.

One triamterene and hydrochlorothiazide capsule is bioequivalent to a single-entity 37.5 mg triamterene and 25 mg hydrochlorothiazide capsule used in the double-blind clinical trial below. (See Clinical Trials.)

In a limited study involving 12 subjects, coadministration of a marketed brand of triamterene and hydrochlorothiazide capsule with a high-fat meal resulted in: (1) an increase in the mean bioavailability of triamterene by about 67% (90% confidence interval = 0.99, 1.90), p-hydroxytriamterene sulfate by about 50% (90% confidence interval = 1.06, 1.77), hydrochlorothiazide by about 17% (90% confidence interval = 0.90, 1.34); (2) increases in the peak concentration of triamterene and p-hydroxytriamterene; and (3) a delay of up to 2 hours in the absorption of the active constituents.

Clinical Trials:

A placebo-controlled, double-blind trial was conducted to evaluate the efficacy of triamterene and hydrochlorothiazide capsules. This trial demonstrated that triamterene and hydrochlorothiazide (37.5 mg triamterene/25 mg hydrochlorothiazide) was effective in controlling blood pressure while reducing the incidence of hydrochlorothiazide-induced hypokalemia. This trial involved 636 patients with mild to moderate hypertension con-

	Median Time to Reach C _{max} (h)	Median Ae mg (±SD)
4	11	27(4)
34	1.3	19.7(6.1)
33.7	2.0	14.3(3.8)

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Blood pressure and serum potassium were monitored at baseline and throughout the trial. All five treatment groups had similar mean blood pressure and serum potassium concentrations at baseline (mean systolic blood pressure range: 137 ± 14 mmHg to 140 ± 16 mmHg; mean diastolic blood pressure range: 86 ± 9 mmHg to 88 ± 8 mmHg; mean serum potassium range: 2.3 to 3.4 mEq/L with the majority of patients having values between 3.1 and 3.4 mEq/L).

While all triamterene regimens reversed hypokalemia, at week 4 the 37.5 mg regimen proved optimal compared with the other tested regimens. On this regimen, 81% of the patients had a significant (p<0.05) reversal of hypokalemia vs. 59% of patients on the placebo/hydrochlorothiazide regimen. The mean serum potassium concentration on 37.5 mg triamterene went from 3.2 ± 0.2 mEq/L at baseline to 3.7 ± 0.3 mEq/L at week 4, a significantly greater (p<0.05) improvement than that achieved with placebo/hydrochlorothiazide (i.e., 3.2 ± 0.2 mEq/L at baseline and 3.5 ± 0.4 mEq/L at week 4). Also, 51% of patients in the 37.5 mg triamterene group had an increase in serum potassium of ≥0.5 mEq/L at week 4 vs. 33% in the placebo group. The 37.5 mg triamterene/25 mg hydrochlorothiazide regimen also maintained control of blood pressure; mean supine systolic blood pressure at week 4 was 138 ± 21 mmHg while mean supine diastolic blood pressure was 87 ± 13 mmHg.

INDICATIONS AND USAGE:

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

Triamterene and hydrochlorothiazide capsules is indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone.

Triamterene and hydrochlorothiazide capsules is also indicated for those patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.

Triamterene and hydrochlorothiazide capsules may be used alone or as an adjunct to other antihypertensive drugs, such as beta-blockers. Since triamterene and hydrochlorothiazide capsules may enhance the action of these agents, dosage adjustments may be necessary.

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

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CONTRAINDICATIONS:

Antikaliuretic Therapy and Potassium Supplementation:

Triamterene and hydrochlorothiazide should not be given to patients receiving other potassium-sparing agents such as spironolactone, amiloride or other formulations containing triamterene. Concomitant potassium-containing salt substitutes should also not be used.

Potassium supplementation should not be used with triamterene and hydrochlorothiazide except in severe cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

Impaired Renal Function:

Triamterene and hydrochlorothiazide is contraindicated in patients with anuria, acute and chronic renal insufficiency or significant renal impairment.

Hypersensitivity:

Hypersensitivity to either drug in the preparation or to other sulfonamide-derived drugs is a contraindication.

Hyperkalemia:

Triamterene and hydrochlorothiazide should not be used in patients with preexisting elevated serum potassium.

WARNINGS:

Hyperkalemia:

Abnormal elevation of serum potassium levels (greater than or equal to 5.5mEq/liter) can occur with all potassium-sparing diuretic combinations, including triamterene and hydrochlorothiazide. Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even without evidence of renal impairment), and in the elderly or severely ill. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving triamterene and hydrochlorothiazide, when dosages are changed or with any illness that may influence renal function.

If hyperkalemia is suspected (warning signs include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because hyperkalemia may not be associated with ECG changes.

If hyperkalemia is present, triamterene and hydrochlorothiazide should be discontinued immediately and a thiazide alone should be substituted. If the serum potassium exceeds 6.5 mEq/liter more vigorous therapy is required. The clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence of renal impairment (see **CONTRAINDICATIONS** section). Patients with mild renal functional impairment should not receive this drug without frequent and continuing monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with impaired renal function. The renal clearances of hydrochlorothiazide and the pharmacologically active metabolite of triamterene, the sulfate ester of hydroxytriamterene, have been shown to be reduced and the plasma levels increased following triamterene and hydrochlorothiazide administration to elderly patients and patients with impaired renal function.

Hyperkalemia has been reported in diabetic patients with the use of potassium-sparing agents even in the absence of apparent renal impairment. Accordingly, serum electrolytes must be frequently monitored if triamterene and hydrochlorothiazide is used in diabetic patients.

Metabolic or Respiratory Acidosis:

Potassium-sparing therapy should also be avoided in severely ill patients in whom respiratory or metabolic acidosis may occur. Acidosis may be associated with rapid elevations in serum potassium levels. If triamterene and hydrochlorothiazide is employed, frequent evaluations of acid/base balance and serum electrolytes are necessary.

PRECAUTIONS:

Impaired Hepatic Function:

Thiazides should be used with caution in patients with impaired hepatic function. They can produce

and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because hyperkalemia may not be associated with ECG changes.

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PRECAUTIONS:

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. Potassium depletion induced by the thiazide may be important in this connection. Administer triamterene and hydrochlorothiazide cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases discontinue triamterene and hydrochlorothiazide for a few days. Attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion.

Hypokalemia:

Hypokalemia is uncommon with triamterene and hydrochlorothiazide; but, should it develop, cor-

(Over)

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corrective measures should be taken such as potassium supplementation or increased intake of potassium-rich foods. Institute such measures cautiously with frequent determinations of serum potassium levels, especially in patients receiving digitalis or with a history of cardiac arrhythmias. If serious hypokalemia (serum potassium less than 3.0 mEq/L) is demonstrated by repeat serum potassium determinations, triamterene and hydrochlorothiazide should be discontinued and potassium chloride supplementation initiated. Less serious hypokalemia should be evaluated with regard to other coexisting conditions and treated accordingly.

