

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

12945/S038

Trade Name: Diamox® Sequels®

Generic Name: acetazolamide sustained release capsules, 500 mg

Sponsor: Duramed Pharmaceuticals, Inc.

Approval Date: 03/15/2005

Indication: For adjunctive treatment of chronic simple (open-angle) glaucoma, secondary glaucoma, and preoperatively in acute angle-closure glaucoma where delay of surgery is desired in order to lower intraocular pressure. Diamox is also indicated for the prevention or amelioration of symptoms associated with acute mountain sickness despite gradual ascent.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

12945/S038

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

12945/S038

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 12-945/S-037 & S-038

Duramed Pharmaceuticals, Inc.
Attn: Nicholas Tantillo
Senior Director, Regulatory Affairs
2 Quaker Road
Pomona, NY 10970

Dear Mr. Tantillo:

Please refer to your supplemental new drug applications dated June 30, 2004, received July 1, 2004, submitted under section 505(b) the Federal Food, Drug, and Cosmetic Act for the Diamox Sequels (acetazolamide sustained-release capsules) 500mg.

These supplemental new drug applications provide for the addition of [REDACTED] (b) (4) as an drug substance manufacturer; transfer of drug product manufacturing and testing to Barr Laboratories, Pomona, NY, and Forrest, VA, and to Duramed Pharmaceuticals, Cincinnati, OH; change to hard gelatin capsules; revision to the drug product specification; and labeling revision.

Your submission of November 16, 2004, constituted a complete response to our November 4, 2004, action letter.

We completed our review of this application, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical in content with the enclosed agreed upon label dated November 16, 2004. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

It is recommended that the **HOW SUPPLIED** section of the package insert to read "Store at controlled room temperature 20° to 25°C (68°-77°F)" without additional qualifications.

The final printed labeling (FPL) must be identical with the enclosed agreed upon labeling text for the package insert, dated November 16, 2004. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS

Word format. If formatted copies of all labeling pieces (i.e., package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-42
Food and Drug Administration
5600 Fishers lane
Rockville, MD 20857

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

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure:

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

/s/

Wiley Chambers

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

12945/S038

OTHER ACTION LETTER(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 12-945/S-037 & S-038

Duramed Pharmaceuticals, Inc.
Attn: Nicholas Tantillo
Senior Director, Regulatory Affairs
2 Quaker Road
Pomona, NY 10970

Dear Mr. Tantillo:

Please refer to your supplemental new drug applications dated June 30, 2004, received July 1, 2004, submitted under section 505(b) the Federal Food, Drug, and Cosmetic Act for the Diamox Sequels (acetazolamide extended-release capsules) 500 mg.

These supplemental new drug applications provide for the addition of (b) (4) as an drug substance manufacturer; transfer of drug product manufacturing and testing to Barr Laboratories, Pomona, NY, and Forrest, VA, and to Duramed Pharmaceuticals, Cincinnati, OH; change to hard gelatin capsules; revision to the drug product specification; and labeling revision.

We have completed our review of these applications, and they are approvable. Before these applications may be approved, however, you must submit draft or final printed labeling, consistent with the enclosed copy, revised as follows:

- 1) The correct established name is "Acetazolamide Extended-Release Capsules". You should revise the labeling accordingly.
- 2) (b) (4). Under **DESCRIPTION**, the sentence should read, "DIAMOX SEQUELS (Acetazolamide Extended-Release Capsules) are an inhibitor of the enzyme carbonic anhydrase."
- 3) (b) (4) you should add "anaphylaxis" after "fulminant hepatic necrosis."
- 4) In your submitted labeling the order of subsections within the **PRECAUTIONS** section has been changed. The correct order of subsections should be General, Information for Patients, Laboratory Tests, Drug Interactions, Drug/laboratory Test Interactions, Carcinogenesis, Pregnancy, Nursing Mothers, Pediatric Use, and Geriatric Use.
- 5) Your submitted labeling replaces the word "Caution" with (b) (4) in the second sentence of the first paragraph in the Information for Patients subsection. This is not acceptable. You should revise the wording to "Caution."

- 6) [REDACTED] (b) (4)

These paragraphs should be added to the Information for Patients subsection:

Acetazolamide treatment may cause electrolyte imbalances, including hyponatremia and hypokalemia, as well as metabolic acidosis. Therefore, periodic monitoring of serum electrolytes is recommended. Particular caution is recommended in patients with conditions that are associated with, or predispose a patient to, electrolyte and acid/base imbalances, such as patients with impaired renal function (including elderly patients; see **PRECAUTIONS, Geriatric Use**), patients with diabetes mellitus, and patients with impaired alveolar ventilation.

Some adverse reactions to acetazolamide, such as drowsiness, fatigue, and myopia, may impair the ability to drive and operate machinery.

- 7) You have included the statement, [REDACTED] (b) (4) in the Drug Interactions subsection. Refer to the July 17, 2003, Approvable Letter for S-034 which contained Draft/Final printed labeling with revisions. This statement should be deleted. (b) (4)

- 8) [REDACTED] (b) (4)
Refer to the July 17, 2003, Approvable Letter which contained the Draft/Final printed labeling with revisions to be made. This subsection should be added to the labeling after the Drug Interactions subsection:

Drug/laboratory test interactions

Sulfonamides may give false negative or decreased values for urinary phenolsulfonphthalein and phenol red elimination values for urinary protein, serum non-protein, and serum uric acid. Acetazolamide may produce an increased level of crystals in the urine.

Acetazolamide interferes with the HPLC method of assay for theophylline. Interference with the theophylline assay by acetazolamide depends on the solvent used in the extraction; acetazolamide may not interfere with other assay methods for theophylline.

- 9) In your submitted labeling, the Pregnancy subsection heading is incorrect. It should read, "Pregnancy: Teratogenic effects: Pregnancy Category C."

- 10) [REDACTED] (b) (4)
This paragraph should be added to the labeling:

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

- 11) [REDACTED] (b) (4)
"Fever" should be added to be consistent with the approved labeling.
- 12) The subsection, [REDACTED] (b) (4), should be deleted from your labeling. Refer to the July 17, 2003, Approvable Letter for S-034 which contained Draft/Final printed labeling with revisions.
- 13) [REDACTED] (b) (4)
The drug product name should be revised to read, "DIAMOX® SEQUELS® (Acetazolamide Extended-Release Capsules)."

To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL, as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
5901-B Ammendale Road
Beltsville, MD 20705-1266

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, MD 20850

Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Raphael Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure:

The next 6 pages of draft labeling
have been withheld (b)(4)

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

/s/

Wiley Chambers

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

12945/S038

LABELING

DIAMOX® SEQUELS® (Acetazolamide Extended-Release Capsules)

Rx only

DESCRIPTION

DIAMOX SEQUELS (Acetazolamide Extended-Release Capsules) are an inhibitor of the enzyme carbonic anhydrase.

DIAMOX is a white to faintly yellowish white crystalline, odorless powder, weakly acidic, very slightly soluble in water and slightly soluble in alcohol. The chemical name for DIAMOX is N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide and has the following chemical structure:

[structure]

MW 222.24

$C_4H_6N_4O_3S_2$

DIAMOX SEQUELS are extended-release capsules, for oral administration, each containing 500 mg of acetazolamide and the following inactive ingredients:

Microcrystalline cellulose, sodium lauryl sulfate and talc.

The ingredients in the capsule shell are D&C red no. 28, D&C yellow no. 10, FD&C red no. 40, gelatin and titanium dioxide.

The ingredients in the imprinting ink are 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 iron oxide.

CLINICAL PHARMACOLOGY

DIAMOX is a potent carbonic anhydrase inhibitor, effective in the control of fluid secretion (e.g., some types of glaucoma), in the treatment of certain convulsive disorders (e.g., epilepsy) and in the promotion of diuresis in instances of abnormal fluid retention (e.g., cardiac edema).

DIAMOX is not a mercurial diuretic. Rather, it is a non-bacteriostatic sulfonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulfonamides.

DIAMOX is an enzyme inhibitor that acts specifically on carbonic anhydrase, the enzyme that catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In the eye, this inhibitory action of acetazolamide decreases the secretion of aqueous humor and results in a drop in intraocular pressure, a reaction considered desirable in cases of glaucoma and even in certain non-glaucomatous conditions. Evidence seems to indicate that DIAMOX has utility as an adjuvant in treatment of certain dysfunctions of the central nervous system (e.g., epilepsy). Inhibition of carbonic anhydrase in this area appears to retard abnormal, paroxysmal, excessive discharge from central nervous system neurons. The diuretic effect of DIAMOX is due to its action in the kidney on the reversible reaction involving hydration of carbon dioxide and dehydration of carbonic acid. The result is renal loss of HCO_3 ion, which carries out sodium, water, and potassium. Alkalinization of the urine and promotion of diuresis are thus affected. Alteration in ammonia

metabolism occurs due to increased reabsorption of ammonia by the renal tubules as a result of urinary alkalization.

DIAMOX SEQUELS provide prolonged action to inhibit aqueous humor secretion for 18 to 24 hours after each dose, whereas tablets act for only eight to 12 hours. The prolonged continuous effect of SEQUELS permits a reduction in dosage frequency.

Plasma concentrations of acetazolamide peak from three to six hours after administration of DIAMOX SEQUELS, compared to one to four hours with tablets. Food does not affect bioavailability of DIAMOX SEQUELS.

Placebo-controlled clinical trials have shown that prophylactic administration of DIAMOX at a dose of 250 mg every eight to 12 hours (or a 500 mg controlled-release capsule once daily) before and during rapid ascent to altitude results in fewer and/or less severe symptoms of acute mountain sickness (AMS) such as headache, nausea, shortness of breath, dizziness, drowsiness, and fatigue. Pulmonary function (e.g., minute ventilation, expired vital capacity, and peak flow) is greater in the DIAMOX treated group, both in subjects with AMS and asymptomatic subjects. The DIAMOX treated climbers also had less difficulty in sleeping.

INDICATIONS AND USAGE

For adjunctive treatment of: chronic simple (open-angle) glaucoma, secondary glaucoma, and preoperatively in acute angle-closure glaucoma where delay of surgery is desired in order to lower intraocular pressure. DIAMOX is also indicated for the prevention or amelioration of symptoms associated with acute mountain sickness despite gradual ascent.

CONTRAINDICATIONS

Hypersensitivity to acetazolamide or any excipients in the formulation. Since acetazolamide is a sulfonamide derivative, cross sensitivity between acetazolamide, sulfonamides and other sulfonamide derivatives is possible.

Acetazolamide therapy is contraindicated in situations in which sodium and/or potassium blood serum levels are depressed, in cases of marked kidney and liver disease or dysfunction, in suprarenal gland failure, and in hyperchloremic acidosis. It is contraindicated in patients with cirrhosis because of the risk of development of hepatic encephalopathy.

Long-term administration of DIAMOX is contraindicated in patients with chronic non-congestive angle-closure glaucoma since it may permit organic closure of the angle to occur while the worsening glaucoma is masked by lowered intraocular pressure.

WARNINGS

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, anaphylaxis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitizations may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue use of this drug.

Caution is advised for patients receiving concomitant high-dose aspirin and DIAMOX, as anorexia, tachypnea, lethargy, metabolic acidosis, coma, and death have been reported.

PRECAUTIONS

General

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paresthesia. Increasing the dose often results in a decrease in diuresis. Under certain circumstances, however, very large doses have been given in conjunction with other diuretics in order to secure diuresis in complete refractory failure.

