CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-514/S-001; S-002; S-003

Generic Name: Midodrine Hydrochloride Tablets, 2.5mg and 5mg

Sponsor: Eon Labs, Inc.
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APPLICATION NUMBER:
76-514/S-001; S-002; S-003

APPROVAL LETTERS
Eon Labs, Inc.
Attention: Dietrich Bartel
4700 Eon Drive
Wilson, NC 27893

Dear Sir:

This is in reference to your supplemental new drug applications dated September 11, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), regarding your abbreviated new drug application for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg.

Reference is also made to your amendments dated January 16, and April 15, 2004.

The supplemental applications provide for:

- S-001 An additional 10 mg strength of Midodrine Hydrochloride Tablets; and
- S-002 Revised labeling to include the 10 mg strength.

We have completed the review of these supplemental applications and have concluded that the additional 10 mg strength of the drug product is safe and effective for use as recommended in the submitted labeling. Accordingly the supplemental applications are approved. The Division of Bioequivalence has determined your Midodrine Hydrochloride Tablets, 10 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (ProAmatine® Tablets, 10 mg, of Shire Pharmaceutical Development, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

FDA granted marketing approval for Shire’s ProAmatine Tablets pursuant to 21 CFR 314.510 (Subpart H) on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint. This effect is
reasonably likely, based upon epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section is subject to the requirement that the applicant agree to study the drug further to verify and describe its clinical benefit where there is uncertainty as to the relation of the surrogate endpoint to the benefit, or of the observed clinical benefit to the ultimate outcome. To date, Shire has not satisfied its post-marketing studies commitment for ProAmatine Tablets.

Under 21 CFR 314.530, for new drugs approved under Section 314.510 and 314.520, FDA may withdraw approval following a hearing if:

1. The post-marketing clinical study fails to verify clinical benefit;

2. The applicant fails to perform the required post-marketing study with due diligence;

3. Use of the drug product after marketing demonstrates that the post-marketing restrictions are inadequate to assure the safe use of the drug product;

4. The applicant fails to adhere to the post-marketing restrictions agreed upon;

5. The promotional materials are false or misleading; or

6. Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

Please note that if approval of the listed drug is withdrawn or suspended for any of the reasons specified in 21 CFR 314.530, the approval of your abbreviated new drug application (ANDA), which relies on the finding of safety and effectiveness for the listed drug, may also be withdrawn pursuant to 21 CFR 314.150 and 314.151, or suspended prior to withdrawal pursuant to 21 CFR 314.153.
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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

Promotional materials for the new strength may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

The materials submitted are being retained in our files.

Sincerely yours,

[Signature]

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

7/2/2004
Eon Labs, Inc.
Attention: Steven W. Brown
4700 Eon Drive
Wilson, NC 27893

Dear Sir:

This is in reference to your supplemental new drug applications dated December 22, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug applications for your drug products (see attachment). The supplemental applications, submitted as "Supplement - Changes Being Effected in 30 Days" provide for:

Adding the following facility as

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for the approved abbreviated new drug applications described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

Paul Schmick
Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Attachment:

76-402/S001 Benazepril Hydrochloride Tablets, 5mg, 10 mg, 20 mg, and 40 mg
76-483/S001 Fosinopril Sodium Tablets, 10 mg, 20 mg, and 40 mg
76-514/S003 Mjodrine Hydrochloride Tablets, 2.5 mg, 5 mg, and 10 mg
76-631/S001 Benazepril Hydrochloride and Hydrochlorothiazide Tablets, 5 mg/6.25 mg, 10 mg/12.5 mg, 20 mg/12.5 mg, and 20 mg/25 mg
APPLICATION NUMBER:

76-514/S-001; S-002; S-003

FINAL PRINTED LABELING
Midodrine Hydrochloride Tablets

**WARNING:** Because midodrine hydrochloride can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. The indication for use of midodrine hydrochloride is the treatment of symptomatic orthostatic hypotension. This drug is based primarily on a change in a number of endpoints that are often non-specific, an increase in supine blood pressure measured one minute after standing, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefit of midodrine hydrochloride, principally improved ability to carry out activities of daily living, have not been verified.

**DESCRIPTION:**
Midodrine hydrochloride is a vasopressor/hypotension agent. Midodrine hydrochloride is an odorless, white, crystalline powder, readily soluble in water and sparingly soluble in methanol having a pKa of 7.8 (0.3% aqueous solution), a pH of 5.5 to 5.9 (1% aqueous solution) and a melting range of 230 to 235°C. It is chemically described as: 1-(2-Aminoethyl)-1H-imidazole hydrochloride, 3-hydroxymidodrine, 3-hydroxymidodrine hydrochloride, 3-hydroxymidodrine hydrochloride (atropine-like), and the structural formula is:

```
H2CO
CH2OH
O
O
OH
N
N
H
O
O
H
O
H
CH2OH
H
```

Each tablet for oral administration contains 5 mg, 5 mg or 10 mg of midodrine hydrochloride and the following inactive ingredients: Pregelatinized starch (100), NF; NF Sodium Starch Glycolate, NF; Colloidal Silica, NF; Magnesium Stearate, NF. In addition, the 5-mg tablets contain Red Iron Oxide, NF, 4-6 Aluminum Lake and FD&C Red No. 40 Aluminum Lake, and the 10-mg tablets contain FD&C Blue No. 1 Aluminum Lake.

**CLINICAL PHARMACOLOGY:**
Mechanism of Action: Midodrine hydrochloride forms an active metabolite, desmethylmidodrine, which is an α1-agonist and works by inhibiting the reuptake of the alpha-2-adrenergic receptors of the sympathetic and parasympathetic systems, resulting in an increase in vasoconstriction and elevation of blood pressure. Desmethylmidodrine does not stimulate cardiac beta-adrenergic receptors. Desmethylmidodrine diffuses poorly across the blood-brain barrier, and is therefore not associated with effects on the central nervous system.

Administration of midodrine hydrochloride results in a rise in standing, sitting, and supine systolic and diastolic blood pressure within 5 minutes of administration of various dosages. Standing systolic blood pressure is elevated by approximately 15 to 30 mmHg at 1 hour after a 15-mg dose of midodrine, with some effect persisting for 2 to 3 hours. Midodrine hydrochloride has no clinically significant effect on standing or supine pulse rates in patients with supine intolerance.

Pharmacokinetics: Midodrine hydrochloride is a prodrug, i.e., the therapeutic effect of orally administered midodrine is due to the major metabolite desmethylmidodrine, formed by deamination of midodrine. Oral and intravenous administration of midodrine is rapidly absorbed. The plasma levels of the prodrug peak after about 1 hour, and decline with a half-life of approximately 25 minutes, while the metabolite reaches peak plasma concentrations about 1 to 2 hours after a dose of midodrine and has a half-life of about 3 to 6 hours. The absolute bioavailability of midodrine (prescribed as desmethylmidodrine) is 30%. The bioavailability of desmethylmidodrine is not affected by food. Approximately, the same amount of desmethylmidodrine is formed after intravenous and oral administration of midodrine. Neither midodrine nor desmethylmidodrine is bound to plasma proteins to any significant extent.

Metabolism and Excretion: Through metabolic studies have not been conducted, but it appears that deamination of midodrine to desmethylmidodrine takes place in many tissues, and both compounds are metabolized in part by the liver. Neither midodrine nor desmethylmidodrine is a substrate for cytochrome oxidase.

Excretion: administration of midodrine hydrochloride is rapid. The normal clearance of desmethylmidodrine is in the range of 365 to 1370 mL/min, mean, about 80% by active renal secretion. The actual mechanism of active secretion has not been studied, but it is possible that it occurs by the low-affinity pathway responsible for the secretion of several other drugs that are bases (see also Potential for Drug Interactions).

Clinical Studies:
Midodrine has been studied in 3 principal clinical trials, one of 6 weeks duration and 2 of 1 to 2 days duration. All studies were conducted, double-blind and parallel-design trials in patients with orthostatic hypotension by any diagnosis and supine-hypotensive fall of systolic blood pressure of at least 20 mmHg accompanied by at least moderate dizziness/light-headedness.