Electrolyte imbalance:

Electrolyte imbalance, often encountered in such conditions as heart failure, renal disease or cirrhosis of the liver, may also be aggravated by diuretics and should be considered during triamterene and hydrochlorothiazide therapy when using high doses for prolonged periods or in patients on a salt-restricted diet. Serum determinations of electrolytes should be performed, and are particularly important if the patient is vomiting excessively or receiving fluids parenterally. Possible fluid and electrolyte imbalance may be indicated by such warning signs as: dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal symptoms.

Hypochloremia:

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Renal Stones:

Triamterene has been found in renal stones in association with the other usual calculus components. Triamterene and hydrochlorothiazide should be used with caution in patients with a history of renal stones.

Laboratory Tests:

Serum Potassium: The normal adult range of serum potassium is 3.5 to 5.0 mEq per liter with 4.5 mEq often being used for a reference point. If hypokalemia should develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods.

Institute such measures cautiously with frequent determinations of serum potassium levels. Potassium levels persistently above 6 mEq per liter require careful observation and treatment. Serum potassium levels do not necessarily indicate true body potassium concentration. A rise in plasma pH may cause a decrease in plasma potassium concentration and an increase in the intracellular potassium concentration. Discontinue corrective measures for hypokalemia immediately if laboratory determinations reveal an abnormal elevation of serum potassium. Discontinue triamterene and hydrochlorothiazide and substitute a thiazide diuretic alone until potassium levels return to normal.

Serum Creatinine and BUN: Triamterene and hydrochlorothiazide may produce an elevated blood urea nitrogen level, creatinine level or both. This apparently is secondary to a reversible reduction of glomerular filtration rate or a depletion of intravascular fluid volume (prerenal azotemia) rather than renal toxicity; levels usually return to normal when triamterene and hydrochlorothiazide is discontinued. If azotemia increases, discontinue triamterene and hydrochlorothiazide. Periodic BUN or serum creatinine determinations should be made, especially in elderly patients and in patients with suspected or confirmed renal insufficiency.

Serum PBI: Thiazide may decrease serum PBI levels without sign of thyroid disturbance.

Parathyroid Function: Thiazides should be discontinued before carrying out tests for parathyroid function. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as bone resorption and peptic ulceration have not been seen.

Drug Interactions:

Angiotensin-converting enzyme inhibitors: Potassium-sparing agents should be used with caution in conjunction with angiotensin-converting enzyme (ACE) inhibitors due to an increased risk of hyperkalemia.

Oral hypoglycemic drugs: Concurrent use with chlorpropamide may increase the risk of severe hyponatremia.

Nonsteroidal anti-inflammatory drugs: A possible interaction resulting in acute renal failure has been reported in a few patients on triamterene and hydrochlorothiazide when treated with indomethacin, a nonsteroidal anti-inflammatory agent. Caution is advised in administering nonsteroidal anti-inflammatory agents with triamterene and hydrochlorothiazide.

Lithium: Lithium generally should not be given with diuretics because they reduce its renal clearance and increase the risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy with triamterene and hydrochlorothiazide.

Surgical considerations: Thiazides have been shown to decrease arterial responsiveness to norepinephrine (an effect attributed to loss of sodium). This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine.

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Other considerations: Concurrent use of hydrochlorothiazide with amphotericin B or corticosteroids or corticotropin (ACTH) may intensify electrolyte imbalance, particularly hypokalemia, although the presence of triamterene minimizes the hypokalemic effect.

Thiazides may add to or potentiate the action of other antihypertensive drugs. See **INDICATIONS AND USAGE** for concomitant use with other antihypertensive drugs.

The effect of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary.

Triamterene and hydrochlorothiazide may raise the level of blood uric acid; dosage adjustments of antigout medication may be necessary to control hyperuricemia and gout.

The following agents given together with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia because of the potassium-sparing nature of triamterene, especially in patients with renal insufficiency: Blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium); salt substitutes (most contain substantial amounts of potassium).

Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium levels by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake.

Chronic or overuse of laxatives may reduce serum potassium levels by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene.

The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalization of the urine.

Drug/Laboratory Test Interactions:

Triamterene and quinidine have similar fluorescence spectra; thus, triamterene and hydrochlorothiazide will interfere with the fluorescent measurement of quinidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis:

Long-term studies have not been conducted with triamterene and hydrochlorothiazide (the triamterene/hydrochlorothiazide combination), or with triamterene alone.

Hydrochlorothiazide: Two-year feeding studies in mice and rats, conducted under the auspices of the National Toxicology Program (NTP), treated the mice and rats with doses of hydrochlorothiazide up to 600 and 100 mg/kg/day, respectively. On a body-weight basis, these doses are 600 times (in mice) and 100 times (in rats) the Maximum Recommended Human Dose (MRHD) for the hydrochlorothiazide component of triamterene and hydrochlorothiazide at 50 mg/day (or 1 mg/kg/day based on 50 kg individuals). On the basis of body-surface area, these doses are 56 times (in mice) and 21 times (in rats) the MRHD. These studies uncovered no evidence of carcinogenic potential of hydrochlorothiazide in rats or female mice, but there was equivocal evidence of hepatocarcinogenicity in male mice.

Mutagenesis:

Studies of the mutagenic potential of the triamterene/hydrochlorothiazide combination, or of triamterene alone have not been performed.

Hydrochlorothiazide: Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (the Ames test), in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* 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 in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test, and in the mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43 to 1300 mcg/mL. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.

Impairment of Fertility:

Studies of the effects of the triamterene/hydrochlorothiazide combination, or of triamterene alone on animal reproductive function have not been conducted.

Hydrochlorothiazide: Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of

Triamterene alone have not been performed.

Hydrochlorothiazide: Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (the Ames test), in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* 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 in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test, and in the mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43 to 1300 mcg/mL. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.

Impairment of Fertility:

Studies of the effects of the triamterene/hydrochlorothiazide combination, or of triamterene alone on animal reproductive function have not been conducted.

Hydrochlorothiazide: 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/day, respectively, prior to mating and throughout gestation. Corresponding multiples of the MRHD are 100 (mice) and 4 (rats) on the basis of body-weight and 9.4 (mice) and 0.8 (rats) on the basis of body-surface area.

PREGNANCY:

Category C:

Teratogenic Effects: Triamterene and hydrochlorothiazide: Animal reproduction studies to determine the potential for fetal harm by triamterene and hydrochlorothiazide have not been conducted. However, a One Generation Study in the rat approximated triamterene and hydrochlorothiazide composition by using a 1:1 ratio of triamterene to hydrochlorothiazide (30:30 mg/kg/day); there was no evidence of teratogenicity at those doses which were, on a body-weight basis, 15 and 30 times, respectively, the MRHD, and on the basis of body-surface area, 3.1 and 6.2 times, respectively, the MRHD.