Information for Patients

Adverse reactions common to all sulfonamide derivatives may occur: anaphylaxis, fever, rash (including erythema multiforme, Steven-Johnson syndrome, toxic epidermal necrolysis), crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, and agranulocytosis. Caution is advised for early detection of such reactions and the drug should be discontinued and appropriate therapy instituted.

In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, DIAMOX which may precipitate or aggravate acidosis should be used with caution. Gradual ascent is desirable to try to avoid acute mountain sickness. If rapid ascent is undertaken and DIAMOX is used, it should be noted that such use does not obviate the need for prompt descent if severe forms of high altitude sickness occur, i.e., high altitude pulmonary edema (HAPE) or high altitude cerebral edema.

Caution is advised for patients receiving concomitant high-dose aspirin and DIAMOX, as anorexia, tachypnea, lethargy, metabolic acidosis, coma, and death have been reported (see **WARNINGS**).

Both increases and decreases in blood glucose have been described in patients treated with acetazolamide. This should be taken into consideration in patients with impaired glucose tolerance or diabetes mellitus.

Acetazolamide treatment may cause electrolyte imbalances, including hyponatremia and hypokalemia, as well as metabolic acidosis. Therefore, periodic monitoring of serum electrolytes is recommended. Particular caution is recommended in patients with conditions that are associated with, or predispose a patient to, electrolyte and acid/base imbalances, such as patients with impaired renal function (including elderly patients; see **PRECAUTIONS, Geriatric Use**), patients with diabetes mellitus, and patients with impaired alveolar ventilation.

Some adverse reactions to acetazolamide, such as drowsiness, fatigue, and myopia, may impair the ability to drive and operate machinery.

Laboratory Tests

To monitor for hematologic reactions common to all sulfonamides, it is recommended that a baseline CBC and platelet count be obtained on patients prior to initiating DIAMOX therapy and at regular intervals during therapy. If significant changes occur, early discontinuance and institution of appropriate therapy are important. Periodic monitoring of serum electrolytes is recommended.

Drug Interactions

Aspirin- See **WARNINGS**

DIAMOX modifies phenytoin metabolism with increased serum levels of phenytoin. This may increase or enhance the occurrence of osteomalacia in some patients receiving chronic phenytoin therapy. Caution is advised in patients receiving chronic concomitant therapy. By decreasing the

gastrointestinal absorption of primidone, DIAMOX may decrease serum concentrations of primidone and its metabolites, with a consequent possible decrease in anticonvulsant effect. Caution is advised when beginning, discontinuing, or changing the dose of DIAMOX in patients receiving primidone.

Because of possible additive effects with other carbonic anhydrase inhibitors, concomitant use is not advisable.

Acetazolamide may increase the effects of other folic acid antagonists.

Acetazolamide decreases urinary excretion of amphetamine and may enhance the magnitude and duration of their effect.

Acetazolamide reduces urinary excretion of quinidine and may enhance its effect.

Acetazolamide may prevent the urinary antiseptic effect of methenamine.

Acetazolamide increases lithium excretion and the lithium may be decreased.

Acetazolamide and sodium bicarbonate used concurrently increases the risk of renal calculus formation.

Acetazolamide may elevate cyclosporine levels.

Drug/laboratory test interactions

Sulfonamides may give false negative or decreased values for urinary phenolsulfonphthalein and phenol red elimination values for urinary protein, serum non-protein, and serum uric acid.

Acetazolamide may produce an increased level of crystals in the urine.

Acetazolamide interferes with the HPLC method of assay for theophylline. Interference with the theophylline assay by acetazolamide depends on the solvent used in the extraction; acetazolamide may not interfere with other assay methods for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of DIAMOX have not been conducted. In a bacterial mutagenicity assay, DIAMOX was not mutagenic when evaluated with and without metabolic activation.

The drug had no effect on fertility when administered in the diet to male and female rats at a daily intake of up to 4 times the recommended human dose of 1000 mg in a 50 kg individual.

Pregnancy: Teratogenic effects: Pregnancy Category C

Acetazolamide, administered orally or parenterally, has been shown to be teratogenic (defects of the limbs) in mice, rats, hamsters, and rabbits. There are no adequate and well-controlled studies in pregnant women. Acetazolamide should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants from DIAMOX, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the

importance of the drug to the mother. Acetazolamide should only be used by nursing women if the potential benefit justifies the potential risk to the child.

Pediatric Use

The safety and effectiveness of DIAMOX SEQUELS in pediatric patients below the age of 12 years have not been established. Growth retardation has been reported in children receiving long-term therapy, believed secondary to chronic acidosis.

Geriatric Use

Metabolic acidosis, which can be severe, may occur in the elderly with reduced renal function.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

ADVERSE REACTIONS

Body as a whole: Headache, malaise, fatigue, fever, pain at injection site, flushing, growth retardation in children, flaccid paralysis, anaphylaxis.

Digestive: Gastrointestinal disturbances such as nausea, vomiting, diarrhea.

Hematological/Lymphatic: Blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, thrombocytopenic purpura, melena.

Hepato-biliary disorders: Abnormal liver function, cholestatic jaundice, hepatic insufficiency, fulminant hepatic necrosis

Metabolic/Nutritional: Metabolic acidosis, electrolyte imbalance, including hypokalemia, hyponatremia, osteomalacia with long-term phenytoin therapy, loss of appetite, taste alteration, hyper/hypoglycemia

Nervous: Drowsiness, paresthesia (including numbness and tingling of extremities and face), depression, excitement, ataxia, confusion, convulsions dizziness

Skin: Allergic skin reactions including urticaria, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis

Special senses: Hearing disturbances, tinnitus, transient myopia

Urogenital: Crystalluria, increased risk of nephrolithiasis with long-term therapy, hematuria, glycosuria, renal failure polyuria

OVERDOSAGE

No specific antidote is known. Treatment should be symptomatic and supportive.

Electrolyte imbalance, development of an acidotic state, and central nervous system effects might be expected to occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Supportive measures are required to restore electrolyte and pH balance. The acidotic state can usually be corrected by the administration of bicarbonate.

Despite its high intraerythrocytic distribution and plasma protein binding properties, DIAMOX may be dialyzable. This may be particularly important in the management of DIAMOX overdose when complicated by the presence of renal failure.

DOSAGE AND ADMINISTRATION

Glaucoma:

The recommended dosage is 1 capsule (500 mg) two times a day. Usually 1 capsule is administered in the morning and 1 capsule in the evening. It may be necessary to adjust the dose, but it has usually been found that dosage in excess of 2 capsules (1 g) does not produce an increased effect. The dosage should be adjusted with careful individual attention both to symptomatology and intraocular tension. In all cases, continuous supervision by a physician is advisable.

In those unusual instances where adequate control is not obtained by the twice-a-day administration of DIAMOX SEQUELS, the desired control may be established by means of DIAMOX (tablets or parenteral). Use tablets or parenteral in accordance with the more frequent dosage schedules recommended for these dosage forms, such as 250 mg every four hours, or an initial dose of 500 mg followed by 250 mg or 125 mg every four hours, depending on the case in question.

Acute Mountain Sickness: Dosage is 500 mg to 1000 mg daily, in divided doses using tablets or extended-release capsules as appropriate. In circumstances of rapid ascent, such as in rescue or military operations, the higher dose level of 1000 mg is recommended. It is preferable to initiate dosing 24 to 48 hours before ascent and to continue for 48 hours while at high altitude, or longer as necessary to control symptoms.

HOW SUPPLIED

DIAMOX® SEQUELS® (Acetazolamide Extended-Release Capsules) are available as 500 mg: Orange opaque cap and orange opaque body filled with white to off-white pellets. Imprinted in black ink, Barr 699. Available in bottles of:
100

NDC 51285-754-02

Store at controlled room temperature 20° to 25°C (68° to 77°F).

DURAMED PHARMACEUTICALS, INC.
Subsidiary of BarrPharmaceuticals, Inc.
Pomona, New York 10970

Revised NOVEMBER 2004

BR-754

Container Label



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

12945/S038

MEDICAL REVIEW(S)

Clinical Review of NDA 12-945
Labeling Amendment

NDA 12-945
SCM-037/SLR-038/ BF

Submission Date: November 16, 2004
Receipt Date: November 17, 2004
Review Date: December 9, 2004

Applicant: Duramed Pharmaceuticals, Inc.
2 Quaker Road
Pomona, New York 10970

Applicant's
Representative: Nicholas Tantillo
Senior Director, Regulatory Affairs
201-930-3650

Drug: Diamox Sequels (Acetazolamide Extended-Release
Capsules) 500 mg

Pharmacologic
Category: Carbonic anhydrase inhibitor

Submitted: The Sponsor has submitted revised electronic labeling in response to the November 4, 2004 Approvable Letter for the Prior Approval Supplements, S-037 and S-038. The labeling for the container label and the package insert are included.

Following is the currently approved labeling for the product. Sponsor's deletions are noted by and insertions by underline.

Reviewer's deletions are noted by and insertions by underline.

DIAMOX® SEQUELS® (Acetazolamide Extended-Release Capsules)

Rx only

Reviewer's Comments:

The sponsor has corrected the established name to "Acetazolamide Extended-Release Capsules" throughout the submitted labeling. Acceptable.

*The sponsor has removed the capitalization of the word (b) (4) before the **DESCRIPTION** section. The sponsor has corrected typographical and grammatical errors throughout the submitted labeling as indicated below.*

DESCRIPTION

DIAMOX SEQUELS (Acetazolamide Extended-Release Capsules) are an inhibitor of the enzyme carbonic anhydrase.

DIAMOX is a white to faintly yellowish white crystalline, odorless powder, weakly acidic, very slightly soluble in water and slightly soluble in alcohol. The chemical name for DIAMOX is N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide and has the following chemical structure:

[structure]

MW 222.24

$C_4H_6N_4O_3S_2$

DIAMOX SEQUELS are extended-release capsules, for oral administration, each containing 500 mg of acetazolamide and the following inactive ingredients:

Microcrystalline cellulose, sodium lauryl sulfate and talc.

The ingredients in the capsule shell are D&C red no. 28, D&C yellow no. 10, FD&C red no. 40, gelatin and titanium dioxide.

The ingredients in the imprinting ink are 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 iron oxide.

Reviewer's Comments:

*In the **DESCRIPTION** section, the sponsor has changed the phrase (b) (4) to "extended-release" in accordance with the established name of the product. Acceptable.*

*The sponsor has corrected several typographical errors in the **DESCRIPTION** section. Acceptable.*

(b) (4)

The next page (containing draft labeling) has been withheld in full (b)(4).

Reviewer's Comments:

*The sponsor has added “anaphylaxis” after “fulminant hepatic necrosis” in the first paragraph of the **WARNINGS** section in the revised labeling in accordance with the November 4, 2004 Approvable Letter.*

The sponsor has corrected (b) (4) to “occur” in the first paragraph. Acceptable.

PRECAUTIONS

Reviewer's Comments:

*The sponsor has revised the order of the subsections within the **PRECAUTIONS** section in the submitted labeling to be in accordance with the November 4, 2004, Approvable Letter and the approved label.*

Reviewer's Comments:

The sponsor has changed [REDACTED] (b) (4) to “leukopenia” in the first paragraph.

The sponsor has replaced the word [REDACTED] (b) (4) with “Caution” in the second sentence of the first paragraph in the Information for Patients subsection. Acceptable.

The sponsor has corrected [REDACTED] (b) (4) to “not” in the second paragraph. Acceptable.