Patients with pre-existing sustained supine hypertension above 180/110 mmHg were randomly excluded. In a 3-week study in 115 patients, midodrine was used concurrently with medications, the midodrine-treated patients had improvements in dizziness/light-headedness and global evaluation, but these effects were made difficult to interpret by a high early-drop out rate (about 35% in 3 weeks. Systolic and diastolic blood pressure rose 16/9 and 20/10 mmHg, respectively, on average.

In a 2-day study, after open-label midodrine, known midodrine responders received midodrine 10 mg or placebo at 6 and 3 hours. One minute standing systolic blood pressures were increased 1 hour after each dose by about 15 mmHg and 3 hours after each dose by about 20 mmHg. 3-minute standing pressures were increased by 10 mmHg over 3 hours. Doses of midodrine 0.5 mg and 2.0 mg were given in 25 patients. In a 1- to 20-mg dose group, increases in standing systolic pressures of about 30 mmHg at 1 hour; the increase was sustained in part for 2 hours after 10 mg and 4 hours after 20 mg. Supine systolic blood pressure was reduced by 200 to 220 mmHg on patients at 10 mg and 20 mg; diastolic pressures after 10 mg were 60 mg per hour, or more for 6 hours.

**INDICATIONS AND USAGE:**
Midodrine hydrochloride tablets are indicated for the treatment of symptomatic orthostatic hypotension (OH).

**CONTRAINDICATIONS:**
Midodrine hydrochloride tablets are contraindicated in patients with severe organic heart disease, acute renal disease, arterial occlusions, phaeochromocytoma or thyrotoxicosis. Midodrine hydrochloride should not be used in patients with persistent and excessive supine hypertension.

**WARNINGS:**
Systolic Hypertension: The most potentially serious adverse reaction associated with midodrine hydrochloride therapy is marked elevation of supine arterial blood pressure (supine hypertensive). Systolic pressure of about 200 mmHg was noted overall in about 14 of patients given 15 mg of midodrine hydrochloride. Systolic elevations of this degree were most likely to be observed in patients with relatively advanced pre-treatment systolic blood pressure (mean 170 mmHg). There is no experience in patients with initial systolic systolic blood pressure above 180 mmHg, as these patients were excluded from the clinical trials. Use of midodrine hydrochloride in such patients is not recommended.

**PRECAUTIONS:**
The potential for supine and sitting hypertension should be evaluated at the beginning of midodrine hydrochloride therapy. Systolic hypertension can often be controlled by preventing the patient from assuming supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supine supi
Information for Patients: Patients should be told that certain agents in over-the-counter products, such as cold remedies and diet aids for weight loss, may contain miltidine hydrochloride. As they may enhance or potentiate the pressor effects of miltidine hydrochloride, patients should be advised to restrict intake of such products. They should be told to avoid taking their dose if they are to be supine for any length of time, i.e., they should take their last daily dose of miltidine hydrochloride 3 to 4 hours before bedtime to minimize side effects upon assuming the supine position.

Laboratory Tests: Since deoxyguanylic acid is eliminated by the kidneys and the dose has a role in its metabolism, evaluation of the patient should include assessment of renal and hepatic function prior to initiating therapy and subsequently, as appropriate.

Drug Interactions: When administered concurrently with miltidine hydrochloride, cardiac glycosides may enhance or precipitate bradyarrhythmia, AV block or atrial fibrillation. The use of drugs that stimulate alpha-adrenergic receptors (e.g., phenylephrine, pseudoephedrine, epinephrine, phenylpropanolamine or dihydroergotamine) may enhance or potentiate the pressor effects of miltidine hydrochloride. Therefore, caution should be used when miltidine hydrochloride is administered concurrently with agents that cause vasoconstriction.

Miltidine hydrochloride has been used in patients concurrently treated with beta-blocking agents (e.g., beta-blocker prophylaxis), with or without salt supplements. The potential for supine hypertension should be carefully considered in these patients and may be minimized by other reducing the dose of furosemide or acetazolamide or decreasing the salt intake prior to institution of treatment with miltidine hydrochloride. Alpha-adrenergic blocking agents, such as prazosin, terazosin, and doxazosin, can antagonize the effects of miltidine hydrochloride. Potential for Drug Interactions: It appears possible, although there is no supporting experimental evidence, that the high renal clearance of deoxyguanylic acid is a factor in the inhibition of baroreceptors by the baroreceptor system also responsible for the secretion of such drugs as angiotensin, catecholamine, procainamide, quinidine, furosemide, and atenolol. Therefore, there may be a potential for drug-drug interaction with these drugs.

Contraindications, Warnings, Impairment of Fertility: Long-term studies have been conducted in rats and mice at doses of 3 to 4 times the maximum recommended human dose on a mg/kg basis, with no indication of carcinogenic effects related to miltidine hydrochloride. Studies investigating the mutagenic potential of miltidine hydrochloride revealed no evidence of mutagenicity. Other than the dominant lethal assay in male mice, in which no impairment of fertility was observed, there have been no studies on the effects of miltidine hydrochloride on fertility.

Pregnancy: Pregnancy Category C. Miltidine hydrochloride increased the rate of embryonic resorption, reduced fetal weight, and reduced fetal survival when given in doses 33 to 67 times the maximum human dose based on body surface area (mg/m²). There are no adequate and well-controlled studies in pregnant women. Miltidine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No teratogenic effects have been observed in studies in rats and rabbits.

Nursing Mothers: It is unknown whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when miltidine hydrochloride is administered to a nursing woman.

Adverse Reactions: The most frequent adverse reactions seen in controlled trials were supine and sitting hypertension, postural hypotension, mainly of the mild variety, and no appreciable cardiovascular and/or urinary frequency changes.

The frequency of these events in a 3-week placebo-controlled trial is shown in the following table:

| Event | Flexidose | Miltidine 12.5mg 
<table>
<thead>
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</thead>
<tbody>
<tr>
<td> </td>
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<td> </td>
</tr>
<tr>
<td>Total # of patients</td>
<td>22</td>
<td>17</td>
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<tr>
<td>Paroxysmal tachycardia</td>
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<td>4</td>
</tr>
<tr>
<td>Micturition disturbance</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Supine hypertension</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Flushing</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Includes hypotension, supine hypotension
2 Includes nonparoxysmal, supine hypertension
3 Includes dry mouth, 10% or less
4 Includes transient'MG 19357
5 Includes dysuria, nocturia, or polyuria

Less frequent adverse reactions were tachycardia, feeling of presyncope or syncope, chest pain, flushing, dizziness, flushing, syncope, nausea, vomiting, diarrhea, dry mouth, nervousness/irritability, and rash. Other adverse reactions that occurred rarely were visual field defect, dizziness, akathisia, tremor, paresthesia, rash, syncope, and/or visual disturbances. The most serious potential adverse reaction associated with miltidine hydrochloride therapy is supine hypertension. The feelings of presyncope, pruritus, paresthesia and rash are placebo reactions associated with the action of miltidine on the alpha-adrenergic receptors of the baroreflexes. Feelings of urinary urgency, retention and frequency are associated with the action of miltidine on the alpha-receptors of the bladder neck.

OVERDOSE: Symptoms of overdose could include hypotension, paresthesia (numbness), a sensation of coldness and urinary retention. There have been reported cases of overdosage with miltidine hydrochloride, both in young males. One patient ingested miltidine hydrochloride 350 mg. experienced syncope, palpitations, and a blood pressure of 200 mm. Hg. The patient recovered fully the next day without sequelae.

Gastric lavage was performed, and the patient recovered fully the next day without sequelae.

The single dosage that would be associated with symptoms of overdose or would be potentially lethal is unknown. The oral LD₅₀ is approximately 30 to 50 mg/kg in rats, 0.75 mg/kg in mice, and 125 to 150 mg/kg in dogs.

