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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

APPROVAL LETTERS

ANDA 76-514/S-001 and S-002

JUL 2 2004

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 oursuant 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.

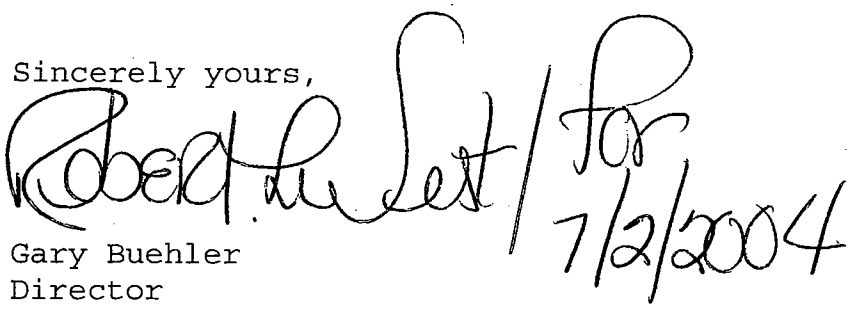
Promotional materials for the new strength may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we 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,



7/2/2004

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

76-514
S-003

ANDA (See attachment)

MAR 24 2005

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 Schwartz for 3/23/05

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 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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

FINAL PRINTED LABELING

Rev. 09/03

0040

Midodrine Hydrochloride Tablets Rx only

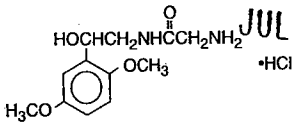
Midodrine Hydrochloride Tablets

Rx only

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 in the treatment of symptomatic orthostatic hypotension is based primarily on a change in a surrogate marker of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of midodrine hydrochloride, principally improved ability to carry out activities of daily living, have not been verified.

DESCRIPTION

Midodrine hydrochloride is a vasopressor/antihypotensive agent. Midodrine hydrochloride is an odorless, white, crystalline powder, soluble in water and sparingly soluble in methanol having a pKa of 7.8 (0.3% aqueous solution), a pH of 3.5 to 5.5 (5% aqueous solution) and a melting range of 200 to 203°C. It is chemically described as: (1) Acetamide, 2-amino-*N*-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-monohydrochloride, (±)-; or (2) (±)-2-amino-*N*-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide monohydrochloride. Midodrine Hydrochloride's molecular formula is $C_{12}H_{18}N_2O_4HCl$, its molecular weight is 290.7 and its structural formula is:



JUL - 2 2004

APPROVED

Each tablet for oral administration contains 2.5 mg, 5 mg, or 10 mg of midodrine hydrochloride and the following inactive ingredients: Pregelatinized Starch 1500, NF, Microcrystalline Cellulose, NF, Colloidal Silicon Dioxide, NF, Magnesium Stearate, NF. In addition, the 5 mg tablets contain FD&C Yellow # 6 Aluminum Lake and FD&C Red # 40 Aluminum Lake, and the 10 mg tablets contain FD&C Blue # 2 Aluminum Lake.

CLINICAL PHARMACOLOGY

Mechanism of Action: Midodrine hydrochloride forms an active metabolite, desglymidodrine, that is an alpha$_1$-agonist, and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure. Desglymidodrine does not stimulate cardiac beta-adrenergic receptors. Desglymidodrine 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 in patients with orthostatic hypotension of various etiologies. Standing systolic blood pressure is elevated by approximately 15 to 30 mmHg at 1 hour after a 10-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 autonomic failure.

Pharmacokinetics: Midodrine hydrochloride is a prodrug, i.e., the therapeutic effect of orally administered midodrine is due to the major metabolite desglymidodrine, formed by deglycination of midodrine. After oral administration, midodrine hydrochloride is rapidly absorbed. The plasma levels of the prodrug peak after about half an hour, and decline with a half-life of approximately 25 minutes, while the metabolite reaches peak blood concentrations about 1 to 2 hours after a dose of midodrine and has a half-life of about 3 to 4 hours. The absolute bioavailability of midodrine (measured as desglymidodrine) is 93%. The bioavailability of desglymidodrine is not affected by food. Approximately the same amount of desglymidodrine is formed after intravenous and oral administration of midodrine. Neither midodrine nor desglymidodrine is bound to plasma proteins to any significant extent.