The safe use of triamterene and hydrochlorothiazide in pregnancy has not been established since there are no adequate and well-controlled studies with triamterene and hydrochlorothiazide in pregnant women. Triamterene and hydrochlorothiazide should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Triamterene: Reproduction studies have been performed in rats at doses as high as 20 times the MRHD on the basis of body-weight, and 6 times the human dose on the basis of body-surface area without evidence of harm to the fetus due to triamterene.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Hydrochlorothiazide: Hydrochlorothiazide was orally administered to pregnant mice and rats during respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively. At these doses, which are multiples of the MRHD equal to 3000 for mice and 1000 for rats, based on body-weight, and equal to 282 for mice and 206 for rats, based on body-surface area, there was 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 and triamterene have been shown to cross the placental barrier and appear in cord blood. The use of thiazides and triamterene in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, pancreatitis, thrombocytopenia and possible other adverse reactions which have occurred in the adult.

Nursing Mothers:

Thiazides and triamterene in combination have not been studied in nursing mothers. Triamterene appears in animal milk; this may occur in humans. Thiazides are excreted in human breast milk. If use of the combination drug product is deemed essential, the patient should stop nursing.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

Adverse effects are listed in decreasing order of frequency; however, the most serious adverse effects are listed first regardless of frequency. The serious adverse effects associated with triamterene and hydrochlorothiazide have commonly occurred in less than 0.1% of patients treated with this product.

Hypersensitivity: anaphylaxis, rash, urticaria, photosensitivity.

Cardiovascular: arrhythmia, postural hypotension.

Metabolic: diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia.

Gastrointestinal: jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain.

Renal: acute renal failure (one case of irreversible renal failure has been reported), interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment.

Hematologic: leukopenia, thrombocytopenia and purpura, megaloblastic anemia.

Musculoskeletal: muscle cramps.

hypochloremia.

Gastrointestinal: jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain.

Renal: acute renal failure (one case of irreversible renal failure has been reported), interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment.

Hematologic: leukopenia, thrombocytopenia and purpura, megaloblastic anemia.

Musculoskeletal: muscle cramps

Central Nervous System: weakness, fatigue, dizziness, headache, dry mouth.

Miscellaneous: impotence, sialadenitis.

Thiazides alone have been shown to cause the following additional adverse reactions:

Central Nervous System: paresthesias, vertigo.

Ophthalmic: xanthopsia, transient blurred vision.

Respiratory: allergic pneumonitis, pulmonary edema, respiratory distress.

Other: necrotizing vasculitis, exacerbation of lupus.

Hematologic: aplastic anemia, agranulocytosis, hemolytic anemia.

Neonate and infancy: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.

OVERDOSAGE:

Electrolyte imbalance is the major concern (see **WARNINGS** section). Symptoms reported include: polyuria, nausea, vomiting, weakness, lassitude, fever, flushed face and hyperactive deep tendon reflexes. If hypotension occurs, it may be treated with pressor agents such as levaterenol to maintain blood pressure. Carefully evaluate the electrolyte pattern and fluid balance. Induce immediate evacuation of the stomach through emesis or gastric lavage. There is no specific antidote.

Reversible acute renal failure following ingestion of 50 tablets of a product containing a combination of 50 mg triamterene and 25 mg hydrochlorothiazide has been reported.

Although triamterene is largely protein-bound (approximately 67%), there may be some benefit to dialysis in cases of overdosage.

DOSAGE AND ADMINISTRATION:

The usual dose of triamterene and hydrochlorothiazide capsules 37.5 mg/25 mg is one or two capsules given once daily, with appropriate monitoring of serum potassium and of the clinical effect. (See **WARNINGS**, **Hyperkalemia**.)

HOW SUPPLIED:

Capsules containing 37.5 mg Triamterene and 25 mg Hydrochlorothiazide are available as opaque brown cap and opaque white body filled with yellow powder and imprinted in black ink in 875 in bottles of:

30 NDC 0555-0875-01
100 NDC 0555-0875-02
1000 NDC 0555-0875-05

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

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

CAUTION: Federal law prohibits dispensing without prescription.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised APRIL 1997
BR-875

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **74970**

CHEMISTRY REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74970

BIOEQUIVALENCE REVIEW(S)

DW

ANDA 74-970

Barr Laboratories, Inc.
Attention: Christine A. Mundkur
2 Quaker Road
P.O. BOX 2900
Pomona NY 10970-0519

FEB 10 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Triamterene and Hydrochlorothiazide Capsules, 37.5 mg/25 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The following interim dissolution testing will need to be 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 23 apparatus 1 (basket) at 100 rpm. The test product should meet the following USP specifications:

NLT 75% (Q) in 45 minutes for Hydrochlorothiazide
NLT 75% (Q) in 45 minutes for Triamterene

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

Sincerely yours,

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Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Triamterene/Hydrochlorothiazide
37.5 mg/25mg Capsule
ANDA # 74-970
Reviewer: Moheb H. Makary
WP 74970SD.996

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
September 30, 1996

Review Of Bioequivalence Studies And Dissolution Data

I. Objective:

The firm has submitted two bioequivalence studies under fasting and nonfasting conditions on its Triamterene/Hydrochlorothiazide, 37.5 mg/25mg Capsule to compare the plasma levels of triamterene, p-hydroxytriamterene sulfate and hydrochlorothiazide, after administration of single dose of 1x37.5 mg/25 mg Capsule of the test formulation with that of SmithKline Beecham reference product (Dyazide^R capsule 37.5 mg/25mg).

II. Background:

Triamterene/hydrochlorothiazide is a diuretic/antihypertensive drug that combines natriuretic and antikaliuretic effects. It is indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone. Each component complements the action of the other. The hydrochlorothiazide component blocks the reabsorption of sodium and chloride ions, and thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. The triamterene component inhibits the reabsorption of sodium in exchange for potassium and hydrogen ions.

Triamterene is rapidly absorbed from GI tract; however, the degree of absorption varies in different individuals. Peak plasma concentrations of 0.05-0.28 ug/mL are achieved within 2-4 hours following administration of 100 to 200 mg single oral dose. The plasma half-life of triamterene is 100-150 minutes. The metabolic and excretory fate of triamterene has not been fully determined. The drug is reportedly metabolized to 6-p-hydroxytriamterene and its sulfate conjugate. Triamterene is excreted in urine as unchanged drug and metabolites. In one study in healthy males, the urinary excretion of 6-p-hydroxytriamterene was up 3 times that of unchanged drug. The formed hydroxytriamterene sulfate is pharmacologically active.

Hydrochlorothiazide (HCTZ) is widely used in the treatment of hypertension. It is rapidly absorbed from the gastrointestinal tract with peak concentrations occurring approximately 1 to 3 hours after dosing. Elimination of HCTZ from the body occurs via excretion of unchanged drug in the urine, with reported elimination half-life of 3 to 9 hours. The onset of diuresis following an acute dose of HCTZ corresponds well with plasma drug

concentration, occurring within 12 hours after administration and is essentially complete within 12 hours of a dose.

In a limited study involving 12 subjects, coadministration of Triamterene/hydrochlorothiazide 37.5 mg/25 mg capsule with a high-fat meal resulted in: 1) an increase in the mean bioavailability of triamterene by about 67%, p-hydroxytriamterene sulfate by about 50%, hydrochlorothiazide by about 17%; 2) increase in the peak concentrations of triamterene and p-hydroxytriamterene; and 3) a delay of up to 2 hours in the absorption of the active constituents.