Deoxyguanylic acid is nontoxic.

Recommended general treatment, based on the pharmacology of the drug, includes induced emesis and administration of alpha-adrenergic blocking drugs (e.g., phentolamine).

DOSE AND ADMINISTRATION: The recommended dose of miltidine hydrochloride tablets is 10 mg. at bedtime. Dosing should take place during the daytime hours when the patient needs to be alert, pursuing the activities of daily life. A suggested dosing schedule of approximately 4-hour intervals is as follows: shortly before or upon arising in the morning, midday, and late afternoon (or later than 6 PM). Doses may be given in 2-hour intervals, if required, to control symptoms, but not more frequently.

Single doses as high as 20 mg have been given to patients, but severe and persistent systolic supine hypotension occurs at high dose (about 1/4 times the maximum human dose based on body surface area (mg/m²)). There are no adequate and well-controlled studies in pregnant women or in patients with impaired renal function.

The supine and standing blood pressure should be monitored regularly, and the administration of antihypertensive drugs should be reduced if systolic blood pressure increases excessively.

Because deoxyguanylic acid is excreted mainly in patients with abnormal renal function should be made; however, this has not been systematically studied. Therefore, it is recommended that treatment of these patients be initiated using 2.5 mg doses.

Dosage in children has not been adequately studied.

Blood levels of miltidine and deoxyguanylic acid were similar when comparing levels in patients 65 or older vs. younger than 65 and when comparing males vs. females, suggesting dose modifications for these groups are not necessary.

HOW SUPPLIED: Miltidine hydrochloride is supplied in 2.5 mg, 5 mg, and 10 mg tablets for oral administration.

Miltidine Hydrochloride Tablets: 2.5 mg are supplied as white, round, flat-faced, beveled edge, denominated "5″ over "60" on one side and blunted on the other side and are available in bottles of 100 and 500.

Miltidine Hydrochloride Tablets: 5 mg are supplied as red/white-orange, round, faceted, beveled edge, denominated "50″ over "60" on one side and blunted on the other side and are available in bottles of 100 and 500.

Miltidine Hydrochloride Tablets: 10 mg are supplied as blue-grey, round, flat-faced, beveled edge tablets, denominated "0″ over "100″ on one side and blunted on the other side and are available in bottles of 100 and 500.

Storage: Store at controlled room temperature. 20°-25°C (68°-77°F) with excursions permitted between 15°-30°C (59°-86°F) [see USP]. Preserve in tight light resistant containers as defined in the USP.

Manufactured by: Eon Labs, Inc., Laverton, NV 89105

Rx: 09/15

MPSURV09010300

MG A19357

Rev. 09/15
FINAL PRINTED LABELING

CONTAINER LABELS

**Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg**

**Usual Dosage:** See accompanying literature for complete prescribing information.

Store at controlled room temperature, 20°-25°C (68°-77°F) with excursions permitted between 15°-30°C (59°-86°F) [see USP].

Protect from light and moisture.

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP.

Issued 11/83

List No.

**NDC 0185-0149-05**

Each tablet contains:

Midodrine HCl ........... 10 mg

**Midodrine Hydrochloride Tablets 10 mg**

Rx only

500 Tablets

Manufactured by:
Eon Labs, Inc.
Laurelton, NY 11413

**Eon Labs**

**NDC 0185-0149-01**

Each tablet contains:

Midodrine HCl ........... 10 mg

**Midodrine Hydrochloride Tablets 10 mg**

Rx only

100 Tablets

Issued 11/83

List No.
APPLICATION NUMBER:
76-514/S-001; S-002; S-003

CSO LABELING REVIEW(S)
Supplement (DRAFT)

ANDA Number: 76-514
Date of Submission: September 11, 2003
Applicant's Name: Eon Labs
Established Name: Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

Labeling Deficiencies:
1. CONTAINER – bottles of 100 and 500 tablets
   Satisfactory in draft as of the September 11, 2003 submission.

2. INSERTS:
   Satisfactory in draft as of the September 11, 2003 submission.

RECOMMENDATIONS:

Request that the firm submit 12 copies of final printed labels and labeling.

FOR THE RECORD:
1. Note that the supplement is for the addition of a new strength (10mg tablets) to the application. It was submitted in conjunction with chemistry supplement SCD.

2. The labeling submitted by the firm was based on the most recently approved labeling for this drug product. This labeling was approved on October 29, 1996 for the RLD, NDA 19-815.

3. Patent/ Exclusivities:
   Patent Data – NDA 19-815

<table>
<thead>
<tr>
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<tr>
<td>None</td>
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<td>There are no unexpired patents for this product in the Orange Book Database.</td>
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   Exclusivity Data – NDA 19-815

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<th>Code</th>
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<td>ODE</td>
<td>Orphan Drug Exclusivity.</td>
<td>9/6/03</td>
<td>None</td>
</tr>
</tbody>
</table>

4. Storage/Dispensing Conditions:
   NDA: Store from 15 to 25°C (59 to 77°F).
   ANDA: Store at controlled room temperature, 20 to 25°C (68 to 77°F) with excursions permitted between 15 to 30°C (59-86°F). (See USP).
   NDA: Dispense in a well-closed container as defined in the USP.
   ANDA: This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP. With a child-resistant closure, (as required).

5. Product Line:
The innovator markets their product in three strengths (2.5 mg, 5 mg and 10 mg). They are packaged in bottles of 100 tablets.
The applicant proposes to market their product as 2.5 mg and 5 mg strength tablets in bottles of 100 and 500 and now as bottles of 100 and 500 for the 10 mg strength tablets.

6. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. (See pgs 172 in volume B. 4.1)

7. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components appearing on page 0090, Vol B. 1.1.
8. Container/Closure (See page 221 in Vol. B. 4.1)
   Containers: HDPE
   Closure: CRC closures for 100 count bottles and non-CRC for the 500 count bottles.

9. All manufacturing will be done by Eon Laboratories, Inc.

10. The drug products submitted for this ANDA are all scored as is the RLD.

Date of Review: 10/30/03    Date of Submission: 9/11/03
Primary Reviewer: Jim Barlow    Date: 10/30/03
Team Leader: John Grace    Date: 10/30/03

cc:
   ANDA: 76-514/S-002
   DUP/ DIVISION FILE
   HFD-613/JBarlow/JGrace (no cc)
   V:\FIRMS\AM\MYLANLTR\REV\76514s2nalr.doc
   Review

APPEARS THIS WAY
ON ORIGINAL
REVIEW OF PROFESSIONAL LABELING #1
Supplement (FPL)

ANDA # 76-514/S-002

NAME OF FIRM: Eon Laboratories, Inc.

NAME OF DRUG: Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

DATE OF SUBMISSION: January 16, 2004

LABELING COMMENTS:

1. CONTAINER – Bottles of 100 and 500 tablets
   Satisfactory in final print as of the January 16, 2004 submission.

2. INSERT:
   Satisfactory in final print as of the January 16, 2004 submission.

RECOMMENDATIONS:
Approve the supplement

FOR THE RECORD:

1. Review based on the labeling of ProAmatine® (NDA 19-815); Approved October 29, 1996

2. This labeling supplements (SL-002) was submitted in conjunction with
   chemistry supplement SCQ-001 for the addition of a new tablet strength. (10 mg tablet)

cc:
ANDA: 76-514/S-002
DUP/Division File
HFD-613/JBarlow/JGrace(no cc:)
V:\FIRMSAM\EON\ltrs&rev\76514s2apr.doc
Review

Endorsements:
HFD-613/JBarlow
HFD-613/JGrace
APPLICATION NUMBER:

76-514/S-001; S-002; S-003

CHEMISTRY REVIEW(S)
1. CHEMISTRY REVIEW NO. 1

2. ANDA # 76-514

3. NAME AND ADDRESS OF APPLICANT

Eon Labs, Inc.
Attn: Dietrich Bartel
4700 Eon Drive
Wilson, NC 27893

Tel: (252) 234-2212
Fax: (252) 234-2323

4. LEGAL BASIS FOR ANDA SUBMISSION:

505 (j), FFD & CA.