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

Renal elimination of midodrine is insignificant. The renal clearance of desglymidodrine is of the order of 385 mL/minute, most, 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 base-secreting 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 controlled trials, one of 3-weeks duration and 2 of 1 to 2 days duration. All studies were randomized, double-blind and parallel-design trials in patients with orthostatic hypotension of any etiology and supine-to-standing fall of systolic blood pressure of at least 15 mmHg accompanied by at least moderate dizziness/lightheadedness.

Patients with pre-existing sustained supine hypertension above 180/110 mmHg were routinely excluded. In a 3-week study in 170 patients, most previously untreated with midodrine, the midodrine-treated patients (10 mg t.i.d., with the last dose not later than 6 P.M.) had significantly higher (by about 20 mmHg) 1-minute standing systolic pressure 1 hour after dosing (blood pressures were not measured at other times) for all 3 weeks. After week 1, midodrine-treated patients had small improvements in dizziness/lightheadedness/unsteadiness scores and global evaluations, but these effects were made difficult to interpret by a high early drop-out rate (about 25% vs 5% on placebo). Supine and sitting blood pressure rose 16/8 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 0, 3, and 6 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 12 mmHg; 3-minute standing pressures were increased also at 1, but not 3, hours after dosing. There were increases in standing time seen intermittently 1 hour after dosing, but not at 3 hours.

In a 1-day, dose-response trial, single doses of 0, 2.5, 10, and 20 mg of midodrine were given to 25 patients. The 10- and 20-mg doses produced increases in standing 1-minute systolic pressure 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 pressure was ≥200 mmHg in 22% of patients on 10 mg and 45% of patients on 20 mg; elevated pressures often lasted 6 hours or more.

INDICATIONS AND USAGE

Midodrine hydrochloride tablets are indicated for the treatment of symptomatic orthostatic hypotension (OH). Because midodrine hydrochloride can cause marked elevation of supine blood pressure (BP>200 mmHg systolic), it should be used in patients whose lives are considerably impaired despite standard clinical care, including non-pharmacologic treatment (such as support stockings), fluid expansion, and lifestyle alterations. The indication is based on midodrine hydrochloride's effect on increases in 1-minute standing systolic blood pressure, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of midodrine hydrochloride, principally improved ability to perform life activities, have not been established. Further clinical trials are underway to verify and describe the clinical benefits of midodrine hydrochloride.

After initiation of treatment, midodrine hydrochloride should be continued only for patients who report significant symptomatic improvement.

CONTRAINDICATIONS

Midodrine hydrochloride tablets are contraindicated in patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma or thyrotoxicosis. Midodrine hydrochloride should not be used in patients with persistent and excessive supine hypertension.

WARNINGS

Supine Hypertension: The most potentially serious adverse reaction associated with midodrine hydrochloride therapy is marked elevation of supine arterial blood pressure (supine hypertension). Systolic pressure of about 200 mmHg was seen overall in about 13.4% of patients given 10 mg of midodrine hydrochloride. Systolic elevations of this degree were most likely to be observed in patients with relatively elevated pre-treatment systolic blood pressures (mean 170 mmHg). There is no experience in patients with initial supine systolic pressure above 180 mmHg, as those patients were excluded from the clinical trials. Use of midodrine hydrochloride in such patients is not recommended. Sitting blood pressures were also elevated by midodrine hydrochloride therapy. It is essential to monitor supine and sitting blood pressures in patients maintained on midodrine hydrochloride.

PRECAUTIONS

General: The potential for supine and sitting hypertension should be evaluated at the beginning of midodrine hydrochloride therapy. Supine hypertension can often be controlled by preventing the patient from becoming fully supine, i.e., sleeping with the head of the bed elevated. The patient should be cautioned to report symptoms of supine hypertension immediately. Symptoms may include cardiac awareness, pounding in the ears, headache, blurred vision, etc.

The patient should be advised to discontinue the medication immediately if supine hypertension persists.

Blood pressure should be monitored carefully when midodrine hydrochloride is used concomitantly with other agents that cause vasoconstriction, such as phenylephrine, ephedrine, dihydroergotamine, phenylpropanolamine, or pseudoephedrine.

A slight slowing of the heart rate may occur after administration of midodrine hydrochloride, primarily due to vagal reflex. Caution should be exercised when midodrine hydrochloride is used concomitantly with cardiac glycosides (such as digitalis), psychopharmacologic agents, beta blockers or other agents that directly or indirectly reduce heart rate. Patients who experience any signs or symptoms suggesting bradycardia (pulse slowing, increased dizziness, syncope, cardiac awareness) should be advised to discontinue midodrine hydrochloride and should be re-evaluated.