Triamterene/Hydrochlorothiazide combination products are available as oral capsules (37.5 mg/25 mg strength) and oral tablets (75mg/50mg and 37.5mg/25mg strengths).

III. Study #P95-003 For Single Dose Fasting Bioequivalence Of Barr's Triamterene/Hydrochlorothiazide, 37.5 mg/25mg Capsule.

Study site:

Analytical site:

Investigators:

Study date: Period I June 15-17, 1996
Period II June 29-July 1, 1996

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

Subjects: Forty (40) healthy male subjects recruited for the study. forty (40) subjects began the study. Thirty-nine subjects completed the study.

Selection criteria: Subjects selected for the study met the following acceptance criteria:

1. Ages 18-35 years, \pm 10% of the ideal weight for his height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests

(blood chemistry, hematology, urinalysis).

3. No concurrent illness, acute or chronic diseases or history of serious cardiovascular, pulmonary, endocrine, immunologic, dermatologic, renal, G.I., hepatic, hematologic, neurologic, or psychiatric disease.
4. No history of alcohol or drug abuse.
5. No history of hypersensitivity to Triamterene/Hydrochlorothiazide or related drugs.
6. Volunteers who currently are not using tobacco products.

Restrictions:

1. No alcohol consumption for at least 48 hours prior to drug administration, each period. Volunteers were instructed to abstain from consuming caffeine and/or xanthine-containing products at least 48 hours prior to days on which dosing was scheduled and during the periods when blood samples were being collected.
2. Volunteers were instructed not to consume any nonprescription medication within 7 days of period I dosing.

Dose and treatment: All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:

Test Product:

a) 1x37.5/25 mg
Triamterene/Hydrochlorothiazide Capsule (Barr), lot #6R87511, batch size capsules, Exp. N/A, potency 97.5% and 99.7%, content uniformity 98.9(%CV=1.4) and 100.2(%CV=1.2) for triamterene and hydrochlorothiazide, respectively.

Reference Product:

b) 1x37.5/25 mg Dyazide^R Capsule (Smithkline Beecham), lot #205E50, Exp. 4/97, potency 97.9% and 97.1%, content uniformity 99.0(%CV=1.6) and 99.6% (%CV=1.5) for triamterene and hydrochlorothiazide, respectively.

Washout period:

Two weeks

Food and fluid intake: Subjects fasted for ten hours prior to dosing. Lunch was served four hours after dosing. No fluid except that given with drug administration was allowed from 1 hour prior to dose administration until 1 hour after dosing. Water was allowed ad lib, if requested, after study hour 1.

Blood samples: Blood samples were collected at 0 (pre-dose), 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24, 36 and 48 hours. Plasma was separated and promptly frozen for analysis of triamterene, p-hydroxytriamterene sulfate and hydrochlorothiazide.

Urine samples: Urine samples were collected (-1-0, 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-24, 24-36 and 36-48 hours) but were not analyzed.

Subjects welfare: Vital signs (including blood pressure and heart rate) were measured prior to each dose and at 6, 12, 24, 48 and 48 hours after each dose.

Analytical Methodology

Statistical Analysis

Statistical analysis was performed on triamterene, p-hydroxytriamterene sulfate and Hydrochlorothiazide data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval. The data analyzed by ANOVA were performed for blood drug concentrations at each sampling time. The 90% confidence intervals using the two one-sided t test method were calculated for AUCLQC, AUCinf and Cmax for each analyte.

IV. In Vivo Results:

Forty (40) healthy male subjects were accepted for entry into the clinical phase of the study. Thirty-nine (39) subjects successfully completed both phases of the study. Subject #29 failed to report for period II check-in. Seventeen adverse events were reported in nine of forty subjects dosed over the course of the study. Of the seventeen reported adverse events, four were probably or possibly related to study drug (headache, nausea). In the opinion of the investigators, the other thirteen adverse events were either remotely related to or unrelated to study drug. None of the adverse events was considered serious or resulted in termination any subject from the study participation.

The plasma levels and pharmacokinetic parameters for p-hydroxytriamterene sulfate, triamterene and hydrochlorothiazide are summarized below:

Table I

Mean Plasma p-Hydroxytriamterene Sulfate Concentrations and Pharmacokinetic Parameters Following a Single Dose of 37.5 mg/25 mg Triamterene/Hydrochlorothiazide Capsules Under Fasting Conditions
(N=39)

<u>Time</u> <u>hr</u>	<u>A</u>	<u>B</u>
	<u>Barr</u> <u>Test Product</u> Lot# 6R87511 ng/mL (%CV)	<u>SmithKline</u> <u>Reference Product</u> Lot # 205E50 ng/mL (%CV)
0	0.00	0.00
0.17	0.45 (624)	0.00
0.33	80.57 (130)	128.47 (94)

0.50	361.44 (77)	557.66 (61)
0.75	722.72 (49)	1007.28 (41)
1.00	895.68 (42)	1035.95 (30)
1.25	924.67 (32)	977.49 (23)
1.50	873.85 (29)	867.10 (27)
2	665.87 (32)	622.08 (32)
2.50	493.69 (31)	452.33 (32)
3	368.03 (32)	341.23 (33)
4	216.15 (31)	203.95 (33)
6	104.96 (30)	102.31 (31)
8	50.77 (31)	49.05 (32)
10	28.22 (32)	26.72 (32)
12	18.65 (42)	15.97 (49)
14	11.82 (78)	8.71 (91)
24	3.32 (202)	1.05 (362)
36	0.60 (438)	0.30 (625)
48	0.00	0.00

	<u>Mean (%CV)</u>	<u>Mean (%CV)</u>	<u>90% CI</u>
AUCTLQC			
ng.hr/mL	2697(21)	2725(21)	
AUCinf			
ng.hr/mL	2822(20)	2810(21)	
Cmax (ng/mL)	1036(27)	1164(27)	
Kel (1/hr)	0.255	0.286	
Half (hr)	3.78	3.04	
Tmax(hr)	1.18	1.00	
LnAUCTLQC			94.9-102.9%
LnAUCinf			95.9-104.1%
LnCmax			84.2-93.5%

1. The p-hydroxytriamterene sulfate plasma levels peaked at 1 and 1.25 hours for the reference and the test products, respectively. There were no statistically significant differences between the plasma p-hydroxytriamterene sulfate levels at all sampling time points except at 0.33, 0.5, 0.75, 1, 12, 14 and 24 hours after dosing.

2. For Barr test product, the mean AUCTLQC, Cmax and AUCinf values are 1.03%, 0.43% and 11.00% lower and higher, respectively, than those for the reference product values. The difference is statistically significant for Cmax. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCTLQC, AUCinf and Cmax.