Basis for submission is ProAmatine, NDA 19-815. The applicant certified that there are no effective patents to NDA 19-815 for ProAmatine ® 10 mg tablets manufactured by Shire Pharmaceuticals. The applicant further stated that the ODE exclusivity has expired on September 06, 2003.

5. SUPPLEMENT(S): S-001 (Chemistry) and S-002 (labeling)

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME

Midodrine Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

S-001: Addition of 10 mg strength of Midodrine Hydrochloride Tablets to the already approved 2.5 mg and 5 mg Midodrine Hydrochloride Tablets

S-002: Associated Labeling revisions
9. AMENDMENTS AND OTHER DATES:
   September 11, 2003: Date of submission
   October 21, 2003: New correspondence (cGMP certification and Debarment Certification)

10. PHARMACOLOGICAL CATEGORY
    Midodrine HCl is a blood pressure medication used in orthostatic hypotension

11. Rx or OTC
    Rx

12. RELATED IND/ND A/DMF(s)
    N/A

13. DOSAGE FORM
    Tablets

14. POTENCY
    2.5 mg, 5 mg and 10 mg

15. CHEMICAL NAME AND STRUCTURE
    Midodrine hydrochloride:
    Acetamide, 2-amino-N-[2,5-dimethoxyphenyl]-2-hydroxyethyl]-monohydrochloride, (±)-.
    CAS #: [3092-17-9]
    Molecular Formula: C₁₂H₁₈N₂O₄HCl; Molecular Weight: 290.7
    Organoleptic Properties: Odorless, white, crystalline powder

    ![Chemical Structure](image)

    Solubility: Water – Soluble, Methanol – Sparingly soluble; pKa: 7.8 (0.3% aqueous solution); pH: 3.5 to 5.5 (5% aqueous solution), Melting Range: 200 to 203°C

15. RECORDS AND REPORTS: None

17. COMMENTS See below
17. COMMENTS See below

18. CONCLUSIONS AND RECOMMENDATIONS: Not Approvable

19. REVIEWER: DATE COMPLETED:
   Raj Bykadi, Ph.D. December 9, 2003

cc: ANDA 76-514/ S-001 and S-002
    Division File
    DUP File
    Field Copy

Endorsements:

HFD-623/R. Bykadi, Ph.D./ Chemistry Reviewer/Date
HFD-623/A. Mueller, Ph.D./ Team Leader/Date
HFD-617/K. Kiester, PM/Date

F/t by: gp

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Page(s) of trade

secret and /or

confidential

commercial

information
OFFICE OF GENERIC DRUGS  
Center for Drug Evaluation and Research  
Review of Supplement to an  
ABBREVIATED NEW DRUG APPLICATION  

Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 76-514

3. NAME AND ADDRESS OF APPLICANT

   Eon Labs, Inc.  
   Attn: Dietrich Bartel  
   4700 Eon Drive  
   Wilson, NC 27893

   Tel: (252) 234-2212  
   Fax: (252) 234-2323

4. LEGAL BASIS FOR ANDA SUBMISSION:  
   505 (j), FFD & CA.

   Basis for submission is ProAmatine, NDA 19-815. The applicant certified that there are no  
   effective patents to NDA 19-815 for ProAmatine® 10 mg tablets manufactured by Shire  
   Pharmaceuticals. The applicant further stated that the ODE exclusivity has expired on  
   September 06, 2003.

5. SUPPLEMENT(S):  S-001 (Chemistry) and S-002 (labeling)

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME  
   Midodrine Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

   S-001: Addition of 10 mg strength of the drug product to the currently approved ANDA for  
   Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg.

   S-002: Associated labeling revisions.

9. AMENDMENTS AND OTHER DATES:
September 11, 2003: Date of submission
October 21, 2003: New correspondence (cGMP certification and Debarment Certification)

January 16, 2004: Minor Amendment (this review)

10. PHARMACOLOGICAL CATEGORY
Midodrine HCl is a blood pressure medication used in orthostatic hypotension

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
N/A

13. DOSAGE FORM
Tablets

14. POTENCY
2.5 mg, 5 mg and 10 mg

15. CHEMICAL NAME AND STRUCTURE
Midodrine hydrochloride:
Acetamide, 2-amino-N-[2,5-dimethoxyphenyl]-2-hydroxyethyl]-monohydrochloride, (\(\forall\))-.
CAS #: [3092-17-9]
Molecular Formula: C_{12}H_{18}N_{2}O_{4}HCl; Molecular Weight: 290.7
Organoleptic Properties: Odorless, white, crystalline powder

[Chemical structure diagram]

Solubility: Water – Soluble, Methanol – Sparingly soluble; pKa: 7.8 (0.3% aqueous solution); pH: 3.5 to 5.5 (5% aqueous solution), Melting Range: 200 to 203°C

15. RECORDS AND REPORTS: None

17. COMMENTS DBE review completed on 6-22-04, hence, could not be approved earlier.

18. CONCLUSIONS AND RECOMMENDATIONS: Approvable
19. **REVIEWER:** Raj Bykadi, Ph.D.  
**DATE COMPLETED:** January 29, 2004

cc: ANDA 76-514/ S-001 and S-002  
Division File  
DUP File  
Field Copy

Endorsements:

HFD-623/R. Bykadi, Ph.D./ Chemistry Reviewer/6/29/04  
HFD-623/A. Mueller, Ph.D./ Team Leader/6/29/04  
HFD-617/S. Eng, PM/C.Kiester for/6/29/04

F/t by: ard/6/29/04

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Redacted

Page(s) of trade

secret and/or

confidential

commercial

information
REVIEW#: No 1

ANDA: See attached list

NAME AND ADDRESS OF APPLICANT:
Eon Labs, Inc.
4700 Eon Drive
Wilson, NC 27893

PURPOSE OF AMENDMENT/SUPPLEMENT
SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED IN 30 DAYS:
To add the following facility as

DATE(S) OF SUBMISSION(S)
December 22, 2004

NONPROPRIETARY NAME: See Attachment

DOSAGE FORM: See attachment
POTENCY: See attachment

Rx or OTC
Rx Only

DOCUMENTATION
In support of the proposed the firm submitted the following:
- A commitment to use the same SOP's and test methods employed in the approved application.
- Certification that all post approval commitments relating to the test method(s) have been fulfilled.
- Certification that the has the capability to perform the intended testing.
- Certification that the is in conformance with cGMP's.
- A full description of the testing to be performed by the

ESTABLISHMENT INSPECTION: Satisfactory (J. D’Ambrogio, 3/16/05 – all supplements)

REMARKS AND CONCLUSION: All supplements approvable.

PROJECT MANAGER:
Simon Eng, PharmD

DATE COMPLETED:
21-MAR-2005
Attachment:

76-402/S001 Benazepril Hydrochloride Tablets, 5mg, 10 mg, 20 mg, and 40 mg
76-483/S001 Fosinopril Sodium Tablets, 10 mg, 20 mg, and 40 mg
76-514/S003 Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg, and 10 mg
76-631/S001 Benazepril Hydrochloride and Hydrochlorothiazide Tablets, 5 mg/6.25 mg, 10 mg/12.5 mg, 20 mg/12.5 mg, and 20 mg/25 mg
APPLICATION NUMBER:

76-514/S-001; S-002; S-003

BIOEQUIVALENCE REVIEW(S)
DIVISION OF BIOEQUIVALENCE REVIEW

<table>
<thead>
<tr>
<th>ANDA No.</th>
<th>76-514 / SCQ-001</th>
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<tbody>
<tr>
<td>Drug Product Name</td>
<td>Midodrine HCl tablet</td>
</tr>
<tr>
<td>Strength</td>
<td>10 mg</td>
</tr>
<tr>
<td>Applicant Name</td>
<td>Eon Labs</td>
</tr>
<tr>
<td>Address</td>
<td>Wilson, North Carolina</td>
</tr>
<tr>
<td>Submission Date(s)</td>
<td>15 Apr 2004</td>
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<tr>
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<tr>
<td>Reviewer</td>
<td>J. Lee</td>
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<td>First Generic</td>
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<tr>
<td>File Location</td>
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I. Executive Summary

This submission is an amendment to a supplement to the sponsor's approved application for the 2.5 and 5 mg strengths of midodrine HCl [app. 11 Sept 03] to include a 10 mg strength tablet. In a 11 Sept 03 submission, the sponsor had submitted comparative dissolution and formulation data in requesting a waiver of in-vivo requirements. The sponsor had used the wrong method in their dissolution testing. The sponsor was requested to repeat the dissolution testing using DBE's interim method. This submission supplies the comparative dissolution testing using DBE's interim method and is acceptable. This supplement, SCQ-001, is acceptable.