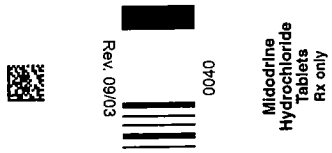
Midodrine hydrochloride should be used cautiously in patients with urinary retention problems, as desglymidodrine acts on the alpha-adrenergic receptors of the bladder neck.

Midodrine hydrochloride should be used with caution in orthostatic hypotensive patients who are also diabetic, as well as those with a history of visual problems who are also taking fludrocortisone acetate, which is known to cause an increase in intraocular pressure and glaucoma.

Midodrine hydrochloride use has not been studied in patients with renal impairment. Because desglymidodrine is eliminated via the kidneys, and higher blood levels would be expected in such patients, midodrine hydrochloride should be used with caution in patients with renal impairment, with a starting dose of 2.5 mg (see **DOSAGE AND ADMINISTRATION**). Renal function should be assessed prior to initial use of midodrine hydrochloride.

Midodrine hydrochloride use has not been studied in patients with hepatic impairment.

Midodrine hydrochloride should be used with caution in patients with hepatic impairment, as the liver has a role in the metabolism of midodrine.



Information for Patients: Patients should be told that certain agents in over-the-counter products, such as cold remedies and diet aids, can elevate blood pressure, and therefore, should be used cautiously with midodrine hydrochloride, as they may enhance or potentiate the pressor effects of midodrine hydrochloride (see **Drug Interactions**). Patients should also be made aware of the possibility of supine hypertension. 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 midodrine hydrochloride 3 to 4 hours before bedtime to minimize nighttime supine hypertension.

Laboratory Tests: Since desglymidodrine is eliminated by the kidneys and the liver 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 concomitantly with midodrine hydrochloride, cardiac glycosides may enhance or precipitate bradycardia, A.V. block or arrhythmia.

The use of drugs that stimulate alpha-adrenergic receptors (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine or dihydroergotamine) may enhance or potentiate the pressor effects of midodrine hydrochloride. Therefore, caution should be used when midodrine hydrochloride is administered concomitantly with agents that cause vasoconstriction.

Midodrine hydrochloride has been used in patients concomitantly treated with salt-retaining steroid therapy (i.e., fludrocortisone acetate), with or without salt supplementation. The potential for supine hypertension should be carefully monitored in these patients and may be minimized by either reducing the dose of fludrocortisone acetate or decreasing the salt intake prior to initiation of treatment with midodrine hydrochloride. Alpha-adrenergic blocking agents, such as prazosin, terazosin, and doxazosin, can antagonize the effects of midodrine hydrochloride.

Potential for Drug Interactions: It appears possible, although there is no supporting experimental evidence, that the high renal clearance of desglymidodrine (a base) is due to active tubular secretion by the base-secreting system also responsible for the secretion of such drugs as metformin, cimetidine, ranitidine, procainamide, triamterene, flecainide, and quinidine. Thus there may be a potential for drug-drug interaction with these drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies have been conducted in rats and mice at dosages of 3 to 4 times the maximum recommended daily human dose on a mg/m^2 basis, with no indication of carcinogenic effects related to midodrine hydrochloride. Studies investigating the mutagenic potential of midodrine hydrochloride revealed no evidence of mutagenicity. Other than the dominant lethal assay in male mice, where no impairment of fertility was observed, there have been no studies on the effects of midodrine hydrochloride on fertility.

Pregnancy: *Pregnancy Category C.* Midodrine hydrochloride increased the rate of embryo resorption, reduced fetal body weight in rats and rabbits, and decreased fetal survival in rabbits when given in doses 13 (rat) and 7 (rabbit) times the maximum human dose based on body surface area (mg/m^2). There are no adequate and well-controlled studies in pregnant women. Midodrine 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 not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when midodrine hydrochloride is administered to a nursing woman.

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

ADVERSE REACTIONS

The most frequent adverse reactions seen in controlled trials were supine and sitting hypertension; paresthesia and pruritus, mainly of the scalp; goosebumps; chills; urinary urge; urinary retention and urinary frequency.