The sponsor has inserted the fifth and sixth paragraphs in the Information for Patients subsection of the submitted labeling in accordance with the July 17, 2003, Approvable Letter for Supplement 034.

[REDACTED] (b) (4)

Reviewer's Comments:

The sponsor has (b) (4) in agreement with the July 7, 2003, Approvable Letter for S-034 which contained Draft/Final printed labeling with revisions.

The sponsor has (b) (4) in the Drug Interactions subsection of the **PRECAUTIONS** section. Acceptable.

(b) (4)

(b) (4)



Reviewer's Comments:

The Sponsor has added the Drug/laboratory Test Interactions subsection in the submitted labeling as requested in the July 17, 2003, Approvable Letter for Supplement 034. Acceptable.

(b) (4)



Reviewer's Comments:

The sponsor has corrected the Pregnancy subsection heading. Acceptable.

(b) (4)



(b) (4)

Reviewer's Comments:

The second paragraph in the Geriatric Use subsection has been added in the sponsor's submitted labeling. Acceptable.

(b) (4)

Reviewer's Comments:

*The sponsor has added "fever" to the **ADVERSE REACTIONS**, Body as a whole subsection to be consistent with the approved labeling.*

(b) (4)

(b) (4)

Reviewer's Comments:

*The sponsor has added the word "system" to the second paragraph of the **OVERDOSAGE** section. Acceptable.*

(b) (4)

Reviewer's Comments:

The sponsor has deleted the (b) (4) from the sponsor's labeling in accordance with the July 17, 2003 approvable Letter for S-034 which contained Draft/Final printed labeling with revisions.

(b) (4)

NDA 12-945
SCM-037/SLR-038
Page 10
NDC 51285-754-02

Store at controlled room temperature 20° to 25°C (68° to 77°F).

DURAMED PHARMACEUTICALS, INC.
Subsidiary of BarrPharmaceuticals, Inc.
Pomona, New York 10970

Revised NOVEMBER 2004

BR-754

Reviewer's Comments:

The sponsor has [REDACTED] (b) (4)

[REDACTED] *Not acceptable. The sponsor should revise the* [REDACTED] (b) (4) *.*

[REDACTED] (b) (4)

[REDACTED] *The storage statement should be revised to read, "Store at controlled room temperature 20° to 25°C (68° to 77° F)."*

(b) (4)



Reviewer's Comments:

The sponsor has corrected the drug product and established names to "Diamox® Sequels® (Acetazolamide Extended-Release Capsules)". Acceptable.

Recommendations:

The submitted revised labeling is not acceptable. The labeling is recommended for approval after

(b) (4)



Rhea Lloyd, MD
Medical Officer

Cc:

NDA 12-945
HFD-550/PM/Rodriguez
HFD-550/Chem/Khorshidi
HFD-550/Chem TL/Ng
HFD-550/Biopharm/Bashaw
HFD-550/MO/Lloyd
HFD-550/DepDirector/Chambers

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/s/

Rhea Lloyd
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Wiley Chambers
1/26/05 03:08:27 PM
MEDICAL OFFICER

Clinical Review of NDA 12-945
Labeling Supplement

NDA 12-945
SLR-038/SCM-037

Submission Date: June 30, 2004
Receipt Date: July 1, 2004
Review Date: July 20, 2004

Applicant: Duramed Pharmaceuticals, Inc.
2 Quaker Road
Pomona, New York 10970

Applicant's Representative: Nicholas Tantillo
Senior Director, Regulatory Affairs
201-930-3650

Drug: Diamox Sequels (Acetazolamide Extended-Release Capsules) 500 mg

Pharmacologic Category: Carbonic anhydrase inhibitor

Submitted: A Prior Approval Supplement for the following changes:

- 1) The transfer of all operations from the Wyeth Pharmaceuticals, Inc., Pearl River, NY site to the Duramed Pharmaceuticals, Inc., and Barr Laboratories Inc., facilities in Pomona, NY, Forrest, VA, and Cincinnati, OH.
- 2) Component, composition and manufacturing equipment changes to switch from soft gelatin to hard gelatin encapsulation.
- 3) The addition of (b) (4) as an active pharmaceutical ingredient ("API") manufacturer.
- 4) Addition of specifications for impurities in the finished product.

Bioavailability studies are submitted in support of the manufacturing changes.

Reviewer's Comment:
The Prior Approval Supplement is subject to Biopharmaceutics and Chemistry reviews.

The Applicant has submitted labeling to reflect the June 19, 2003, transfer of ownership from Wyeth Pharmaceuticals to Duramed Pharmaceuticals Inc. and the above manufacturing changes.

Following is the currently approved labeling for the product. Sponsor's deletions are noted by and additions by underline within the review.

(b) (4)

Reviewer's Comments:

The correct established name is "Acetazolamide Extended-Release Capsules". The sponsor should revise the labeling accordingly.

(b) (4)

Reviewer's Comments:

(b) (4)

*Under **DESCRIPTION**, the sentence should read, "DIAMOX SEQUELS (Acetazolamide Extended-Release Capsules) are an inhibitor of the enzyme carbonic anhydrase."*

DIAMOX is a white to faintly yellowish white crystalline, odorless powder, weakly acidic, very slightly soluble in water and slightly soluble in alcohol. The chemical name for DIAMOX is N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide and has the following chemical structure:

[structure]

MW 222.24

$C_4H_6N_4O_3S_2$

DIAMOX SEQUELS are sustained release capsules, for oral administration, each containing 500mg of acetazolamide and the following inactive ingredients:

Microcrystalline cellulose, sodium lauryl sulfate and talc.

The ingredients in the capsule shell are D&C red no. 28, D&c yellow no. 10, FD&c red no. 40, gelatin and titanium dioxide.

The ingredients in the imprinting ink are 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 iron oxide.

Reviewer's Comment:

Acceptable, pending biopharmaceutics and chemistry reviews.

CLINICAL PHARMACOLOGY

DIAMOX is a potent carbonic anhydrase inhibitor, effective in the control of fluid secretion (e.g., some types of glaucoma), in the treatment of certain convulsive disorders (e.g., epilepsy) and in the promotion of diuresis in instances of abnormal fluid retention (e.g., cardiac edema).

DIAMOX is not a mercurial diuretic. Rather, it is a non-bacteriostatic sulfonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulfonamides.

DIAMOX is an enzyme inhibitor that acts specifically on carbonic anhydrase, the enzyme that catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In the eye, this inhibitory action of acetazolamide decreases the secretion of aqueous humor and results in a drop in intraocular pressure, a reaction considered desirable in cases of glaucoma and even in certain non-glaucomatous conditions. Evidence seems to indicate that DIAMOX has utility as an adjuvant in treatment of certain dysfunctions of the central nervous system (e.g., epilepsy). Inhibition of carbonic anhydrase in this area appears to retard abnormal, paroxysmal, excessive discharge from central nervous system neurons. The diuretic effect of DIAMOX is due to its action in the kidney on the reversible reaction involving hydration of carbon dioxide and dehydration of carbonic acid. The result is renal loss of HCO_3 ion, which carries out sodium, water, and potassium. Alkalinization of the urine and promotion of diuresis are thus affected. Alteration in ammonia metabolism occurs due to increased reabsorption of ammonia by the renal tubules as a result of urinary alkalinization.

DIAMOX SEQUELS provide prolonged action to inhibit aqueous humor secretion for 18 to 24 hours after each dose, whereas tablets act for only eight to 12 hours. The prolonged continuous effect of SEQUELS permits a reduction in dosage frequency.

Plasma concentrations of acetazolamide peak from three to six hours after administration of DIAMOX SEQUELS, compared to one to four hours with tablets. Food does not affect bioavailability of DIAMOX SEQUELS.

Placebo-controlled clinical trials have shown that prophylactic administration of DIAMOX at a dose of 250 mg every eight to 12 hours (or a 500 mg controlled-release capsule once daily) before and during rapid ascent to altitude results in fewer and/or less severe symptoms of acute mountain sickness (AMS) such as headache, nausea, shortness of breath, dizziness, drowsiness, and fatigue. Pulmonary function (e.g., minute ventilation, expired vital capacity, and peak flow) is greater in the DIAMOX treated group, both in subjects with AMS and asymptomatic subjects. The DIAMOX treated climbers also had less difficulty in sleeping.

Reviewer's Comments:

*The first sentence in the sixth paragraph of the **CLINICAL PHARMACOLOGY** section differs from the approved labeling. This change is acceptable.*

INDICATIONS AND USAGE

For adjunctive treatment of: chronic simple (open-angle) glaucoma, secondary glaucoma, and preoperatively in acute angle-closure glaucoma where delay of surgery is desired in order to lower intraocular pressure. DIAMOX is also indicated for the prevention or amelioration of symptoms associated with acute mountain sickness despite gradual ascent.

CONTRAINDICATIONS

Hypersensitivity to acetazolamide or any excipients in the formulation. Since acetazolamide is a sulfonamide derivative, cross sensitivity between acetazolamide, sulfonamides and other sulfonamide derivatives is possible.

Acetazolamide therapy is contraindicated in situations in which sodium and/or potassium blood serum levels are depressed, in cases of marked kidney and liver disease or dysfunction, in suprarenal gland failure, and in hyperchloremic acidosis. It is contraindicated in patients with cirrhosis because of the risk of development of hepatic encephalopathy.

Long-term administration of DIAMOX is contraindicated in patients with chronic non-congestive angle-closure glaucoma since it may permit organic closure of the angle to occur while the worsening glaucoma is masked by lowered intraocular pressure.

(b) (4)

Reviewer's Comments:

(b) (4)

he sponsor should add

"anaphylaxis" after "fulminant hepatic necrosis."

*The sponsor's submitted labeling includes "metabolic acidosis" as a reported condition in patients receiving high-dose aspirin and DIAMOX in the second paragraph of the **WARNINGS** section. Metabolic acidosis has been reported, see paragraph below. This addition is acceptable.*

Reviewer's Comments:

*In the sponsor's submitted labeling the order of subsections within the **PRECAUTIONS** section has been changed. The correct order of subsections should be General, Information for Patients, Laboratory Tests, Drug Interactions, Drug/laboratory Test Interactions, Carcinogenesis, Pregnancy, Nursing Mothers, Pediatric Use, and Geriatric Use.*

General

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paresthesia. Increasing the dose often results in a decrease in diuresis. Under certain circumstances, however, very large doses have been given in conjunction with other diuretics in order to secure diuresis in complete refractory failure.

(b) (4)

Reviewer's Comments:

The sponsor's submitted labeling replaces the word "Caution" with (b) (4) in the second sentence of the first paragraph in the Information for Patients subsection. This is not acceptable. The sponsor should revise the wording to "Caution."

In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, DIAMOX which may precipitate or aggravate acidosis should be used with caution.

(b) (4)

(b) (4)

Reviewer's Comments:

The sponsor's submitted labeling includes "metabolic acidosis" as a reported condition in patients receiving high-dose aspirin and DIAMOX in the fourth paragraph of the Information for Patients subsection. Metabolic acidosis has been reported, see paragraph below. This addition is acceptable.

Both increases and decreases in blood glucose have been described in patients treated with acetazolamide. This should be taken into consideration in patients with impaired glucose tolerance or diabetes mellitus.