As stated in the Executive Summary, the sponsor is supplementing their approved application on their 2.5 and 5 mg midodrine HCl tablets with a 10 mg strength tablet. Acceptable fasted and fed bio-studies were conducted on the 5 mg midodrine HCl tablet. [sub 26 Sept 02; HNguyen] and a waiver was granted for the 2.5 mg tablet.

Comparative dissolution data for the 10 mg tablet vs ProAmatine® was submitted in the 11 Sept 03 supplement using the wrong method. In this submission, the sponsor has submitted comparative dissolution testing using the DBE interim method as requested. The dissolution summary is attached.

Additionally, the sponsor has provided analytical results on 3 month accelerated and RT stability on lot #RDW00211.

Formulation data between the sponsor's 2.5, 5 and 10 mg tablets are attached.

Comment:

1. The comparative dissolution testing using the DBE interim method is acceptable. The firm already uses the same method for its approved midodrine 2.5 and 5 mg tablets.
2. The stability data indicate that the test product can easily meet the dissolution specification (NLT — in 15 min) after 3 months under challenge conditions.

Recommendation:

1. The dissolution testing conducted by Eon Labs on its midodrine HCl 10 mg tablet, batch #RDW00211, is acceptable.

2. The dissolution testing should be incorporated into the firm's manufacturing and controls and stability program. The dissolution testing should be conducted in ————. The test product should meet the following specification:

   Not less than ——of the labeled amount of the drug in the tablet is dissolved in 15 minutes

3. The Division of Bioequivalence finds that the information submitted by the sponsor demonstrates that midodrine HCl 10 mg tablet falls under 21 CFR 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Eon's midodrine HCl 10 mg tablet is deemed bioequivalent to ProAmatine® 10 mg tablet manufactured by Shire US.

4. This supplement, SCQ-001, is acceptable.

C. Lee 6/22/04
J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED GJPSINGH
FT INITIALED GJPSINGH

Concur: [Signature] Date: 6/22/04

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

JLee/jl/06-15-04

cc: ANDA #76-514 (original, duplicate), HFD-655 (Lee), Drug File, Division File
IN - VITRO DISSOLUTION TESTING

Method Ref.: DBE interim  
USP 27 Apparatus: II  
RPM: 50  
No. Units Tested: 12  
Reference Drug: ProAmatine® 10 mg tablet  
Medium: 0.1N HCl  
Volume: 900 mL  
Tolerance: Q=—— in 15 min.  
Assay Method: ———

<table>
<thead>
<tr>
<th>Sampling Times (Minutes)</th>
<th>Test Product:</th>
<th>Ref Product:</th>
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<tr>
<td></td>
<td>Lot No.:</td>
<td>Lot No.:</td>
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<tr>
<td></td>
<td>RDW00211</td>
<td>214911 (exp. 12/03)</td>
</tr>
<tr>
<td></td>
<td>Strength:</td>
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<td></td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Mean (%)</td>
<td>Range</td>
<td>% CV</td>
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<tr>
<td>5</td>
<td>98.5</td>
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<td>10</td>
<td>99.6</td>
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</tr>
<tr>
<td>101.8</td>
<td>———</td>
<td>2.7</td>
</tr>
</tbody>
</table>

The sponsor states that the dissolution testing was conducted on 6/16/03. Since midodrine HCl is highly soluble, the dissolution profiles reached asymptote very rapidly so that a 30 min time point was not used as previously done.
## Midodrine HCl Dissolution Stability Data

<table>
<thead>
<tr>
<th>Tablets</th>
<th>3 Months, Accelerated</th>
<th>3 Months, Room Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tablet Count per Bottle 100</td>
<td>Tablet Count per Bottle 500</td>
</tr>
<tr>
<td>1</td>
<td></td>
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<tr>
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<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average, %</td>
<td>100.5</td>
<td>96.8</td>
</tr>
<tr>
<td>Range, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSD, %</td>
<td>2.1</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Reference: TJM 0608-052, 053 and DLC 0608-046.
### COMPARISON OF COMPOSITION FOR MIDODRINE HYDROCHLORIDE TABLETS, 2.5 MG, 5 MG AND 10 MG

<table>
<thead>
<tr>
<th>Component</th>
<th>Midodrine Hydrochloride Tablets, 2.5 mg</th>
<th>Midodrine Hydrochloride Tablets, 5 mg</th>
<th>Midodrine Hydrochloride Tablets, 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amount per tablet (mg)</td>
<td>% w/w</td>
<td>Amount per tablet (mg)</td>
</tr>
<tr>
<td>Midodrine Hydrochloride</td>
<td>2.5</td>
<td>1.92</td>
<td>5.0</td>
</tr>
<tr>
<td>Pregelatinized Starch 1500, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FD&amp;C Yellow # 6 Aluminum Lake</td>
<td></td>
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<tr>
<td>FD&amp;C Red # 40 Aluminum Lake</td>
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<tr>
<td>Colloidal Silicon Dioxide, NF</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate, NF</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total Tablet Weight</td>
<td>130.0</td>
<td>100.0</td>
<td>130.0</td>
</tr>
</tbody>
</table>

midodrine HCl 2.5 mg - white, round, flat-faced, beveled edge tablets, debossed "E" above "40" on one side and bisected on the other side

midodrine HCl 5 mg - reddish orange, round, flat-faced, beveled edge tablets, debossed "E" above "43" on one side and bisected on the other side

midodrine HCl 10 mg - blue-grey, round, flat-faced, beveled edge tablets, debossed "E" above "149" on one side and bisected on the other side

ProAmatine® 2.5 mg - white, round, and biplanar, with a beveled edge, and is scored on one side with "RPC" above and "2.5" below the score, and "003" on the other side

ProAmatine® 5 mg - orange, round, and biplanar, with a beveled edge, and is scored on one side with "RPC" above and "5" below the score, and "004" on the other side

ProAmatine® 10 mg - blue, round, and biplanar, with a beveled edge, and is scored on one side with "RPC" above and "10" below the score, and "007" on the other side
BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-514\SCQ-001  APPLICANT: Eon Labs

DRUG PRODUCT: Midodrine HCl 10 mg tablet

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

We acknowledge the incorporation of DBB's dissolution method and specification as follows:

The dissolution testing should be conducted in _______________________.

The test product should meet the following specifications:

Not less than —(Q) of the labeled amount of the drug in the tablet is dissolved in 15 minutes.

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

Sincerely yours,

[Signature]

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

APPEARS THIS WAY ON ORIGINAL
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-514/SCQ-001  SPONSOR: Eon Labs

DRUG AND DOSAGE FORM: Midodrine HCl tablet

STRENGTH(S): 10 mg

TYPES OF STUDIES: N/A

STUDY SUMMARY: N/A

DISSOLUTION: OK per DBE interim. Waiver granted per 21 CFR 320.22 (d)(2).