Table II

Mean Plasma Triamterene Concentrations and
Pharmacokinetic Parameters Following a Single Dose of
37.5 mg/25 mg Triamterene/Hydrochlorothiazide Capsules Under
Fasting Conditions
(N=39)

Time hr	A	B		
	Barr <u>Test Product</u> Lot# 6R87511 ng/mL (%CV)	SmithKline <u>Reference Product</u> Lot # 205E50 ng/mL (%CV)		
0	0.00	0.00		
0.17	1.34 (370)	1.18 (240)		
0.33	27.04 (105)	44.19 (78)		
0.50	61.82 (70)	91.21 (52)		
0.75	81.97 (54)	106.03 (38)		
1.00	85.06 (43)	96.02 (27)		
1.25	84.84 (33)	90.84 (27)		
1.50	78.74 (32)	81.92 (28)		
2	63.27 (32)	64.05 (27)		
2.50	51.00 (32)	51.74 (30)		
3	42.01 (34)	42.10 (29)		
4	28.52 (33)	28.52 (31)		
6	11.64 (34)	11.71 (34)		
8	5.74 (39)	5.90 (36)		
10	2.83 (62)	2.67 (63)		
12	1.12 (143)	0.85 (147)		
14	0.52 (254)	0.33 (267)		
24	0.09 (625)	0.06 (625)		
36	0.00	0.00		
48	0.00	0.00		
	<u>Mean (%CV)</u>	<u>Mean (%CV)</u>	<u>90% CI</u>	
AUCTLQC				
ng.hr/mL	284 (28)	303 (26)		
AUCinf				
ng.hr/mL	296 (29)	320 (30)		
Cmax (ng/mL)	102 (33)	117 (32)		
Kel (1/hr)	0.337	0.338		
Half (hr)	3.03	4.49		
Tmax (hr)	1.03	0.84		
LnAUCTLQC			87.2-97.9%	
LnAUCinf			87.0-97.5%	
LnCmax			80.3-90.7%	

1. The triamterene plasma levels peaked at 0.75 and 1.00 hours for the reference and the test products, respectively. There were no statistically significant differences between the plasma triamterene levels at all sampling time points except at 0.33, 0.5, 0.75 and 1 hours after dosing.

2. For Barr test product, the mean AUCTLQC, AUCinf and Cmax values are 6.27%, 7.50% and 12.82% lower, respectively, than those for the reference product values. The differences are statistically significant. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCTLQC, AUCinf and Cmax.

Table III

Mean Plasma Hydrochlorothiazide Concentrations and Pharmacokinetic Parameters Following a Single Dose of 37.5 mg/25 mg Triamterene/Hydrochlorothiazide Capsules Under Fasting Conditions (N=39)

Time hr	A	B	<u>90% CI</u>
	<u>Barr</u> Lot# 6R87511 ng/mL (%CV)	<u>SmithKline</u> Reference Product Lot # 205E50 ng/mL (%CV)	
0	0.00	0.00	
0.17	0.00	0.00	
0.33	1.33 (501)	4.12 (204)	
0.50	14.54 (137)	28.01 (81)	
0.75	47.81 (63)	78.12 (52)	
1.00	82.73 (51)	113.88 (44)	
1.25	112.79 (47)	138.89 (34)	
1.50	133.06 (38)	146.61 (27)	
2	140.44 (27)	141.23 (23)	
2.50	133.89 (20)	127.49 (21)	
3	120.17 (23)	114.79 (18)	
4	100.13 (21)	90.11 (18)	
6	54.56 (22)	52.56 (27)	
8	38.53 (22)	37.68 (20)	
10	29.70 (27)	28.65 (21)	
12	25.20 (46)	22.21 (21)	
14	18.49 (29)	18.45 (24)	
24	6.74 (97)	6.46 (108)	
36	0.64 (442)	0.43 (625)	
48	0.36 (624)	0.27 (625)	
	<u>Mean (%CV)</u>	<u>Mean (%CV)</u>	

AUCTLQC		
ng.hr/mL	911(27)	896(26)
AUCinf		
ng.hr/mL	1069(28)	1046(26)
Cmax (ng/mL)	156(26)	156(27)
Kel (1/hr)	0.097	0.10
Half (hr)	8.35	8.50
Tmax(hr)	2.01	1.78

LnAUCTLQC	96.3-106.7%
LnAUCinf	96.3-106.0%
LnCmax	95.9-104.2%

1. The Hydrochlorothiazide plasma levels peaked at 1.5 and 2.00 hours for the reference and the test products, respectively. There were no statistically significant differences between the plasma HCTZ levels at all sampling time points except at 0.5, 0.75, 1, 1.25 and 4 hours after dosing.

2. For Barr test product, the mean AUCTLQC and AUCinf values are 1.67% and 2.20% higher, respectively, than those for the reference product values. The differences are not statistically significant. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCTLQC, AUCinf and Cmax.

V. Single Dose Post-Prandial Bioequivalence Study #P95-051:

Study site:

Analytical site:

Investigators:

Study date: Period I June 8-10, 1996
 Period II June 22-24, 1996
 Period III July 6-8, 1996

Study design: Open-label, randomized, 3-way crossover, single-dose study under fasting and nonfasting conditions.

Subjects: Twenty-four (24) healthy male subjects recruited for the study. Twenty-four (24) subjects began the study. Twenty-two subjects completed the study.

Selection criteria: Same as in the study #P95-003 above.

Dose and treatment: All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:

Treatment A: 1 x 37.5 mg/25 mg (Fasting)
Triamterene/Hydrochlorothiazide, capsules
(Barr), lot #6R87511

Treatment B: 1 x 37.5 mg/25 mg
(Nonfasting) Triamterene/Hydrochlorothiazide capsules
(Barr), lot #6R87511.

Treatment C: 1 x 37.5 mg/25 mg Dyazide^R capsules (Smith
(Nonfasting) Kline Beecham), lot #205E50

Food and fluid
intake:

Subjects were required to fast overnight for 10 hours prior to dosing in each treatment phase. Subjects on regimen A ingested the capsules with 240 mL of water. Subjects on regimen B and C ingested the capsules with 240 mL of water within 30 minutes after a standardized high-fat breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice). No fluid except that given with drug administration was allowed from 1 hour prior to dose administration until 1 hour after dosing. Water was allowed ad lib, if requested, after study hour 1.

Blood samples: Same as study #P95-003 above.

Urine samples: Same as study #P95-003 above.

Analytical Methodology

Same as study #P95-003 above.

Statistical Analysis

Statistical analysis was performed on triamterene, p-hydroxytriamterene sulfate and Hydrochlorothiazide data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval. The data analyzed by ANOVA were performed for blood drug concentrations at each sampling time.

The 90% confidence intervals using the two one-sided t test method were calculated for AUCTLQC, AUCinf and Cmax for each analyte.

VI. In Vivo Results:

Twenty-four (24) healthy male subjects were accepted for entry into the clinical phase of the study. Twenty-two (22) subjects successfully completed both phases of the study. Subjects #7 and 21 dropped from the study when they failed to report for period II check-in. Forty-seven adverse events were reported in fifteen subjects dosed over the course of the study. Of the forty-seven reported adverse events, twelve were probably or possibly related to study drug (headache, hot flushes, coughing, heart burn). In the opinion of the investigators, the other thirty-five adverse events were either remotely related to or unrelated to study drug. None of the adverse events was considered serious or resulted in termination of any subject from participation.