Reviewer's Comments:

(b) (4)

Acetazolamide treatment may cause electrolyte imbalances, including hyponatremia and hypokalemia, as well as metabolic acidosis. Therefore, periodic monitoring of serum electrolytes is recommended. Particular caution is recommended in patients with conditions that are associated with, or predispose a patient to, electrolyte and acid/base imbalances, such as patients with impaired renal function (including elderly patients; see **PRECAUTIONS, Geriatric Use**), patients with diabetes mellitus, and patients with impaired alveolar ventilation.

Some adverse reactions to acetazolamide, such as drowsiness, fatigue, and myopia, may impair the ability to drive and operate machinery.

Laboratory Tests

To monitor for hematologic reactions common to all sulfonamides, it is recommended that a baseline CBC and platelet count be obtained on patients prior to initiating DIAMOX therapy and at regular intervals during therapy. If significant changes occur, early discontinuance and institution of appropriate therapy are important. Periodic monitoring of serum electrolytes is recommended.

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comments:

(b) (4)

Refer to the July 17, 2003, Approvable Letter which contained the Draft/Final printed labeling with revisions to be made. This subsection should be added to the labeling after the Drug Interactions subsection:

Drug/laboratory test interactions

Sulfonamides may give false negative or decreased values for urinary phenolsulfonphthalein and phenol red elimination values for urinary protein, serum non-protein, and serum uric acid. Acetazolamide may produce an increased level of crystals in the urine.

Acetazolamide interferes with the HPLC method of assay for theophylline. Interference with the theophylline assay by acetazolamide depends on the solvent used in the extraction; acetazolamide may not interfere with other assay methods for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of DIAMOX have not been conducted. In a bacterial mutagenicity assay, DIAMOX was not mutagenic when evaluated with and without metabolic activation.

The drug had no effect on fertility when administered in the diet to male and female rats at a daily intake of up to 4 times the recommended human dose of 1000 mg in a 50kg individual.

(b) (4)

Reviewer's Comments:

(b) (4)

Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants from DIAMOX, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother. Acetazolamide should only be used by nursing women if the potential benefit justifies the potential risk to the child.

Pediatric Use

The safety and effectiveness of DIAMOX SEQUELS in pediatric patients below the age of 12 years have not been established. Growth retardation has been reported in children receiving long-term therapy, believed secondary to chronic acidosis.

Geriatric Use

Metabolic acidosis, which can be severe, may occur in the elderly with reduced renal function.

Reviewer's Comments:

(b) (4)

(b) (4)

Reviewer's Comments:

(b) (4)

OVERDOSAGE

No specific antidote is known. Treatment should be symptomatic and supportive.

Electrolyte imbalance, development of an acidotic state, and central nervous effects might be expected to occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Supportive measures are required to restore electrolyte and pH balance. The acidotic state can usually be corrected by the administration of bicarbonate.

Despite its high intraerythrocytic distribution and plasma protein binding properties, DIAMOX may be dialyzable. This may be particularly important in the management of DIAMOX overdose when complicated by the presence of renal failure.

DOSAGE AND ADMINISTRATION

Glaucoma:

The recommended dosage is 1 capsule (500mg) two times a day. Usually 1 capsule is administered in the morning and 1 capsule in the evening. It may be necessary to adjust the dose, but it has usually been found that dosage in excess of 2 capsules (1 g) does not produce an increased effect. The dosage should be adjusted with careful individual attention both to symptomatology and intraocular tension. In all cases, continuous supervision by a physician is advisable.

In those unusual instances where adequate control is not obtained by the twice-a-day administration of DIAMOX SEQUELS, the desired control may be established by means of DIAMOX (tablets or parenteral). Use tablets or parenteral in accordance with the more frequent dosage schedules recommended for these dosage forms, such as 250 mg every four hours, or an initial dose of 500 mg followed by 250 mg or 125 mg every four hours, depending on the case in question.

Acute Mountain Sickness: Dosage is 500 mg to 1000 mg daily, in divided doses using tablets or sustained-release capsules as appropriate. In circumstances of rapid ascent, such as in rescue or military operations, the higher dose level of 1000 mg is recommended. It is preferable to initiate dosing 24 to 48 hours before ascent and to continue for 48 hours while at high altitude, or longer as necessary to control symptoms.

Interference with Laboratory Tests

Sulfonamides may give false negative or decreased values for urinary phenolsulfonphthalein and phenol red elimination values for urinary protein, serum non-protein and for serum uric acid. Acetazolamide may produce an increased level of crystals in the urine.

Acetazolamide interferes with the HPLC method of assay for theophylline. Interference with the theophylline assay by acetazolamide depends on the solvent used in the extraction; acetazolamide may not interfere with other assay methods for theophylline.

Reviewer's Comment:

(b) (4)

(b) (4)

Reviewer's Comments:

(b) (4)

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Store at controlled room temperature 20° to 25°C (68° to 77°F).

Reviewer's Comments:

The sponsor's change to the storage statement is acceptable.

DURAMED PHARMACEUTICALS, INC.
Subsidiary of Barr Laboratories, Inc.
Pomona, NY 10970

(b) (4)

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Reviewer's Comments:

The sponsor has updated the manufacturing / ownership information as requested. Acceptable.

Reviewer's Comments:

The revised label includes updated ownership information, ID matrix code number, and revision date. Acceptable.

The sponsor has added the statement "NEW APPEARANCE" to the container label to reflect the change in appearance of the capsule. Acceptable.

Recommendations:

- 1) The correct established name is “Acetazolamide Extended-Release Capsules”. (b) (4)
[REDACTED]
- 2) [REDACTED] (b) (4)
Under **DESCRIPTION**, the sentence should read, “DIAMOX SEQUELS (Acetazolamide Extended-Release Capsules) are an inhibitor of the enzyme carbonic anhydrase.”
- 3) [REDACTED] (b) (4)
and the sponsor should add “anaphylaxis” after “fulminant hepatic necrosis.”
- 4) In the sponsor’s submitted labeling the order of subsections within the **PRECAUTIONS** section has been changed. The correct order of subsections should be General, Information for Patients, Laboratory Tests, Drug Interactions, Drug/laboratory Test Interactions, Carcinogenesis, Pregnancy, Nursing Mothers, Pediatric Use, and Geriatric Use.
- 5) The sponsor’s submitted labeling replaces the word “Caution” with “(b) (4)” in the second sentence of the first paragraph in the Information for Patients subsection. This is not acceptable. The sponsor should revise the wording to “Caution.”
- 6) [REDACTED] (b) (4)
These paragraphs should be added to the Information for Patients subsection:

Acetazolamide treatment may cause electrolyte imbalances, including hyponatremia and hypokalemia, as well as metabolic acidosis. Therefore, periodic monitoring of serum electrolytes is recommended. Particular caution is recommended in patients with conditions that are associated with, or predispose a patient to, electrolyte and acid/base imbalances, such as patients with impaired renal function (including elderly patients; see **PRECAUTIONS, Geriatric Use**), patients with diabetes mellitus, and patients with impaired alveolar ventilation.

Some adverse reactions to acetazolamide, such as drowsiness, fatigue, and myopia, may impair the ability to drive and operate machinery.
- 7) [REDACTED] (b) (4)
[REDACTED] in the Drug Interactions subsection. Refer to the July 17, 2003, Approvable Letter for S-034 which contained Draft/Final printed labeling with revisions. (b) (4)

- (b) (4)
- 8) (b) (4)
refer to the July 17, 2003, Approvable Letter which contained the Draft/Final printed labeling with revisions to be made. This subsection should be added to the labeling after the Drug Interactions subsection:

Drug/laboratory test interactions

Sulfonamides may give false negative or decreased values for urinary phenolsulfonphthalein and phenol red elimination values for urinary protein, serum non-protein, and serum uric acid. Acetazolamide may produce an increased level of crystals in the urine.

Acetazolamide interferes with the HPLC method of assay for theophylline. Interference with the theophylline assay by acetazolamide depends on the solvent used in the extraction; acetazolamide may not interfere with other assay methods for theophylline.

- 9) In the sponsor's submitted labeling, the Pregnancy subsection heading is incorrect. It should read, "Pregnancy: Teratogenic effects: Pregnancy Category C."

- 10) (b) (4)
This paragraph should be added to the labeling:

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

- 11) (b) (4)
"Fever" should be added to be consistent with the approved labeling.

- 12) The subsection, (b) (4) should be deleted from the sponsor's labeling. Refer to the July 17, 2003, Approvable Letter for S-034 which contained Draft/Final printed labeling with revisions.

- 13) (b) (4)
The drug product name should be revised to read, "DIAMOX® SEQUELS® (Acetazolamide Extended-Release Capsules)."

This prior approval supplement is approvable pending the above changes, Biopharmaceutics and Chemistry reviews.

Rhea Lloyd, MD
Medical Officer

Cc:

NDA 12-945
HFD-550/PM/Rodriguez
HFD-550/Chem/Khorshidi
HFD-550/Chem TL/Ng
HFD-550/Biopharm/Bashaw
HFD-550/MO/Lloyd
HFD-550/DepDirector/Chambers

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/s/

Rhea Lloyd
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Wiley Chambers
11/1/04 04:02:37 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

12945/S038

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 1		1. ORGANIZATION HFD-550 DAAODP	2. NDA NUMBER 12-945
3. NAME AND ADDRESS OF APPLICANT (City and State) Duramed Pharmaceuticals, Inc. A subsidiary of Barr Laboratories Inc., 5040 Duramed Drive Cincinnati, Ohio 45213		4. AF NUMBER	
		5. SUPPLEMENT(S) NUMBER(S) DATES(S) SCM-037 7/1/04 Original SLR-038 7/1/08 Original	
6. NAME OF DRUG: Diamox® (acetazolamide) Sequels® Sustained Release capsules, 500 mg	7. NONPROPRIETARY NAME: Acetazolamide		
8. SUPPLEMENT PROVIDES FOR: -Transfer of all operation from Wyeth (Pearl River, NY) site to Duramed and Barr facilities in Pomona, NY, Forest, VA and Cincinnati, OH. -Component, composition and manufacturing equipment changes to switch from soft-gelatin encapsulation to hard gelatin encapsulation. -Addition of (b) (4) as an API manufacturer. -Addition of specifications for impurities in the finished product. PA supplement		9. AMENDMENT(S), REPORT(S), ETC. NUMBER(S) DATE(S) *SLR-038 (BF) 11/16/04 *SCM-037 (BF) 11/16/04 * Subject of this review	
10. PHARMACOLOGICAL CATEGORY Adjunctive treatment of edema	11. HOW DISPENSED RX <u>X</u> OTC	12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Capsule	14. POTENCY 500 mg		
15. CHEMICAL NAME AND STRUCTURE See review text		16. RECORDS AND REPORTS CURRENT YES___NO REVIEWED YES___NO	
17. COMMENTS:			
18. RECOMMENDATION: From CMC standpoint, this supplement is approved. cc: Orig. NDA 12-945/SLR-038, SCM-038 HFD-550/div. File HFD-550/H Khorshidi HFD-550/W Chambers HFD-550/R Rodriguez F/T by: Hkhorshidi Doc# N:\NDA\12-945\SLR-038, SCM-037\Chem\2005.3.10. REV			
19. REVIEWER NAME: Hossein S. Khorshidi	SIGNATURE		DATE COMPLETED 3/10/05

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this page is the manifestation of the electronic signature.**

/s/

Hossein Khorshidih
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CHEMIST

Linda Ng
3/10/05 02:52:51 PM
CHEMIST
PM to prepare AP letter

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

12945/S038

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

NDA#	12-945 (SCM-037)
DRUG NAME	Acetazolamide (Diamox Sequels)
FORMULATION	Extended-release capsules, 500 mg
SUBMISSION DATE	September 6, 2007
SPONSOR	Duramed Research, Inc., Bala Cynwyd, PA 19004
REVIEWER	Charles R. Bonapace, Pharm.D.
SECONDARY REVIEWER	John A. Lazor, Pharm.D.
PROTOCOL#	AA04181 and AA04622

CLINICAL PHARMACOLOGY REVIEW

BACKGROUND:

The ownership/site of manufacture of acetazolamide extended-release (ER) capsules was transferred from Wyeth Labs to DuraMed Research, Inc. Wyeth Labs is a division of Lederle Pharmaceutical and DuraMed Research, Inc. is a division of Barr Laboratories. In support of the site change, DuraMed Research, Inc. performed two in vivo bioavailability studies to demonstrate that the drug product produced at the old and new sites were bioequivalent under fasted (Study AA04181) and fed (Study AA04622) conditions. Both studies were conducted by (b) (4) in (b) (4) between January 2000 and December 2004. Based on a letter sent to the sponsor dated January 10, 2007, the Agency recommended that the sponsor repeat the pharmacokinetic studies, re-assay the pharmacokinetic samples at a different facility or commission a scientific audit by a qualified independent expert to verify the results obtained by (b) (4).