DSI INSPECTION STATUS

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<th>Inspection needed:</th>
<th>Inspection status:</th>
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<tbody>
<tr>
<td>YES / NO</td>
<td>Inspection requested: (date)</td>
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<tr>
<td>First Generic</td>
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<tr>
<td>No N/A</td>
<td>Inspection completed: (date)</td>
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<tr>
<td>New facility</td>
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<tr>
<td>For cause</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

PRIMARY REVIEWER: J. Lee  BRANCH: II

INITIAL: E-J.  DATE: 6/22/04

TEAM LEADER: GJP Singh  BRANCH: II

INITIAL: [Signature]  DATE: 6/22-04

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

INITIAL: [Signature]  DATE: 6/22/04
7. DISSOLUTION WAIVER (DIW)  
Strengths: 10 mg  
Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments:  
Waiver for the 10 mg tablet is granted per 21 CFR 320.22 (d)(2).
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-514/SCQ-001  SPONSOR: Eon Labs

DRUG AND DOSAGE FORM: Midodrine HCl tablet

STRENGTH(S): 10 mg

TYPES OF STUDIES: N/A

STUDY SUMMARY: N/A

DISSOLUTION: OK per DBE interim. Waiver granted per 21 CFR 320.22 (d)(2).

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PRIMARY REVIEWER: J. Lee  BRANCH: II

INITIAL: C.L.  DATE: 6/22/04

TEAM LEADER: GJP Singh  BRANCH: II

INITIAL:  DATE: 6/22/04

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

INITIAL:  DATE: 6/22/04
# COMPARISON OF COMPOSITION FOR MIDODRINE HYDROCHLORIDE TABLETS, 2.5 MG, 5 MG AND 10 MG

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<td><strong>Total Tablet Weight</strong></td>
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<td><strong>100.0</strong></td>
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DIVISION OF BIOEQUIVALENCE REVIEW

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<tr>
<td>Strength</td>
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<tr>
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<td>Eon Labs</td>
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</tr>
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<td>11 Sept 2003</td>
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<tr>
<td>Reviewer</td>
<td>J. Lee</td>
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I. Executive Summary

This submission is a supplement to the sponsor's approved application for the 2.5 and 5 mg strengths of midodrine HCl [app. 11 Sept 03] to include a 10 mg strength tablet. The sponsor has submitted comparative dissolution and formulation data in requesting a waiver of in-vivo requirements. The sponsor has used the wrong method in their dissolution testing. A waiver for the 10 mg drug product under 21 CFR 320.22 (d)(2) is denied. The sponsor must repeat the dissolution testing using DBE's interim method. This supplement is deficient.

As stated in the Executive Summary, the sponsor is supplementing their approved application on their 2.5 and 5 mg midodrine HCl tablets with a 10 mg strength tablet. Acceptable fasted and fed bio-studies were conducted on the 5 mg midodrine HCl tablet [sub 26 Sept 02; HNguyen] and a waiver was granted for the 2.5 mg tablet.

The 5 mg ProAmatine® tablet is the RLD. Per control doc #01-266, Lachman Consultants submitted a suitability petition (#01P-0081) for midodrine HCl 10 mg tablet. This petition for a change in strength (from 2.5 and 5 mg to include the 10 mg tablet) was approved on 8 May 01. On 29 Aug 01, Mary Fanning, M.D. of OGD, concluded that the 5 mg dose would be appropriate for a single dose BE study in normals due to safety reasons (The e-mail is attached).

ANDA #76-577, Mylan's midodrine HCl tablet application was approved (10 Sept 03) based on fasted and fed bio-studies on the 5 mg tablet, with waivers granted for the 2.5 and 10 mg tablets.

The firm had conducted dissolution testing with the DBE interim method for its 2.5 and 5 mg tablets in the earlier submission dated 9/26/2002. It is not clear why the firm changed the dissolution medium in this submission. Comparative dissolution data for the 10 mg tablet vs ProAmatine® was submitted.
Formulation data between the sponsor's 2.5, 5 and 10 mg tablets are attached.

Comment:

1. The comparative dissolution testing for the 10 mg tablets were conducted using the sponsor's method:

   specification: NL ≤ in 30 min

   The sponsor should repeat the dissolution testing using DBE's interim method:

   sampling times: 5, 10, 15, 20 and 30 min

Recommendation:

1. The waiver request for the sponsor's 10 mg midodrine HCl tablet under 21 CFR 320.22 (d)(2) is denied to comment #1.

   The sponsor should address comment #1.

J. Lee 3/30/04
Division of Bioequivalence
Review Branch II

RD INITIALED SNURKAR
FT INITIALED SNURKAR Mohanwal 3/30/04

Concur: Barbara Sant Date: 3/31/04
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/03-22-04

cc: ANDA #76-514 (original, duplicate), HFD-655 (Lee), Drug File, Division File
## IN - VITRO DISSOLUTION TESTING

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<td>ProAmatine® 10 mg tablet</td>
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**APPEARS THIS WAY ON ORIGINAL**
### COMPARISON OF COMPOSITION FOR MIDODRINE HYDROCHLORIDE TABLETS, 2.5 MG, 5 MG AND 10 MG

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<th>Component</th>
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<th>Midodrine Hydrochloride Tablets, 10 mg</th>
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<td>Amount per tablet (mg)</td>
<td>% w/w</td>
<td>Amount per tablet (mg)</td>
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midodrine HCl 2.5 mg - white, round, flat-faced, beveled edge tablets, debossed "E" above "40" on one side and bisected on the other side
midodrine HCl 5 mg - reddish orange, round, flat-faced, beveled edge tablets, debossed "E" above "43" on one side and bisected on the other side
midodrine HCl 10 mg - blue-grey, round, flat-faced, beveled edge tablets, debossed "E" above "149" on one side and bisected on the other side

ProAmatine® 2.5 mg - white, round, and biplanar, with a beveled edge, and is scored on one side with "RPC" above and "2.5" below the score, and "003" on the other side
ProAmatine® 5 mg - orange, round, and biplanar, with a beveled edge, and is scored on one side with "RPC" above and "5" below the score, and "004" on the other side
ProAmatine® 10 mg - blue, round, and biplanar, with a beveled edge, and is scored on one side with "RPC" above and "10" below the score, and "007" on the other side
Attachment

-----Original Message-----
From: Fanning, Mary
Sent: Wednesday, August 29, 2001 12:18 PM
To: Buehler, Gary J
Cc: Sanchez, Aida L; Chuang, Lin Whei L; Huang, Yih Chain; Conner, Dale P; Parise, Cecelia M
Subject: CD #01-195

Gary,

I spoke to Doug Throckmorton in Cardiorenal about safety issues that might arise in a PK study of Midodrine in normal volunteers. We agreed that the reference listed drug, the 5 mg dose would be safe in a single dose study. If a multiple dose study was required the firm should be advised that they will need to outline a careful plan for observation, blood pressure monitoring and withdrawal of patients if the blood pressure should rise above a pre-determined level. We would certainly be amenable to reviewing a proposed protocol from a safety perspective.

Mary
BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-514  APPLICANT: Eon Labs

DRUG PRODUCT: Midodrine HCl 10 mg tablet

The Division of Bioequivalence has completed its review of your submission(s) [supplement-S001] acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please redo the dissolution testing on the 10 mg tablet using the Division of Bioequivalence's interim method as follows:

   sampling times: 5, 10, 15, 20 and 30 min

Since the 10 mg ProAmatine® tablet in this supplement has expired, please use a fresh lot of the reference drug.