The plasma levels and pharmacokinetic parameters for p-hydroxytriamterene sulfate, triamterene and hydrochlorothiazide are summarized below:

Table IV

Mean Plasma Hydroxytriamterene Concentrations and Pharmacokinetic Parameters Following a Single Dose of 37.5 mg/25 mg Triamterene/Hydrochlorothiazide (X37.5mg/25 mg Capsules) Under Fasting and Nonfasting Conditions (N=22)

Time hr	A	B	C	B/C
	Barr Test Product Lot# 6R87511 Fasting ng/mL (%CV)	Reference Product Lot #6R87511 Nonfasting ng/mL (%CV)	SmithKline Test Product Lot #205E50 Nonfasting ng/mL (%CV)	
0	0.00	0.00	0.00	
0.17	0.00 (.)	0.00 (.)	0.00 (.)	
0.33	98.46 (90.4)	0.00 (.)	0.73 (469)	
0.50	406.50 (56.4)	6.50 (274)	10.74 (158)	
0.75	758.14 (43.0)	28.63 (179)	60.91 (121)	
1.00	910.18 (28.1)	66.79 (150)	136.50 (102)	
1.25	914.36 (18.4)	135.38 (125)	242.51 (78.7)	
1.5	855.41 (18.1)	208.32 (102)	362.32 (62.8)	
2.0	633.86 (21.1)	318.59 (74.1)	509.96 (44.1)	
2.5	458.50 (25.0)	459.36 (52.8)	606.50 (29.0)	
3.0	340.50 (25.3)	572.01 (40.4)	593.00 (19.0)	
4	201.23 (27.2)	584.68 (29.1)	473.59 (20.2)	
6.0	99.46 (26.2)	264.00 (42.2)	219.59 (37.6)	
8	48.41 (27.3)	108.60 (42.5)	100.91 (46.9)	
10	28.06 (30.7)	54.11 (42.7)	51.98 (50.5)	
12	16.73 (41.6)	30.50 (45.9)	28.40 (50.7)	
14	9.66 (77.3)	19.14 (59.1)	15.96 (73.1)	
24	2.50 (274)	1.27 (469)	0.46 (469)	
36	0.00 (.)	0.00 (.)	0.00 (.)	
48	0.00 (.)	0.00 (.)	0.00 (.)	
	<u>Mean (%CV)</u>	<u>Mean (%CV)</u>	<u>Mean (%CV)</u>	
AUCLQC				
ng.hr/mL	2585.69 (15.2)	2783.79 (15.8)	2786.13 (11.8)	0.99
AUCinf				
ng.hr/mL	2682.20 (14.4)	2858.97 (16.3)	2850.80 (12.1)	1.00
Cmax (ng/mL)	1004.73 (17.0)	722.64 (19.0)	690.82 (19.9)	1.04
Kel (1/hr)	0.297	0.289	0.298	
Half (hr)	2.39	2.64	2.44	
Tmax (hr)	1.170	3.23	2.77	

1. The p-hydroxytriamterene sulfate plasma levels peaked at 2.5 and 4 hours for the reference and test products, respectively, under nonfasting conditions.

2. For Barr test product, the means AUCinf and Cmax values are 0.3% and 4.6% 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 0.8-1.2 for AUCTLQC, AUCinf and Cmax.

3. The mean AUCTLQC of the test product was increased by 7.7% and the mean Cmax was reduced by 28.1%, when dosed under nonfasting conditions compared to fasting conditions. This increase in AUC value is in agreement with the reference product's data (PDR) which indicated that food intake increases the mean bioavailability of triamterene sulfate and causes a delay of up to 2 hours in the absorption of the active constituents. However, the study data shows that food intake resulted in a decrease in the Cmax value instead of an increase (PDR 1995).

Table V

Mean Plasma Triamterene Concentrations and Pharmacokinetic Parameters Following a Single Dose of 37.5 mg/25 mg Triamterene/Hydrochlorothiazide (1X37.5mg/25 mg Capsules) Under Fasting and Nonfasting Conditions (N=22)

<u>Time hr</u>	<u>A</u>	<u>B</u>	<u>C</u>
	<u>Barr Test Product Lot# 6R87511 Fasting ng/mL (%CV)</u>	<u>Barr Reference Product Lot #6R87511 Nonfasting ng/mL (%CV)</u>	<u>SmithKline Test Product Lot #205E50 Nonfasting ng/mL (%CV)</u>
0	0.00	0.00	0.00
0.17	0.79 (263)	0.00 (.)	0.00 (.)
0.33	32.58 (81.2)	0.52 (387)	0.73 (251)
0.50	66.04 (57.0)	2.49 (272)	3.93 (180)
0.75	84.57 (42.3)	5.99 (228)	11.71 (144)
1.00	89.56 (37.4)	11.88 (165)	20.01 (104)
1.25	86.41 (36.6)	20.61 (132)	33.71 (74.4)
1.5	81.36 (39.5)	28.24 (116)	43.36 (59.9)
2.0	63.79 (38.7)	39.29 (73.7)	55.42 (40.7)
2.5	50.13 (43.5)	54.09 (57.9)	66.50 (34.9)
3.0	41.59 (43.2)	64.00 (39.3)	65.30 (31.6)
4	27.80 (45.2)	63.63 (29.0)	56.44 (37.9)
6.0	11.75 (46.1)	29.53 (40.3)	26.30 (52.1)
8	6.47 (66.3)	13.40 (40.8)	12.28 (54.4)
10	3.42 (63.2)	6.49 (41.9)	6.23 (60.6)
12	1.43 (115)	3.34 (62.2)	2.99 (84.7)
14	0.43 (218)	1.62 (102)	1.38 (135)
24	0.11 (469)	0.15 (469)	0.00 (.)
36	0.00 (.)	0.00 (.)	0.00 (.)

48	0.00 (.)	0.00 (.)	0.00 (.)	
	<u>Mean (%CV)</u>	<u>Mean (%CV)</u>	<u>Mean (%CV)</u>	<u>B/C</u>
AUCTLQC				
ng.hr/mL	290.11 (36.7)	318.79 (24.6)	323.27 (28.7)	0.99
AUCinf				
ng.hr/mL	304.16 (35.1)	328.53 (24.4)	333.05 (28.4)	0.99
Cmax (ng/mL)	102.54 (31.6)	81.02 (28.1)	76.56 (29.7)	1.06
Kel (1/hr)	0.338	0.345	0.341	
Half (hr)	2.34	2.34	2.09	
Tmax (hr)	0.95	3.09	2.71	

1: The triamterene plasma levels peaked at 2.5 and 3 hours for the reference and test products, respectively, under nonfasting conditions.

2. For Barr test product, the means AUCTLQC, AUCinf and Cmax values are 1.4%, 1.4% and 5.8% 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 0.8-1.2 for AUCTLQC, AUCinf and Cmax.