The sponsor requested (b) (4) to conduct an audit of the two clinical studies mentioned above. The audit team consisted of seven individuals with experience in relevant aspects of bioanalytical and bioequivalence studies, including bioassays, methods validation, and Good Laboratory Practices (GLP). The audit focused on the bioanalytical segment of the acetazolamide study commencing with the receipt of bioassay samples through the analytical testing at the (b) (4) facility and reporting of the results.

The validation run batch data for acetazolamide in whole blood were reviewed by the (b) (4) audit team and consisted of 21 batches that were linked to data included in the acetazolamide method validation package. The validation run batch data for acetazolamide in plasma consisted of 17 batches. Chromatographic data were reviewed using the Analyst LC/MS/MS data acquisition system. Chromatograms were evaluated with respect to retention time, noise level, interference, integrity of the peak, and appropriateness of peak area integration.

The validation study records reviewed for each batch included the following:

- Sample, standard, QC, and blank chromatograms (100%)
- Peak integration and data acceptance decisions
- Chromatographic performance attributes of peak shape
- Signal/Noise (S/N) response, interference, and system suitability performance
- Calibration curve and quality control acceptance/rejection decisions based on appropriate SOP criteria
- Sample, solution preparation, equipment set-up, and sample processing

Validation Study Audit Results –Human Whole Blood

The initial (b) (4) audit of the whole blood validation results found evidence of on-going method development during validation, unresolved issues with stock solution preparation and stability, unresolved issues with signal saturation at high concentration, and inconsistent reporting of test results from accepted validation batch runs without reconciliation to previously obtained test results. Based on the findings in the initial review of the original validation report (VAL 141.0 [13 Feb. 2004]), (b) (4) was unable to certify the bioanalytical portion of acetazolamide in whole blood.

Subsequent review of data and discussion with (b) (4) resulted in the preparation of validation report number VAL 141.1 (14 June 2007). This validation report was issued to address the preliminary (b) (4) audit findings and to further clarify validation and stability assessments contained in the original validation report, VAL 141.0 (13 Feb. 2004).

The audited validation data reported in validation report number VAL 141.1 (14 June 2007), meet acceptance and rejection criteria and reflect the capabilities of this selective method for the determination of acetazolamide in human whole blood. Validation data support the method LLOQ of 0.100 µg/mL within the 20% precision and accuracy criteria and a standard curve range from 0.100 µg/mL to 50.0 µg/mL. The validation data support the selectivity of the method in human whole blood matrices and appropriate sample stabilities. With the exception of the sensitivity requirement of five times signal to noise, the acetazolamide validated method performance meets the acceptance criteria defined in the (b) (4) method validation SOP GL-BI-10601-00 (6 Jan. 2003).

Validation Study Audit Results –Human Plasma

The initial (b) (4) audit of the plasma validation results found evidence of on-going method development during validation, unresolved issues with stock solution preparation and stability, unresolved issues with signal saturation at high concentration, and inconsistent reporting of test results from accepted validation batch runs without reconciliation to previously obtained test results. Based on the findings in the initial review of the original validation report (VAL 133.0 [13 Feb. 2004]), (b) (4) was unable to certify the bioanalytical portion of acetazolamide in human plasma.

Subsequent review of data and discussion with (b) (4) resulted in the preparation of validation report number VAL 133.1 (17 May 2007). This report was issued to address preliminary (b) (4) audit findings and to further clarify validation and stability assessments contained in the original report validation report, VAL 133.0 (13 Feb. 2004).

The audited validation data report in validation report number VAL 133.1 (17 May 2007), meet acceptance and rejection criteria and reflect the capabilities of this selective method for the determination of acetazolamide in human plasma. Validation data support the method LLOQ of 0.100 µg/mL within the 20% precision and accuracy criteria and a standard curve range from 0.100 µg/mL to 50.0 µg/mL. The validation data support the selectivity of the method in human plasma matrices and appropriate sample stabilities. With the exception of the sensitivity requirement of five times signal to noise, the acetazolamide validated method performance meets the acceptance criteria defined in the (b) (4) method validation SOP GL-BI-10601-00 (6 Jan. 2003).

Production Study

Of the 20,916 chromatograms reviewed, both for acetazolamide and the internal standard (hydrochlorothiazide), several chromatograms had significant anomalies (excluding general compliance issues). There were generally no documented investigations of the root cause for the anomalies or deviations except for occasional comments in data sheets (e.g., poor chromatography, loss of sensitivity, equipment failure or malfunction). However, since such production runs were repeated and a successful

run was achieved, the lack of documentation was not deemed to be likely to have a material adverse impact on the acceptability of the data resulting from the successful runs or the overall study results.

The following significant issues were identified that could potentially impact the quality of the production batch data as discussed below:

1. The (b) (4) method validation SOP, in effect during the acetazolamide study, was not in compliance with the 2001 Guidance for Industry, Bioanalytical Method Validation in that it did not set any specific requirement for signal to noise (S/N). The (b) (4) practice at that time was to require a S/N of not less than 3.0. The failure to meet a S/N ratio of 5.0 resulted in two issues:

a. Failing S/N response of Standard B (the LLOQ Standard) in the case where two other standards had already failed. One production batch (18-CHQ) in plasma concentrations from the fed study (Study AA04622) which contained data collected from subject #046 and some re-runs of samples from subject #006 fell into this category. The S/N response of Standard B (the LLOQ Standard), was estimated by the (b) (4) auditors to be <5.0 but >3.0. As such, the batch does not appear to meet the S/N ratio recommended by the 2001 Guidance for Industry, Bioanalytical Method Validation. Therefore, since standards C and E had failed, this batch should be rejected. Samples excluded from this batch are shown in Table 1.

Table 1. Subjects excluded by (b) (4) from Study AA04622

Batch #	Study #	Matrix	Subject #	Period	Time point
18-CHQ	AA04622	Plasma	006	1 & 2	All
18-CHQ	AA04622	Plasma	046	1 & 2	All

b. Batches failing to meet the S/N ratio of <5.0 but otherwise meeting batch acceptance criteria (e.g., minimal or no failing standards or QC samples). In these cases, the LLOQ should become the concentration of the next higher standard, for this assay from 0.1 µg/mL to 0.2 µg/mL. The result would be that samples reported between the original LLOQ and the revised LLOQ would be reported as BLQ instead of having quantitatively reportable values.

Four batches fall into this category: 08-CHQ, 08-CHT, 12-CHT, and 21-CHT. Samples from those batches that were originally assigned a value greater than BLQ, but less than 0.2 µg/mL, are no longer quantifiable. Upon review, only five samples from the four batches fell into this category. The specific samples in this category are shown in Table 2.

Table 2. Samples in which the originally assigned value was changed to BLQ by (b) (4)

Batch #	Study #	Matrix	Subject #	Period	Time point	Reported value (µg/mL)	(b) (4) value (µg/mL)
08-CHQ	AA04622	Plasma	021	1	72 hrs	0.181	BLQ
08-CHQ	AA04622	Plasma	021	2	72 hrs	0.163	BLQ
08-CHQ	AA04622	Plasma	022	1	72 hrs	0.155	BLQ
12-CHT	AA04181	Whole blood	020	1	72 hrs	0.171	BLQ
12-CHT	AA04181	Whole blood	021	1	0.5 hrs	0.105	BLQ

In addition, there is a consistent absence of written justification for changing parameters that affect peak integration. These modifications have the greatest affect on the concentration standards, QC samples, and subject samples containing low concentrations of acetazolamide. The most serious example of this was found in Batch 09-CHQ (the Plasma – Fed study) which contained data from the plasma samples

collected from subjects #024, #025 and #026. Standards C and E failed and were rejected. The integration parameters for Standard B (the LLOQ standard) were closely examined to rule out potential failure of a third standard, which would result in standard curve failure for the batch. The manual peak integration that yielded the peak area is questionable in that the baseline was redrawn four times when the peak was not detected. As such, the selection of the area to be integrated also appears to be subjective. The peak was not detected during the initial automatic integration and one of the additional reintegrations. The S/N was report to be 4.2. Thus, the data for the three subjects shown in Table 3 should be rejected.

Table 3. Subjects excluded by (b) (4) from Study AA04622

Batch #	Study #	Matrix	Subject #	Period	Time point
09-CHQ	AA04622	Plasma	024	1 & 2	All
09-CHQ	AA04622	Plasma	025	1 & 2	All
09-CHQ	AA04622	Plasma	026	1 & 2	All

Study AA04181

Study AA04181 was conducted to demonstrate bioequivalence between acetazolamide 500 mg extended-release capsules manufactured by Barr Laboratories, Inc. (test) and Lederle Pharmaceutical (reference) under fasted conditions. The bioanalytical data supporting the concentrations of acetazolamide in plasma were found to be acceptable and are not discussed in this review. (b) (4) recommended the concentration of acetazolamide in whole blood to be assigned a value of BLQ for the 72 hr time point of Subject #020 (Period 1, test product) and the 0.5 hrs time point of Subject #021 (Period 1, test product). The geometric mean ratio and 90% confidence interval for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} for acetazolamide in whole blood reported in the final study report (submitted March 11, 2004) and with the recommendations by (b) (4) are shown in Table 4.

NOTE: DuraMed Research, Inc. is a division of Barr Laboratories and Wyeth Labs is a division of Lederle Pharmaceutical.

Table 4. Geometric mean ratios (90% confidence intervals) for acetazolamide in whole blood reported in final study report and with (b) (4) recommendations

Parameter	Final study report	(b) (4) recommendations
AUC_{0-t}	0.965 (0.926 – 1.007)	0.964 (0.924 – 1.005)
$AUC_{0-\infty}$	0.928 (0.849 – 1.014)	0.927 (0.848 – 1.014)
C_{max}	0.959 (0.903 – 1.018)	0.959 (0.903 – 1.018)

Similar to the original results presented in the final study report, the 90% confidence intervals of the geometric mean ratio for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} of acetazolamide in whole blood are within the range of 0.80 to 1.25. Thus, acetazolamide extended-release capsules produced by Barr Laboratories, Inc. (DuraMed Research, Inc. is a division of Barr Laboratories) and Lederle Pharmaceutical (Wyeth Labs is a division of Lederle Pharmaceutical) are bioequivalent under fasted conditions.