Sincerely yours,

[Signature]

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
BIOEQUIVALENCE - DEFICIENCIES      Submission Date: 11 Sept 03

7. DISSOLUTION WAIVER (DIW)      Strengths: 10 mg

Outcome: UN

WinBio Comments
Waiver request denied due to unacceptable dissolution testing.
APPLICATION NUMBER:

76-514/S-001; S-002; S-003

ADMINISTRATIVE DOCUMENTS
ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application: ANDA 76514/003
Stamp: 29-DEC-2004
Regulatory Due:

Applicant: EON LABS LORIDE
4700 EON DR
WILSON, NC 27893

Priority: Org Code: 600

Action Goal:
District Goal: 29-MAY-2005
Brand Name:
Estab. Name: MIDODRINE HYDROCH

Generic Name:
Dosage Form: (TABLET)
Strength: 2.5 MG 5 MG AND 1

Application Comment:
ESTING LAB

SPONSOR ALSO USES EON LABS CFN 2431929 TO DO TESTING ON
MATERIAL/COMPONENTS, IN-PROCESS, FINISHED PRODUCT, AND O
STABILITY TESTING. THANKS. (SIMON 1/11/05) (on 11-JAN-20
ENG (HFD-615) 301-827-5846)

FDA Contacts: S. ENG (HFD-615) 301-827-5846 , Project
Manager
A. MUELLER (HFD-623) 301-827-5848 , Team Lea
der

Overall Recommendation: ACCEPTABLE on 16-MAR-2005 by J. D AMBROGIO (HFD-322)
301-827-
9049

Establishment: CFN 2431929 FEI 2431929
EON LABORATORIES MANUFACTURING INC
227-15 NORTH CONDUIT AVE
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|               |            |      |            | DISTRICT RECOMMENDATION     |

APPEARS THIS WAY ON ORIGINAL
Patent and Exclusivity Search Results from query on 019815 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

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Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

Appears this way on original
Patent and Exclusivity Search Results from query on 019815 002.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

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Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

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APPEARS THIS WAY ON ORIGINAL
Patent and Exclusivity Search Results from query on 019815 003.

**Patent Data**

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

**Exclusivity Data**

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Thank you for searching the Electronic Orange Book

**Patent and Exclusivity Terms**

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APPEARS THIS WAY
ON ORIGINAL
Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

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View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Orange Book Data Updated Through May, 2004
Orange Book Patent Data Only - Daily
Patent Data Last Updated: June 29, 2004

APPEARS THIS WAY ON ORIGINAL
Application Number Search Results from "OB_Rx" table for query on "19815."

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Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Orange Book Data Updated Through May, 2004
Orange Book Patent Data Only - Daily
Patent Data Last Updated: June 29, 2004
Search results from the "OB_Rx" table for query on "019815."

Active Ingredient: MIDODRINE HYDROCHLORIDE
Dosage Form;Route: TABLET; ORAL
Proprietary Name: PROAMATINE
Applicant: SHIRE PHARM
Strength: 2.5MG
Application Number: 019815
Product Number: 001
Approval Date: Sep 6, 1996
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code: AB
Patent and Exclusivity Info for this product: View

Active Ingredient: MIDODRINE HYDROCHLORIDE
Dosage Form;Route: TABLET; ORAL
Proprietary Name: PROAMATINE
Applicant: SHIRE PHARM
Strength: 5MG
Application Number: 019815
Product Number: 002
Approval Date: Sep 6, 1996
Reference Listed Drug: Yes
RX/OTC/DISCN: RX
TE Code: AB
Patent and Exclusivity Info for this product: View

Active Ingredient: MIDODRINE HYDROCHLORIDE
Dosage Form;Route: TABLET; ORAL
Proprietary Name: PROAMATINE
Applicant: SHIRE PHARM
Strength: 10MG
Application Number: 019815
Product Number: 003
Approval Date: Mar 20, 2002
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code: AB
Patent and Exclusivity Info for this product: View

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FDA/Center for Drug Evaluation and Research
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

APPLICANT INFORMATION

NAME OF APPLICANT Eon Labs, Inc.

DATE OF SUBMISSION December 22, 2004

TELEPHONE NO. (Include Area Code) (252) 234-2222

FACSIMILE (FAX) Number (Include Area Code) (252) 234-2323

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

4700 Eon Drive
Wilson, NC 27893
CFN 1062246

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 76-514

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Midodrine Hydrochloride Tablets

PROPRIETARY NAME (trade name) IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any)

DOSAGE FORM: Tablet

STRENGTHS: 2.5 mg, 5 mg and 10 mg

ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: Orthostatic Hypotension

APPLICATION INFORMATION

APPLICATION TYPE

☐ NEW DRUG APPLICATION (21 CFR 314.50) ☑ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Proamatine®

Holder of Approved Application Shire Pharmaceuticals

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☑ CBE-30 ☐ PRIOR APPROVAL (PA)

REASON FOR SUBMISSION Supplement CBE-30

PROPOSED MARKETING STATUS (check one) ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED One

THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attachment

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, IDEs, BMFs, and DMFs referenced in the current application)

RECEIVED

FORM FDA 356h (9/02) DEC 2 9 2004 PAGE 1

OGD / CDER
This application contains the following items:  (Check all that apply)

☐ 1. Index
☐ 2. Labeling (check one)  ☐ Draft Labeling  ☐ Final Printed Labeling
☐ 3. Summary (21 CFR 314.50(c))
☒ 4. Chemistry section
  A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d)(1), 21 CFR 601.2)
  B. Samples (21 CFR 314.50(e)(1), 21 CFR 601.2(a)) (Submit only upon FDA’s request)
  C. Methods validation package (e.g. 21 CFR 314.50(e)(2)(i), 21 CFR 601.2)
☐ 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50(d)(2), 21 CFR 601.2)
☐ 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50(d)(3), 21 CFR 601.2)
☐ 7. Clinical Microbiology (e.g. 21 CFR 314.50(d)(4))
☐ 8. Clinical data section (e.g. 21 CFR 314.50(d)(5), 21 CFR 601.2)
☐ 9. Safety update report (e.g. 21 CFR 314.50(d)(5)(vi)(b), 21 CFR 601.2)
☐ 10. Statistical section (e.g. 21 CFR 314.50(d)(6), 21 CFR 601.2)
☐ 11. Case report tabulations (e.g. 21 CFR 314.50(i)(1), 21 CFR 601.2)
☐ 12. Case report forms (e.g. 21 CFR 314.50(i)(2), 21 CFR 601.2)
☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
☐ 15. Establishment description (21 CFR Part 600, if applicable)
☐ 16. Debarment certification (FD&C Act 306(k)(1))
☒ 17. Field copy certification (21 CFR 314.50(l)(3))
☐ 18. User Fee Cover Sheet (Form FDA 3397)
☐ 19. Financial Information (21 CFR Part 54)
☐ 20. OTHER (Specify)

CERTIFICATION
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
3. Labeling regulations in 21 CFR Parts 201, 206, 610, 616, 660, and/or 809.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.91.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

[Signature]

ADDRESS (Street, City, State, and ZIP Code)
4700 Eon Drive, Wilson, NC 27893

TELEPHONE NUMBER
(252) 234-2224

PRESENTED TO FDA:

Steven W. Brown, R.Ph.
Director, Regulatory Affairs

DATE
22 December 2004

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER, HFM-96
1401 Rockville Pike
Rockville, MD 20852

Food and Drug Administration
CDER, HFO-94
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (9/02) PAGE 2
APPLICATION NUMBER:

76-514/S-001; S-002; S-003

CORRESPONDENCE
December 22, 2004

Mr. Gary J. Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

SUPPLEMENT - CHANGES BEING EFFECTED IN 30 DAYS

Re: ANDA 76-514
Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg; ANDA 76-514, that was approved on September 11, 2003 for 2.5 mg and 5 mg and July 2, 2004 for 10 mg.

Pursuant to Section 506A of the Federal Food, Drug, and Cosmetic Act, and in accordance with the "Guidance for Industry - Changes to an Approved NDA or ANDA", we are submitting a supplemental application for Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg. The supplement provides for . This change is classified as a Moderate Change according to Section VI.C.1.d. of the guidance which requires a CBE-30 supplement.

The name and place of business of the is:

CFN

associated with the drug product (that is enumerated on the enclosed list), including:

RECEIVED
DEC 29 2004
OGD / CDER
In support of this request, enclosed are cGMP and GDEA certifications, along with a list of tests that may be performed by the site. The change in the site meets the conditions specified in Section VI.C.1.d of the Guidance, in that: 1) the approved test procedures will be used, 2) all post-approval commitments made by Eon Labs relating to the test methods have been met, and 3) the new testing facility has the capability to perform the intended tests.