3. The mean AUCTLQC of the test product was increased by 9.9% and the mean Cmax was reduced by 21.0%, when dosed under nonfasting conditions compared to fasting conditions. This increase in AUC value is in agreement with the reference product's data (PDR) which indicated that food intake increases the mean bioavailability of triamterene and causes a delay of up to 2 hours in the absorption of the active constituents. However, the study data shows that food intake resulted in a decrease in the Cmax value instead of an increase (PDR 1995).

Table VI

Mean Plasma HCTZ Concentrations and Pharmacokinetic Parameters Following a Single Dose of 37.5 mg/25 mg Triamterene/Hydrochlorothiazide (1X37.5mg/25 mg Capsules) Under Fasting and Nonfasting Conditions (N=22)

<u>Time</u> <u>hr</u>	<u>A</u>	<u>B</u>	<u>C</u>
	<u>Barr</u>	<u>Barr</u>	<u>SmithKline</u>
	<u>Test Product</u>	<u>Reference Product</u>	<u>Test Product</u>
	Lot# 6R87511	Lot #6R87511	Lot #205E50
	Fasting	Nonfasting	Nonfasting
	ng/mL (%CV)	ng/mL (%CV)	ng/mL (%CV)

0	0.00	0.00	0.00	
0.17	0.00 (.)	0.00 (.)	0.00 (.)	
0.33	0.51 (469)	0.00 (.)	0.00 (.)	
0.50	13.05 (97.5)	0.00 (.)	0.00 (.)	
0.75	44.15 (58.0)	1.38 (469)	2.16 (270)	
1.00	75.25 (49.9)	4.76 (282)	10.01 (136)	
1.25	110.39 (38.3)	15.69 (161)	20.82 (96.4)	
1.5	132.26 (30.7)	20.84 (124)	34.54 (68.0)	
2.0	137.86 (25.7)	41.41 (79.2)	63.48 (39.5)	
2.5	128.17 (20.7)	57.74 (52.5)	84.27 (25.3)	
3.0	114.03 (17.6)	81.18 (38.1)	97.23 (20.0)	
4	90.46 (19.9)	105.41 (17.9)	102.29 (15.3)	
6.0	53.87 (18.0)	73.37 (20.0)	68.56 (19.1)	
8	37.57 (14.9)	46.36 (20.7)	44.45 (18.2)	
10	29.24 (16.0)	32.84 (21.8)	31.71 (19.3)	
12	23.01 (19.0)	25.91 (19.3)	25.50 (20.4)	
14	18.79 (17.1)	20.91 (21.6)	20.44 (24.5)	
24	6.31 (94.8)	8.61 (73.9)	6.76 (96.1)	
36	0.46 (469)	0.00 (.)	0.00 (.)	
48	0.00 (.)	0.00 (.)	0.00 (.)	
	<u>Mean (%CV)</u>	<u>Mean (%CV)</u>	<u>Mean (%CV)</u>	<u>B/C</u>
AUCTLQC				
ng.hr/mL	863.82 (19.5)	779.24 (16.8)	778.10 (17.4)	1.00
AUCinf				
ng.hr/mL	1012.38 (19.3)	961.90 (18.8)	943.73 (18.4)	1.02
Cmax (ng/mL)	146.77 (23.4)	110.41 (12.6)	107.34 (13.1)	1.03
Kel (1/hr)	0.098	0.086	0.101	
Half (hr)	8.37	9.23	7.96	
Tmax (hr)	1.96	3.93	3.54	

1. The hydrochlorothiazide (HCTZ) plasma levels peaked at 4 hours for both the reference and test products under nonfasting conditions.

2. For Barr test product, the means AUCTLQC, AUCinf and Cmax values are 0.15%, 1.9% and 2.9% 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 0.8-1.2 for AUCTLQC, AUCinf and Cmax.

VII. In Vitro Dissolution Testing

(USP Method, Test 3, Fifth Supplement, Page 3440)

Method: USP 23 apparatus 1 at 100 rpm
 Medium: 900 mL of 0.1 HCl
 Sampling Time: 10, 20, 30, 45 and 75 minutes
 Number of Capsules: 12

Test Product: Barr's triamterene/hydrochlorothiazide 37.5 mg/25 mg capsules, lot # 6R87511

Reference

product: SmithKline Beecham's Dyazide[®] 37.5 mg/25 mg capsules, lot # 205E50.

Specification: NLT 75% in 45 minutes for Hydrochlorothiazide
NLT 75% in 45 minutes for Triamterene

The dissolution testing results are presented in Table VII.

VII. Formulation:

The formulation of Barr's triamterene/hydrochlorothiazide 37.5mg/25 mg capsules is shown in Table VIII.

VIII. Comments:

1. The firm's in vivo single-dose bioequivalence studies # P95-003 and P95-051 on its triamterene/hydrochlorothiazide 37.5 mg/25 mg capsule under fasting and nonfasting conditions are acceptable. The 90% confidence intervals for triamterene, p-hydroxytriamterene sulfate and hydrochlorothiazide are all within the acceptable range of 80-125% for AUCLQC, AUCinf and Cmax under fasting conditions. The ratios of the test mean to the reference mean for triamterene, p-hydroxytriamterene sulfate and hydrochlorothiazide are within the acceptable range of 0.8-1.2 for AUCLQC, AUCinf and Cmax under nonfasting conditions.

2. The in vitro dissolution testing submitted by the firm on its Triamterene/Hydrochlorothiazide 37.5 mg/25 mg Capsules is acceptable.

VII. Recommendations:

1. The single-dose bioequivalence studies under fasting and nonfasting conditions conducted by Barr Laboratories, Inc., on its Triamterene/Hydrochlorothiazide 37.5 mg/25 mg capsule, lot #6R87511, comparing it to Dyazide[®] 37.5 mg/25 mg capsule, manufactured by SmithKline Beecham, have been found acceptable by the Division of Bioequivalence. The study demonstrates that Barr's Triamterene/Hydrochlorothiazide Capsule, 37.5 mg/25 mg is bioequivalent to the reference product, Dyazide[®], 37.5 mg/25 mg Capsule, manufactured by SmithKline Beecham.

2. The dissolution testing conducted by Barr Laboratories, Inc., on its triamterene/hydrochlorothiazide 37.5 mg/25 mg capsule, lot #6R87511 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 0.1 HCl, at 37°C using USP 23 apparatus 1 (basket) at 100 rpm. The test product should meet the following USP specifications:

NLT 75% in 45 minutes for Hydrochlorothiazide
NLT 75% in 45 minutes for Triamterene

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is acceptable.

The firm should be informed of the above recommendations.

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

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Date: 2/2/97

Concur: _____
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Date: 2/3/97

MMakary/1-27-97 wp 74970SD.996
cc: ANDA #74-970, original, HFD-658 (Makary), Drug File, Division File.