Study AA04622

Study AA04622 was conducted to demonstrate bioequivalence between acetazolamide 500 mg extended-release capsules manufactured by Barr Laboratories, Inc. (test) and Lederle Pharmaceutical (reference) under fed conditions. The bioanalytical data supporting the concentrations of acetazolamide in whole blood were found to be acceptable and are not discussed in this review. (b) (4) recommended the exclusion of all acetazolamide concentration data in plasma from Subjects #006, 024, 025, 026, and 046. In addition, (b) (4) recommended acetazolamide concentrations in plasma to be assigned a value of BLQ for

the 72 hr time point of Subject #021 (Periods 1 and 2) and the 72 hr time point of Subject #022 (Period 1, reference product). The geometric mean ratio and 90% confidence interval for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} for acetazolamide in plasma reported in the final study report (submitted March 11, 2004) and with the recommendations by (b) (4) are shown in Table 5.

Table 5. Geometric mean ratios (90% confidence intervals) for acetazolamide in plasma reported in final study report and with (b) (4) recommendations

Parameter	Final study report	(b) (4) recommendations
AUC_{0-t}	0.963 (0.947 – 0.979)	0.958 (0.941 – 0.974)
$AUC_{0-\infty}$	0.972 (0.955 – 0.989)	0.968 (0.950 – 0.987)
C_{max}	0.851 (0.819 – 0.884)	0.846 (0.815 – 0.878)

The 90% confidence intervals of the geometric mean ratio for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} of acetazolamide in whole blood were within the range of 0.80 to 1.25 as reported in the final study report (submitted March 11, 2004) and with (b) (4) recommendations. Thus, acetazolamide extended-release capsules produced by Barr Laboratories, Inc. and Lederle Pharmaceutical are bioequivalent under fed conditions.

COMMENTS:

The audit performed by (b) (4) did not identify significant deviations or non-conformances that would be likely to materially adversely affect the study. However, significant non-conformances in the production run batch audit results were observed that required a reanalysis of the data from both studies with the affected samples excluded or values revised. The pharmacokinetic analyses for both studies using the revised values recommended by (b) (4) demonstrate that the drug product manufactured by Barr Laboratories, Inc. and Lederle Pharmaceutical are bioequivalent and support the transfer of ownership/site of manufacture of acetazolamide extended-release capsules.

RECOMMENDATIONS:

This submission was reviewed by the Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 and found to be acceptable from a clinical pharmacology point of view. No additional pharmacokinetic studies are necessary to support SCM-037 and the bioanalytical concerns with (b) (4) located in (b) (4).

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 4

RD/FT Initialed by John A. Lazor, Pharm.D. _____
Division Director, DCP4

cc:
Division File: NDA 12-945
DAIOP (CSO/Rodriguez)
DCP4 (Division File, Lazor, Bonapace)

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

/s/

Charles Bonapace
1/8/2008 09:50:58 AM
BIOPHARMACEUTICS

John Lazor
1/16/2008 04:42:55 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults	
From: E.Dennis Bashaw, Pharm.D.			To: DOCUMENT ROOM (LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission
DATE: 10/13/04	IND No.: Serial No.:	NDA No. 12-945 SCM- 037/SLR-038	DATE OF DOCUMENT 6/30/04
NAME OF DRUG Acetazolamide	PRIORITY CONSIDERATION PA		Date of informal/Formal Consult: 36/30/04
NAME OF THE SPONSOR: [DURA-MED (a division of BARR Labs.)]			
TYPE OF SUBMISSION CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE			
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input type="checkbox"/> PHASE IV RELATED </div> <div style="width: 33%;"> <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE XX BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) </div> <div style="width: 33%;"> <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION XX OTHER (<i>SPECIFY BELOW</i>): <div style="text-align: right;">[Transfer of Site of Manufacture]</div> </div> </div>			
REVIEW ACTION			
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail) </div> <div style="width: 33%;"> <input type="checkbox"/> Oral communication with Name: [] <input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: [] </div> <div style="width: 33%;"> <input type="checkbox"/> Formal Review/Memo (attached) XX See comments below <input type="checkbox"/> • See submission cover letter <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): <div style="text-align: right;">[]</div> </div> </div>			
REVIEW COMMENT(S)			
XX NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR			
<u>Recommendation</u> Included in this supplement were two in vivo biostudies supporting the change of ownership/site of manufacture from Wyeth Labs (Pearl River, N.J.) to Dura-Med (Pomona, N.Y.). These biostudies demonstrated that the product produced at the old and new site were bioequivalent under both fed and fasted conditions. Based on the submitted data and our review of it the Office of Clinical Pharmacology and Biopharmaceutics has no objection to the approval of this manufacturing supplement.			
<u>Background</u> Acetazolamide is an enzyme inhibitor that acts specifically on carbonic anhydrase, the enzyme which catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In the eye, this inhibitory action of acetazolamide decreases the secretion of aqueous humor and results in a drop in intraocular pressure, a reaction considered desirable in cases of glaucoma and even in certain nonglaucomatous conditions. The			

sustained-release capsules provide prolonged duration of action, inhibiting aqueous humor secretion for 18 to 24 hours after each dose, whereas tablets act for only eight to 12 hours.

Diamox Sequels (Acetazolamide Sustained Release Capsules 500mg) has been bought from Wyeth Labs by Dura-Med. As such they have submitted a manufacturing supplement containing in vivo biopharmaceutic trials to allow them to move production from the Wyeth site in Pearl River, N.J. to their site in Pomona, N.Y.

STUDY SUMMARIES

Study AA04181

Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Barr1 and Lederle Pharmaceutical (Diamox® Sequels®) 500 mg Acetazolamide Sustained-Release Capsules in Healthy Adult Volunteers under Fasting Conditions

The objective of this study was to compare the single-dose relative bioavailability of Barr and Lederle Pharmaceutical (Diamox® Sequels®) 500 mg acetazolamide sustained-release capsules under fasting conditions. It was an open-label randomized, 2-way crossover, single-dose, relative bioavailability study in a total of 42 healthy adult volunteers (21 males and 21 females). A total of 39 volunteers (21 males and 18 females) completed the clinical phase of the study. The study methods and procedures are summarized in the appendix on pages 4-7. The results are summarized below:

Geometric Means of Acetazolamide in Plasma

Source ¹	AUC0-t	AUC0-inf	Cmax	Tmax	T1/2
Dura-Med (Barr)	123.3 (23.7%)	132.9 (26.9%)	5.5 (26.3%)	3.75 (38.8%)	16 (58.6%)
Wyeth (Lederle)	131.3 (22.6%)	143.1 (26.2%)	6 (27.6%)	4.20 (88.4%)	16 (45.3%)

Geometric Means of Acetazolamide in Whole Blood

Source ¹	AUC0-t	AUC0-inf	Cmax	Tmax	T1/2
Dura-Med (Barr)	365 (16.4%)	481 (27.7%)	9.4 (22.6%)	7.43 (75.1%)	32 (63.6%)
Wyeth (Lederle)	378 (19.5%)	520 (33.6%)	9.8 (24.8%)	7.97 (82.8%)	36 (76.4%)

Ratios of LSM (90% Confidence Intervals)

Parameter	Acetazolamide in Plasma Barr (A) vs. Lederle (B)	Acetazolamide in Whole Blood Barr (A) vs. Lederle (B)
AUC 0-t	93.8% (88.6 – 99.3%)	96.5% (92.6 – 100.7%)
AUCinf	92.9% (87.3 – 98.9%)	92.8% (84.9 – 101.4%)
Cmax	91.7% (85.2 – 98.7%)	95.9% (90.3 – 101.8%)

Based on the results presented here the products are bioequivalent under fasted conditions.

Study AA04622

¹ Note: Dura-Med is a division of Barr Laboratories and the two names have been used interchangeably by the sponsor in this supplement. The sponsor also occasionally calls the Wyeth facility at Pearl River, N.J. as the "Lederle Site" as it was originally owned by Lederle before they themselves were bought out by American Home Products, the parent of Wyeth Pharmaceuticals.

Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Barr and Lederle Pharmaceutical (Diamox Sequels) 500 mg Acetazolamide Sustained-Release Capsules in Healthy Adult Volunteers under Fed Conditions

The objective of this study was to compare the single-dose relative bioavailability of Barr and Lederle Pharmaceutical (Diamox® Sequels®) 500 mg acetazolamide sustained-release capsules under fed conditions using the standard FDA high fat breakfast. It was an open-label, randomized, 2-way crossover, single-dose, relative bioavailability study conducted in a total of 46 healthy adult volunteers (21 males and 25 females). A total of 44 volunteers (21 males and 23 females) completed the clinical phase of the study. The study methods and procedures are summarized in the appendix on pages 8-11. The results are summarized below:

Geometric Means of Acetazolamide in Plasma

Source ¹	AUC0-t	AUC0-inf	Cmax	Tmax	T1/2
Dura-Med (Barr)	196.3 (22.1%)	203.3 (22.9%)	10.6 (26%)	8.67 (37.9%)	13.3 (31.9%)
Wyeth (Lederle)	203.9 (20.1%)	208.3 (20.2%)	12.5 (26.2%)	8.93 (53.7%)	12.4 (26.3%)

Geometric Means of Acetazolamide in Whole Blood

Source ¹	AUC0-t	AUC0-inf	Cmax	Tmax	T1/2
Dura-Med (Barr)	432 (14.5%)	521 (17.5%)	15.4 (18.5%)	9.58 (33.2%)	28.2 (22.7%)
Wyeth (Lederle)	438 (13.5%)	511 (15.2%)	17 (17%)	9.61 (47.1%)	25.5 (19.5%)

Ratios of LSM (90% Confidence Intervals)

Parameter	Acetazolamide in Plasma Barr (A) vs. Lederle (B)	Acetazolamide in Whole Blood Barr (A) vs. Lederle (B)
AUC 0-t	96.3% (94.7 – 97.9%)	98.8% (97.1 – 100.5%)
AUCinf	97.2% (95.5 – 98.9%)	102.1% (99.5 – 104.8%)
Cmax	85.1% (81.9 – 88.4%)	90.2% (87.2 – 93.3%)

Based on the results presented here the products are bioequivalent under fed conditions.

Labeling

No changes are required to the Clinical Pharmacology Sections of the current package insert.

SIGNATURE OF REVIEWER: _____

Date _____

SIGNATURE OF TEAM LEADER: _____

Date _____

CC.: HFD # [880]; TL: [Selen]; DD: [Lazor]

Project Manager: _____ **Date**

**Comparative. Randomized, Single-Dose, 2-Way Crossover Bioavailability Study
of Barr and Lederle Pharmaceutical (Diamox® Sequels®) 500 mg Acetazolamide
Sustained-Release Capsules in Healthy Adult Volunteers under Fasting
Conditions**

OBJECTIVE: The objective of this study was to compare the single-dose relative bioavailability of Barr and Lederle Pharmaceutical (Diamox® Sequels®) 500 mg acetazolamide sustained-release capsules under fasting conditions.

STUDY DESIGN: This was an open-label randomized, 2-way crossover, single-dose, relative bioavailability study conducted at the (b) (4)
(b) (4) was the Principal Investigator for this study.

A total of 42 healthy adult volunteers (21 males and 21 females) enrolled in the study, three did not complete the clinical phase of the study. Subject No. 14 withdrew herself after Period 1, but before Period 2 dosing, Subject No. 27 did not want to continue on study during Period 1 and Subject No. 42 was removed from the study after Period 1 due to adverse events. Thus, a total of 39 volunteers (21 males and 18 females) completed the clinical phase of the study.