In addition, it is our intention to utilize the analytical testing facilities and capabilities of our corporate headquarters located at:

Eon Labs, Inc.          CFN 2431929
227 N. Conduit Avenue
Laurelton, NY 11413
P: (718) 276-8607
F: (718) 276-8635

Eon Labs, Inc., Laurelton, NY, may perform any, or all, of the following testing associated with the drug product: raw material/components, in-process, finished product, and/or stability testing.

As provided for in the Industry Guidance document, it is our intention to implement these changes 30 days from the date of this supplement.

We certify that a true copy of this Supplemental New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg, has been sent to the Food and Drug Administration, Atlanta District Office, 60 Eighth St. NE, Atlanta, Georgia 30309.

Please advise us at (252) 234-2224, between 9:00 a.m. and 5:00 p.m., if you require any additional information.

Sincerely,

Eon Labs, Inc.

[Signature]

Steven W. Brown, R.Ph.
Director, Regulatory Affairs
December 22, 2004

Ms. Mary H. Woleske
District Director
Atlanta District
Food and Drug Administration
60 Eighth Street NE
Atlanta, GA 30309

SUPPLEMENT - CHANGES BEING EFFECTED IN 30 DAYS

Re: ANDA 76-514
Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

Dear Ms. Woleske:

Enclosed is the field copy of our Supplemental New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg. It contains all chemistry, manufacturing, and controls information related to the.

We certify that this is a true copy of the technical sections contained in the archival and review copies of our Supplemental New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg, submitted to the Office of Generic Drugs.

Please advise us at (252) 234-2224, between 9:00 a.m. and 5:00 p.m., if you require any additional information.

Sincerely,

Eon Labs, Inc.

Steven W. Brown, R.Ph.
Director, Regulatory Affairs
April 15, 2004

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: Bioequivalency Amendment — ANDA 76-514
     Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

Dear Mr. Buehler:

In accordance with 21 CFR 314.96, this submission constitutes a bioequivalency amendment to
ANDA 76-514. It is being filed in response to a fax letter from Dr. Dale P. Connor of the
Division of Bioequivalence, OGD, to Eon Labs, Inc. on April 13, 2004 and contains our response
to the deficiencies outlined in that letter.

Since this amendment contains CMC data, we are filing this amendment to the Field Office. We
hereby certify that the field copy of this submission being filed to the FDA Atlanta District
Office, 60 Eight St. NE, Atlanta, GA 30309 is identical to the archive and review copies filed to
the OGD, FDA, Rockville, MD.

If there are any questions concerning this amendment, please contact either Mr. Steven W.
Brown, R.Ph., Director, Regulatory Affairs, by telephone at (252) 234-2224, or Mr. Dietrich
Bartel, B.S., Assistant Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

[Signature]
Dietrich Bartel, B.S.
Assistant Director, Regulatory Affairs,
Eon Labs, Inc.

[Stamp]
RECEIVED
APR 16 2004
OGD/CDER
January 16, 2004

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: MINOR AMENDMENT – ANDA 76-514/S-001 and S-002
Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

Dear Mr. Buehler:

In accordance with 21 CFR 314.120, this submission constitutes an amendment to the Supplement filed under Section 505 (j) of the Federal Food, Drug and Cosmetic Act to ANDA 76-514 on September 11, 2003. It is being filed in response to a letter from Dr. Rashmikant Patel of the Division of Chemistry I, OGD, to Eon Labs, Inc. on December 15, 2003. This submission contains our response to the deficiencies outlined in the letter.

We certify that an identical copy of this submission (except for labeling) is also being filed to the FDA Atlanta District Office, 60 Eight St. NE, Atlanta, GA 30309.

If there are any questions concerning this amendment, please contact either Mr. Steven W. Brown, R.Ph., Director, Regulatory Affairs, by telephone at (252) 234-2224, or Mr. Dietrich Bartel, B.S., Assistant Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

Dietrich Bartel
Assistant Director, Regulatory Affairs,
Eon Labs, Inc.

Mr. G. Buehler January 16, 2004
Eon Labs, Inc.
Attn: Dietrich Bartel
4700 Eon Drive
Wilson, NC 27893

Dear Sir:

This is in reference to your supplemental new drug application dated September 11, 2003 submitted pursuant to 505 (j) of the Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg.

The supplemental application, submitted as a “Prior Approval Supplement” provides for the following changes:

S-001: Additional 10 mg strength of Midodrine Hydrochloride Tablets to the already approved 2.5 mg and 5 mg Midodrine Hydrochloride Tablets

S-002: Associated Labeling revisions

The supplemental application is deficient and, therefore, not approvable under the section 505 of the act for the following reasons:

Deficiencies:

1. On page no. 58, you listed as a component in the composition statement, whereas, the package insert on page #48 lists FD&C Red #40 as a component for the 5 mg tablets. Please clarify.

2. We refer to pages 127 and 159 of your blank and executed manufacturing records. We recommend that you include a friability test as an in-process control for the tablets.

3. Please provide justification for the hardness specifications for Midodrine HCl tablets by providing the dissolution, thickness and friability data at the upper and lower end of the proposed hardness limits.

Comments:

1. The Division of Labeling requests that you submit 12 copies of final printed labels and labeling.
2. The data for the 10 mg dosage form has been submitted to the Division of Bioequivalence for a review. Any deficiencies will be communicated under a separate cover to you.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this supplemental application. Your amendment should respond to all the deficiencies listed. Partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered as a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

[Signature]

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Appears this way on original
October 21, 2003

Mr. Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration, HFD-600
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

RE: ANDA 76-514
Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated September 26, 2002, submitted pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, and in accordance with the provisions of the regulations 21 CFR§314.94, for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg; ANDA 76-514.

Reference is also made to the telephone call of September 11, 2003, requesting that we supply certain items to complete the Supplemental Abbreviated New Drug Application for an additional strength of the drug product, Midodrine Hydrochloride Tablets, 10 mg.

Therefore, enclosed are a Debarrament Certification, Sample Statement, and cGMP Certification.

We certify that a true copy of this New Correspondence to our Supplemental Abbreviated New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg, has been sent to the Food and Drug Administration, Atlanta District Office, 60 Eighth Street NE, Atlanta, Georgia 30309.

Please advise us if you require any additional information.

Sincerely,

Eon Labs, Inc.

Steven W. Brown, R.Ph.
Director, Regulatory Affairs

Eon Labs 4700 Eon Drive, Wilson, NC 27893
Telephone 252 234-2222  Fax 252 234-2600  www.eonlabs.com
September 11, 2003

Gary J. Buehler
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: Supplemental ANDA # 76-514
Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

Dear Mr. Buehler:

Pursuant to the provisions of 21 CFR 314.70 (b)(2)(v), we are hereby submitting a supplement to add the 10 mg strength of the drug product to the currently approved Abbreviated New Drug Application (ANDA #76-514) for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg. An ANDA qualification batch of the 10 mg strength, Lot #RDW00211, has been manufactured to provide supporting data. This supplement consists of the following information, divided by sections:

Patent and exclusivity information, labeling, dissolution profiles, components and composition statements, raw material Certificates of Analysis and control data, manufacturing and packaging records including blank and executed Batch Records, container/closure information, finished product controls, and stability data.

A full table of contents is provided.

Please note that all good manufacturing practices, procedures, and methods that were previously submitted and approved in the original ANDA for the 2.5 mg and 5 mg strengths will also apply to the manufacture, testing, release, packaging, labeling, storage and distribution of the 10 mg strength of the drug product.

We certify that a true copy of the chemistry, manufacturing and controls data of this supplement has been submitted to the FDA District Field Office, 60 Eight St., Atlanta, Georgia. Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Office.

Mr. G. J. Buehler    September 11, 2003    Page 1 of 2
If there are any comments or questions about this application, please contact me at (252) 2234-2212, or via facsimile at (252) 234-2323.

Sincerely,

Eon Labs, Inc.

Dietrich Bartel
Assistant Director, Regulatory Affairs