Table VII In Vitro Dissolution Testing

Drug (Generic Name): Triamterene/Hydrochlorothiazide
 Dose Strength: 37.5 mg/25 mg Capsules
 ANDA No.:74-970
 Firm: Barr Laboratories, Inc.
 Submission Date: September 30, 1996
 File Name: 74970SD.996

I. Conditions for Dissolution Testing:

USP 23 Basket:X Paddle: RPM: 100
 No. Units Tested: 12 Capsules
 Medium:900 mL of 0.1 HCl
 Specifications: NLT 75% of the labeled amounts of triamterene
 and hydrochlorothiazide are dissolved in 45 minutes.
 Reference Drug: Dyazide
 Assay Methodology:

II. Results of In Vitro Dissolution Testing: Triamterene

Sampling Times (minutes)	Test Product Lot # 6R87511 Strength(mg) 37.5/25			Reference Product Lot # 205E50 Strength(mg) 37.5/25		
	Mean %	Range	%CV	Mean %	Range	%CV
10	51		10.5	71		7.0
20	80		6.2	88		3.6
30	93		4.3	94		2.9
45	98		3.2	98		2.3
75	100		2.0	100		1.8

Hydrochlorothiazide

Sampling Times (minutes)	Test Product Lot # 6R87511 Strength(mg) 37.5/25			Reference Product Lot # 205E50 Strength(mg) 37.5/25		
	Mean %	Range	%CV	Mean %	Range	%CV
10	53		8.8	80		5.8
20	83		5.3	94		3.3
30	94		3.8	97		2.1
45	98		3.1	100		1.9
75	100		1.9	100		1.7

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **74970** _____

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA:74-970 DRUG PRODUCT:Triamterene and HCTZ USP

FIRM:Barr DOSAGE FORM:Capsules STRENGTH:37.5/25 mg

CGMP STATEMENT/EIR UPDATE STATUS: **Not acceptable as of 9/3/97.**

BIO STUDY: **Satisfactory** per Bio review dated 2/3/97 (M.H. Makary).

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Compendial product. FDA MV not needed.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): **Satisfactory**

Three months of accelerated (40°C/75%RH) and RT (25°-30°C) stability data generated from the finished drug product stored in 75cc/CRC (30's), 75cc/CRC (100's), 75cc/metal (100's) and 500cc/metal (1000's) container/closure systems are provided. Data are within specs.

Containers and closure system are the same as those listed in the container/closure system.

LABELING: **Satisfactory** per Labeling review dated 6/11/97 (C.Park).

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.):

Biobatch: capsules (Lot 6R87511)

NDS source: Triamterene , **Acceptable**
HCTZ **Acceptable**

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

Same as the biobatch, lot 6R87511.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):

Production batch size: capsules. Manufacturing process is essentially the same as that of the biobatch.

Conclusion: ANDA 74-970 is approvable pending satisfactory EER.

CHEMIST:J.Fan

J.Fan

DATE:

SUPERVISOR:V.Sayeed, Ph.D.

DATE:

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CENTER FOR DRUG EVALUATION AND RESEARCH

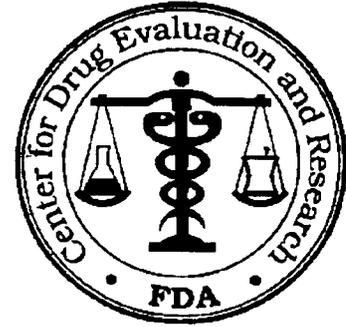
APPLICATION NUMBER 74970

CORRESPONDENCE

MINOR AMENDMENT

ANDA 74-970

OCT 10 1997



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Barr Laboratories, Inc.
ATTN: Claire M. Lathers, Ph.D.

PHONE: 914-362-1100
FAX: 914-362-2043

FROM: James Wilson

PROJECT MANAGER (301) 827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Triamterene and Hydrochlorothiazide Capsules, 37.5 mg/25 mg..

Reference is also made to your amendment(s) dated June 2, 1997.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address..

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Barr Laboratories, Inc.

505(j)(2)(a)(ek)
Cura Merie H. W. Deibel
10/2/96

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

September 30, 1996
10/24/96
AM

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

We are submitting herewith, in duplicate, an Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act, Triamterene and Hydrochlorothiazide Capsules, USP 37.5 mg/25 mg.

The application is provided both as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of 21 (twenty-one) volumes. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 4 (four) volumes. The bioequivalence part of the review copy is contained in orange binders and consists of 17 (seventeen) volumes.

The format of this application is in accordance with Office of Generic Drugs, Policy and Procedure Guide #30-91. The contents of this application has also been revised in accordance the October 14, 1994 communication from Dr. Janet Woodcock, Director (CDER) and Mr. Ronald Cheesemore (ORA). Numerous SOPs are no longer submitted in the application, however these procedures are kept current and are available for inspection by the FDA District Field Investigators.

....continued

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

N 5700
10/24/97
[Signature]

October 21, 1997

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Document Control Room 150
Rockville, MD 20855

ORIG AMENDMENT

N/A

Minor Amendment

REFERENCE: ANDA 74-970
Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg

Reference is made to our pending Abbreviated New Drug Application dated *September 30, 1996* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg.**

The following response is to your letter dated *October 10, 1997* in which the following is stated:

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

COMMENT:

1. You indicated that the _____ used in imprinting inks are exempted from certification requirements as per 21 CFR 73.1200 (e) and that the manufacturer of the imprinting inks. _____ states that the ingredients used in its products meet the requirements listed in USP, FCC or 21 CFR for the intended use in ingested drugs. This is not adequate. Please provide calculation(s) and data for these imprinting ingredients to demonstrate that the _____ content in the imprinting inks are in compliance with requirements as stipulated in 21 CFR 73.1200 (c).

RECEIVED

OCT 22 1997

GENERIC DRUGS

[Handwritten mark]

REFERENCE: **ANDA 74-970**
Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg

RESPONSE:

Barr Laboratories, Inc. contacted the manufacturer of the capsules regarding the above comment. the manufacturer of the capsules contacted the manufacturer of the ink. Based upon the data provided by the manufacturer of the ink, the amount of ink on the ink, calculated the amount of ink per capsule. According to the amount of ink found on each printed capsule is less than a amount of ink per capsule. (See Pages 1 to 2). As per the approved labeling for Triamterene and Hydrochlorothiazide Capsules, USP 37.5 mg/25 mg, the maximum labeled daily dose is two capsules. (See Exhibit 1, *Dosage and Administration* from PHYSICIAN'S DESK REFERENCE 1997, 51st Edition). Therefore, the total maximum daily amount ingested from Barr's Triamterene and Hydrochlorothiazide Capsules, USP 37.5 mg/25 mg is less than amount per day. This amount is well within the daily limit of amount established for ingestion in 21 CFR §1200 (c).

COMMENT:

2. You have failed to provide the stability data for the amount of impurities for your finished drug product. Please provide this information, also revise your stability summary report to include this information in all future submissions.

RESPONSE:

Barr updated its Stability Summary Report Three Months Accelerated (40°C + 75% RH) And Twelve Months Controlled Room Temperature 25°C – 30°C) for Triamterene and Hydrochlorothiazide Capsules, USP 37.5 mg/25 mg, Batch No.: 6R87511 to include through the 12 month controlled room temperature storage station. In addition, as per the above comment, Barr included the stability data for both accelerated and controlled room temperature storage for the 4-