Test Product A:

Acetazolamide Sustained-Release Capsules 500 mg
Manufactured by Barr Laboratories, Inc.
Batch No.: 205993001R
Manufactured date: 20 Aug 2003
Expiration date: 20 Aug 2004

Reference Product B: Diamox® Acetazolamide Sequels Sustained-Release Capsules 500 mg
Distributed by Lederle Pharmaceutical Division of American Cyanamid Co.
Control No.: 493-387
Expiration date: February-2006

METHODS: Subjects reported to the clinic on the evening prior to each dosing and received a dinner at 20:00 hours. The subjects then fasted for 10-hours overnight before dosing and for at least 4 hours thereafter. Water was not permitted for 1 hour before and 1 hour after dosing, but was allowed at all other times. On Day 1, an (b) (4) standardized meal schedule was initiated with lunch at 12:30 hours, dinner at 17:00 hours and a snack at 21:00 hours. On Day 2, an (b) (4) standardized meal schedule (including breakfast) was initiated. During housing, post-dose meal plans were identical for both periods.

Blood samples were collected as specified in the protocol before dosing and at the following times thereafter: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 36, 48, 60 and 72 hours post-dosing. There was a 14 day washout period between the two doses.

Acetazolamide was analyzed in plasma and whole blood using validated LC-MS/MS methods developed at (b) (4) in (b) (4). The analytical range was 0.100 to 49.9 mcg/mL for both methods.

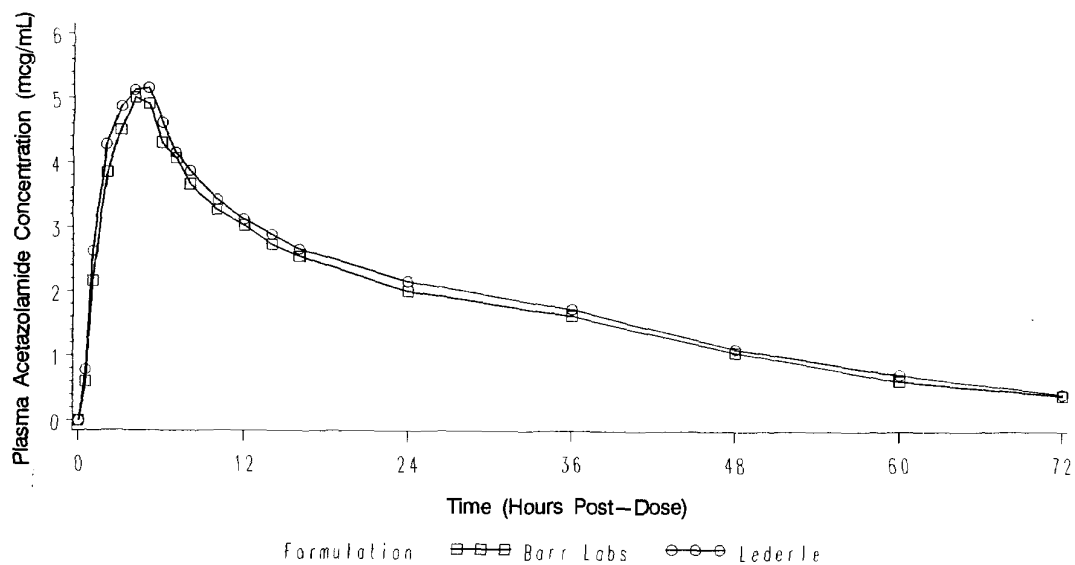
RESULTS: The results of this trial are summarized in the following tables and mean plasma level time curves for plasma and whole blood.

Summary of Results - Acetazolamide in Plasma
Pharmacokinetic Parameters
(N = 37)

	ln AUC D-t* (mcg·h/mL)	ln AUCinf* (mcg·h/mL)	ln Cmax* (mcg/mL)	tmax (h)	Half-life (h)	kel (1/h)	CL/F (L/h)	Varea/F (L)
Barr Labs (A)								
Mean	123.286	132.965	5.54377	3.759	16.042	0.05188	3.888	83.92
CV	23.7	26.9	26.3	38.8	58.6	33.8	26.4	41.2
n	37	36	37	37	36	36	36	36
Lederle (B)								
Mean	131.335	143.160	6.03980	4.204	16.055	0.05164	3.608	78.00
CV	22.6	26.2	27.6	88.4	45.3	40.5	26.3	33.7
n	37	35	37	37	35	35	35	35
Least-Squares Mean								
Barr Labs (A)	123.197	132.672	5.54719					
Lederle (B)	131.288	142.795	6.04766					
Ratio of Least-Squares Means (A/B)%	93.8	92.9	91.7					
90% Confidence Intervals (A/B)%								
lower limit:	88.6%	87.3%	85.2%					
upper limit:	99.3%	98.9%	98.7%					
p-Value (ANOVA)								
A vs B	0.0679	0.0539	0.0541					
Period	0.6964	0.8370	0.5633					
Sequence	0.5611	0.5123	0.3568					

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
PhAST STAB 2.3-000

Mean Plasma Acetazolamide Concentrations
(Linear Plot)

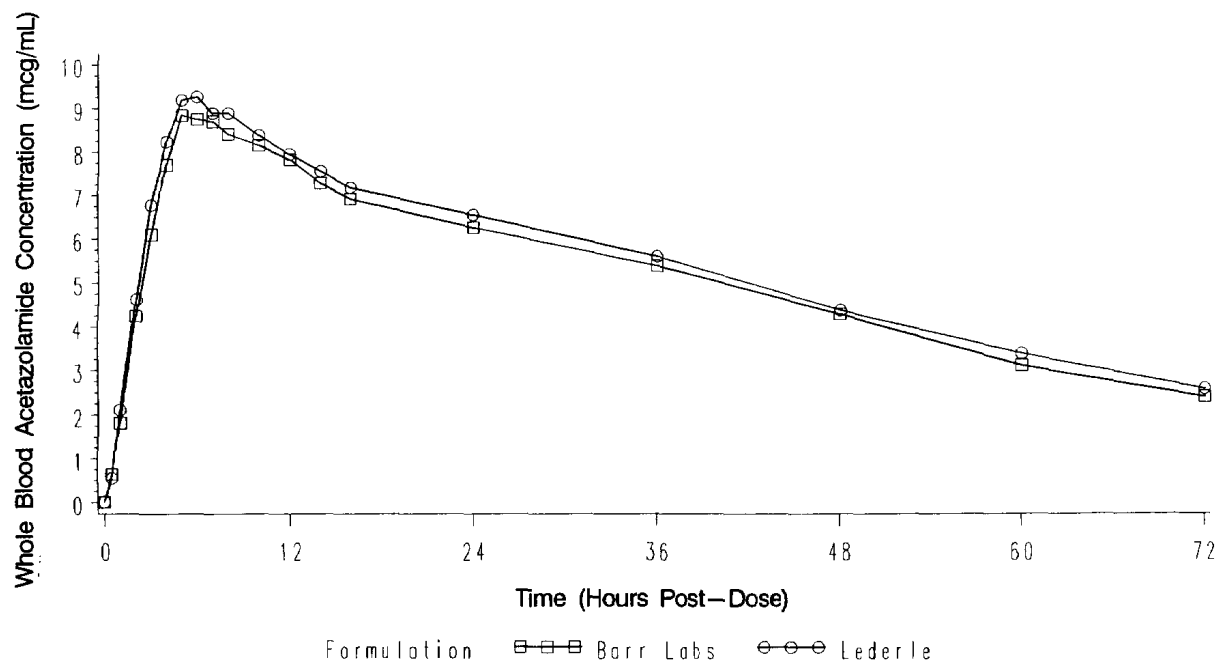


Summary of Results - Acetazolamide in Whole Blood
Pharmacokinetic Parameters
(N = 37)

	ln AUC 0-t* (mcg·h/mL)	ln AUCinf* (mcg·h/mL)	ln Cmax* (mcg/mL)	tmax (h)	Half-life (h)	kel (1/h)	CL/F (L/h)	Varea/F (L)
Barr Labs (A)								
Mean	365.09	481.36	9.41269	7.432	32.26	0.025878	1.0727	44.93
CV	16.4	27.7	22.6	75.1	63.6	38.1	23.7	27.4
n	37	36	37	37	36	36	36	36
Lederle (B)								
Mean	378.23	520.15	9.81862	7.973	36.05	0.024237	1.0078	44.74
CV	19.5	33.6	24.8	82.8	76.4	37.9	29.4	25.9
n	37	36	37	37	36	36	36	36
Least-Squares Mean								
Barr Labs (A)	364.94	479.47	9.42059					
Lederle (B)	378.02	516.78	9.82746					
Ratio of Least-Squares Means (A/B)%	96.5	92.8	95.9					
90% Confidence Intervals (A/B)%								
lower limit:	92.6%	84.9%	90.3%					
upper limit:	100.7%	101.4%	101.8%					
p-Value (ANOVA)								
A vs B	0.1626	0.1645	0.2439					
Period	0.8183	0.9731	0.9506					
Sequence	0.5201	0.7326	0.3549					

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
PhAST STAB 2.3-000

Mean Whole Blood Acetazolamide Concentrations
(Linear Plot)



Acetazolamide in Plasma:

The ratios of least-squares means (with the 90% confidence intervals) for the pharmacokinetic parameters AUC 0-t, AUCinf and Cmax were 93.8% (88.6-99.3%), 92.9% (87.3-98.9%) and 91.7% (85.2-98.7%), respectively. The mean Tmax values in plasma for the Barr Laboratories and Lederle Pharmaceutical products were 3.759 and 4.204 hours, respectively.

Acetazolamide in Whole Blood

The ratios of least-squares means (with the 90% confidence intervals) for the pharmacokinetic parameters AUC 0-t, AUCinf and Cmax were 96.5% (92.6-100.7%), 92.8% (84.9-101.8%) and 95.9% (90.3-101.8%), respectively. The mean Tmax values in whole blood for the Barr Laboratories and Lederle Pharmaceutical products were 7.432 and 7.973 hours, respectively.

CONCLUSIONS: The ratios of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t, AUCinf, and Cmax for acetazolamide in plasma and whole blood were within the 80-125% FDA acceptance range. Based on these results, the Barr Laboratories and Lederle Pharmaceutical (Diamox Sequels) 500 mg acetazolamide sustained-release capsules are bioequivalent under fasting conditions.

Comparative. Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Barr and Lederle Pharmaceutical (Diamox Sequels) 500 mg Acetazolamide Sustained-Release Capsules in Healthy Adult Volunteers under Fed Conditions

OBJECTIVE: The objective of this study was to compare the single-dose relative bioavailability of Barr and Lederle Pharmaceutical (Diamox® Sequels®) 500 mg acetazolamide sustained-release capsules under fed conditions.

STUDY DESIGN: This was an open-label, randomized, 2-way crossover, single-dose, relative bioavailability study conducted at the [REDACTED] (b) (4). [REDACTED] (b) (4) was the Principal Investigator for this study.

A total of 46 healthy adult volunteers (21 males and 25 females) enrolled in the study, two did not complete the clinical phase of the study. Subject No. 1 was withdrawn because she vomited approximately 6 hours post-dose in Period 1,. Subject No. 2 left after the 6-hour sample collection in Period 2 due to a death in the family. Thus, a total of 44 volunteers (21 males and 23 females) completed the clinical phase of the study.