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

Adverse Events

	Placebo n=88		Midodrine n=82	
Event	**# of reports**	**% of patients**	**# of reports**	**% of patients**
Total # of reports	22		77	
Paresthesia[1]	4	4.5	15	18.3
Piloerection	0	0	11	13.4
Dysuria[2]	0	0	11	13.4
Pruritus[3]	2	2.3	10	12.2
Supine hypertension[4]	0	0	6	7.3
Chills	0	0	4	4.9
Pain[5]	0	0	4	4.9
Rash	1	1.1	2	2.4

1 Includes hyperesthesia and scalp paresthesia
2 Includes dysuria (1), increased urinary frequency (2), impaired urination (1), urinary retention (5), urinary urgency (2)
3 Includes scalp pruritus
4 Includes patients who experienced an increase in supine hypertension
5 Includes abdominal pain and pain increase

Less frequent adverse reactions were headache; feeling of pressure/fullness in the head; vasodilation/flushing face; confusion/thinking abnormality; dry mouth; nervousness/anxiety and rash. Other adverse reactions that occurred rarely were visual field defect; dizziness; skin hyperesthesia; insomnia; somnolence; erythema multiforme; canker sore; dry skin; dysuria; impaired urination; asthenia; backache; pyrosis; nausea; gastrointestinal distress; flatulence and leg cramps.

The most potentially serious adverse reaction associated with midodrine hydrochloride therapy is supine hypertension. The feelings of paresthesia, pruritus, piloerection and chills are pilomotor reactions associated with the action of midodrine on the alpha-adrenergic receptors of the hair follicles. Feelings of urinary urgency, retention and frequency are associated with the action of midodrine on the alpha-receptors of the bladder neck.

OVERDOSAGE

Symptoms of overdose could include hypertension, piloerection (gooseburnps), a sensation of coldness and urinary retention. There are 2 reported cases of overdosage with midodrine hydrochloride, both in young males. One patient ingested midodrine hydrochloride drops, 250 mg, experienced systolic blood pressure of greater than 200 mmHg, was treated with an IV injection of 20 mg of phentolamine, and was discharged the same night without any complaints.

The other patient ingested 205 mg of midodrine hydrochloride (41 5-mg tablets), and was found lethargic and unable to talk, unresponsive to voice but responsive to painful stimuli, hypertensive and bradycardic. Gastric lavage was performed, and the patient recovered fully by the next day without sequelae.

The single doses that would be associated with symptoms of overdosage or would be potentially life-threatening are unknown. The oral LD_{50} is approximately 30 to 50 mg/kg in rats, 675 mg/kg in mice, and 125 to 160 mg/kg in dogs.

Desglymidodrine is dialyzable.

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

DOSAGE AND ADMINISTRATION

The recommended dose of midodrine hydrochloride tablets is 10 mg, 3 times daily. Dosing should take place during the daytime hours when the patient needs to be upright, 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 (not later than 6 P.M.). Doses may be given in 3-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 hypertension occurs at a high rate (about 45%) at this dose. In order to reduce the potential for supine hypertension during sleep, midodrine hydrochloride should not be given after the evening meal or less than 4 hours before bedtime. Total daily doses greater than 30 mg have been tolerated by some patients, but their safety and usefulness have not been studied systematically or established. Because of the risk of supine hypertension, midodrine hydrochloride should be continued only in patients who appear to attain symptomatic improvement during initial treatment.

The supine and standing blood pressure should be monitored regularly, and the administration of midodrine hydrochloride should be stopped if supine blood pressure increases excessively.

Because desglymidodrine is excreted renally, dosing in patients with abnormal renal function should be cautious; although this has not been systematically studied, it is recommended that treatment of these patients be initiated using 2.5-mg doses.

Dosing in children has not been adequately studied.

Blood levels of midodrine and desglymidodrine 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

Midodrine hydrochloride is supplied as 2.5-mg, 5-mg and 10-mg tablets for oral administration.

Midodrine Hydrochloride Tablets, 2.5-mg are supplied as white, round, flat-faced, bevelled edge, debossed "E" over "40" on one side and bisected on the other side and are available in bottles of 100 and 500.

Midodrine Hydrochloride Tablets, 5-mg are supplied as reddish-orange, round, flat-faced, bevelled edge, debossed "E" over "43" on one side and bisected on the other side and are available in bottles of 100 and 500.

Midodrine Hydrochloride Tablets, 10-mg are supplied as blue-grey, round, flat-faced, bevelled edge tablets, debossed, "E" over "149" on one side and bisected on the other side and are available in bottles of 100 and 500.