Test Product A:
Acetazolamide Sustained-Release Capsules 500 mg
Manufactured by Barr Laboratories, Inc.
Batch No.: 206993001R
Manufactured date: 20 Aug 2003
Expiration date: 20 Aug 2004

Reference Product B:
Diamox® Acetazolamide Sequel Sustained-Release Capsules 500 mg
Distributed by Lederle Pharmaceutical Division of American Cyanamid Company
Control No.: 493-387
Expiration date: February-2006

METHODS: Subjects reported to the clinic on the evening prior to each dosing and received a dinner at 20:00 hours. The subjects then fasted for 10-hours overnight until 30 minutes prior to dosing when they received a high-fat breakfast at 07:30 hours. The subjects also fasted for at least 4 hours after dosing. Water was not permitted for 1 hour before and 1 hour after dosing, but was allowed at all other times. On Day 1, in addition to the breakfast served before dosing, lunch was served at 12:30 hours, dinner at 17:00 hours and a snack at 21:00 hours. On Day 2, an [REDACTED] (b) (4) standardized meal schedule (including breakfast) was initiated. During housing, post-dose meal plans were identical for both periods.

A single oral 500 mg dose was administered with 240 mL of tap water at room temperature, 30 minutes after administration of a standard high fat breakfast. Blood samples were then to be collected before dosing and at the following times: 0.5, 1,2,3,4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 36, 48, 60 and 72 hours post-dosing. There was a 14-day washout between the 2 doses.

Acetazolamide was analyzed in plasma and whole blood using validated LC-MS/MS methods developed at [REDACTED] (b) (4). The analytical range was 0.100 to 49.9 mcg/mL for both methods.

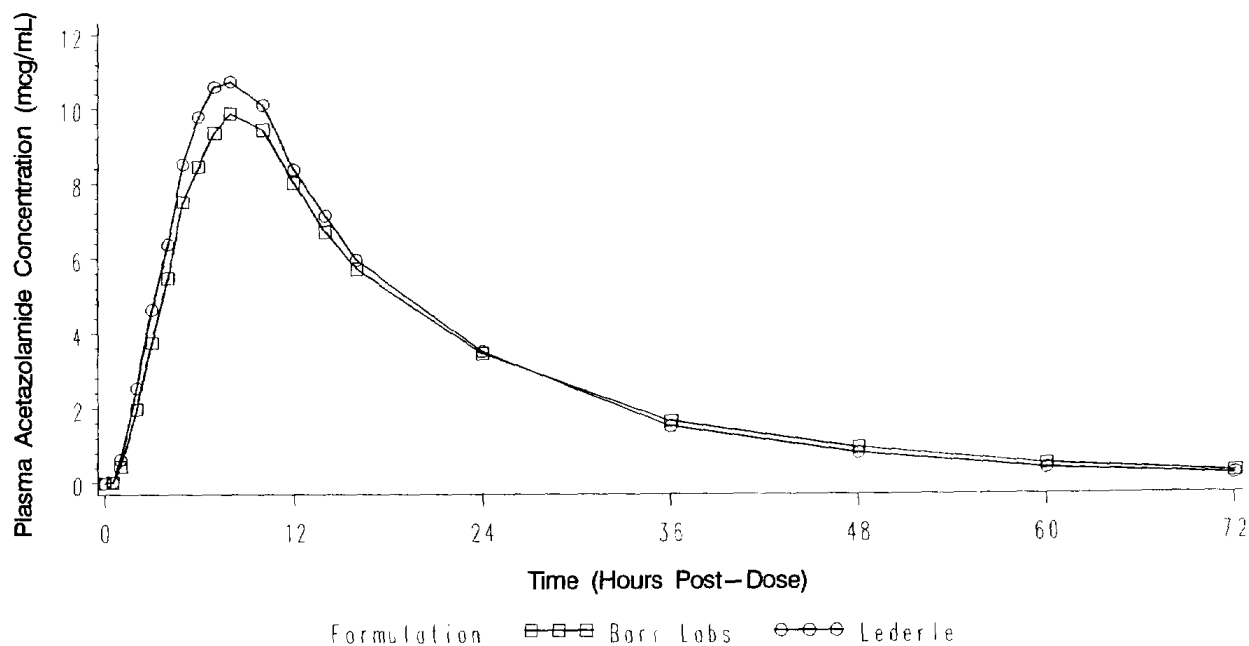
RESULTS: The results of this trial are summarized in the following Tables and mean plasma level time curves for both plasma and whole blood.

Summary of Results - Acetazolamide in Plasma
Pharmacokinetic Parameters
(N = 43)

	ln AUC 0-t* (mcg·h/mL)	ln AUCinf* (mcg·h/mL)	ln Cmax* (mcg/mL)	tmax (h)	Half-life (h)	kel (1/h)	CL/F (L/h)	Varea/F (L)
Barr Labs (A)								
Mean	196.30	202.38	10.61468	8.675	13.308	0.05616	2.531	47.33
CV	22.1	22.9	26.0	37.9	31.9	25.1	21.7	29.1
n	43	43	43	43	43	43	43	43
Lederle (B)								
Mean	203.92	208.30	12.47344	8.930	12.414	0.05909	2.445	43.42
CV	20.1	20.2	26.2	53.7	26.3	22.5	18.8	28.5
n	43	43	43	43	43	43	43	43
Least-Squares Mean								
Barr Labs (A)	196.31	202.39	10.61192					
Lederle (B)	203.88	208.24	12.47014					
Ratio of Least-Squares Means (A/B)%								
	96.3	97.2	85.1					
90% Confidence Intervals (A/B)%								
lower limit:	94.7%	95.5%	81.9%					
upper limit:	97.9%	98.9%	88.4%					
p-Value (ANOVA)								
A vs B	0.0004	0.0089	0.0001					
Period	0.2660	0.2044	0.9945					
Sequence	0.9054	0.8906	0.7680					

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
PhAST STAB 2.3-000

Mean Plasma Acetazolamide Concentrations
(Linear Plot)

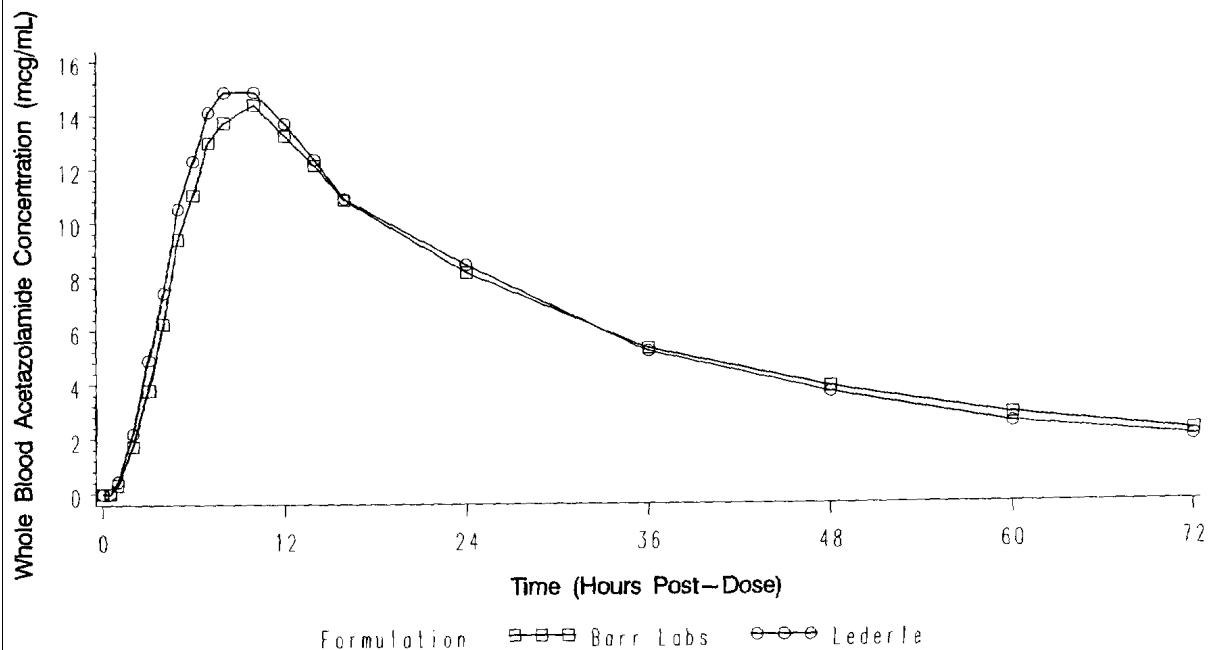


Summary of Results - Acetazolamide in Whole Blood
Pharmacokinetic Parameters
(N = 43)

	ln AUC 0-t* (mcg·h/mL)	ln AUCinf* (mcg·h/mL)	ln Cmax* (mcg/mL)	tmax (h)	Half-life (h)	kel (1/h)	CL/F (L/h)	Varea/F (L)
Barr Labs (A)								
Mean	432.43	521.39	15.40031	9.583	28.19	0.02576	0.9732	38.75
CV	14.5	17.5	18.5	33.2	22.7	21.2	17.4	18.6
n	43	43	43	43	43	43	43	43
Lederle (B)								
Mean	438.12	510.88	17.06499	9.606	25.47	0.02824	0.9894	35.90
CV	13.5	15.2	17.0	47.1	19.5	19.6	14.7	18.4
n	43	43	43	43	43	43	43	43
Least-Squares Mean								
Barr Labs (A)	432.75	521.93	15.39742					
Lederle (B)	438.22	511.10	17.06731					
Ratio of Least-Squares Means (A/B)%	98.8	102.1	90.2					
90% Confidence Intervals (A/B)%								
lower limit:	97.1%	99.5%	87.2%					
upper limit:	100.5%	104.8%	93.3%					
p-Value (ANOVA)								
A vs B	0.2284	0.1816	0.0001					
Period	0.0367	0.0917	0.4884					
Sequence	0.3099	0.1827	0.9656					

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
PhAST STAB 2.3-000

**Mean Whole Blood Acetazolamide Concentrations
(Linear Plot)**



Acetazolamide in Plasma

The ratios of least-squares means (with the 90% confidence intervals) for the pharmacokinetic parameters AUC 0-t, AUCinf and Cmax were 96.3% (94.7- 97.9%), 97.2% (95.5- 98.9%) and 85.1% (81.9- 88.4%), respectively. The mean tmax values in plasma for the Barr Laboratories and Lederle Pharmaceutical products were 8.675 and 8.930 hours, respectively.

Acetazolamide in Whole Blood

The ratios of least-squares means (with the 90% confidence intervals) for the pharmacokinetic parameters AUC 0-t, AUCinf and Cmax were 98.8% (97.1-100.5%), 102.1% (99.5-104.8%) and 90.2% (87.2-93.3%), respectively. The mean tmax values in whole blood for the Barr Laboratories and Lederle Pharmaceutical products were 9.583 and 9.606 hours, respectively.

CONCLUSIONS: The ratios of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t, AUCinf and Cmax for acetazolamide in plasma and whole blood were within the 80-125% FDA acceptance range. Based on these results, the Barr Laboratories and Lederle Pharmaceutical (Diamox® Sequels) 500 mg acetazolamide sustained-release capsules are bioequivalent under fed conditions.

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/s/

Dennis Bashaw
10/22/04 04:15:04 PM
BIOPHARMACEUTICS

Arzu Selen
10/26/04 01:49:20 PM
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