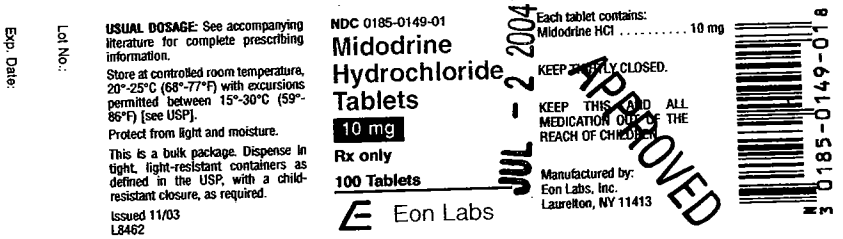
Storage: Store at controlled room temperature, 20°-25°C (68°-77°F) with excursions permitted between 15°-30°C (59°-86°F) [See USP]. Preserve in tight light resistant containers as defined in the USP.

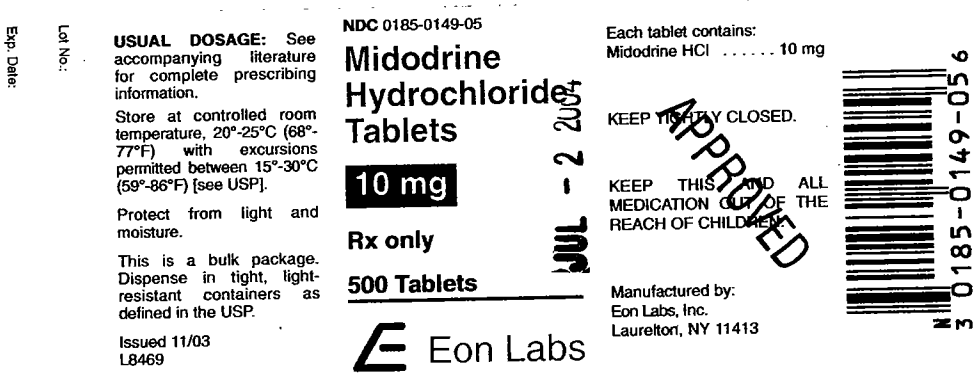
Manufactured by:
Eon Labs, Inc.
Laurelton, NY 11413

Rev. 09/03
MF0040REV09/03
OS8009
MG #18357

FINAL PRINTED LABELING

CONTAINER LABELS





CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING #1

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

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	***None***	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-815

Code	Reference	Expiration	Labeling Impact
ODE	Orphan Drug Exclusivity.	9/6/03	None

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 21CFR 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: 10/30/2003

cc:

ANDA: 76-514/S-002
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\MYLAN\LTRS&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 4/28/04
HFD-613/JGrace Signed for Grace 4/28/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

CHEMISTRY REVIEW(S)

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. 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/NDA/DMF(s)
N/A

13. DOSAGE FORM

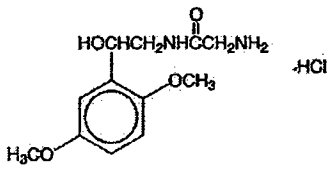
Tablets

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, (±)-.
CAS #: [3092-17-9]
Molecular Formula: $C_{12}H_{18}N_2O_4HCl$; Molecular Weight: 290.7
Organoleptic Properties: Odorless, white, crystalline powder



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 R. Bykadi Dec 12, 2003
HFD-623/A. Mueller, Ph.D./ Team Leader/Date A. Mueller 12-12-03
HFD-617/K. Kiester, PM/Date K. Kiester 12/10/03

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

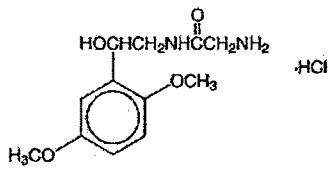
11 Rx or OTC
Rx

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, (∀)-.
CAS #: [3092-17-9]
Molecular Formula: $C_{12}H_{18}N_2O_4HCl$; Molecular Weight: 290.7
Organoleptic Properties: Odorless, white, crystalline powder



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: DATE COMPLETED:

Raj Bykadi, Ph.D. 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 R. Bykadi 6-30-04
HFD-623/A. Mueller, Ph.D./ Team Leader/6/29/04 A Mueller 6-30-04
HFD-617/S. Eng, PM/C.Kiester for/6/29/04 C Kiester 6/30/04

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

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

Change

Abbreviated New Drug Supplemental Application Regulatory Assessment

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 [redacted]

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 [redacted] 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 [redacted] has the capability to perform the intended testing.
- Certification that the [redacted] is in conformance with cGMP's.
- A full description of the testing to be performed by the [redacted]

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-514 / SCQ-001
Drug Product Name	Midodrine HCl tablet
Strength	10 mg
Applicant Name	Eon Labs
Address	Wilson, North Carolina
Submission Date(s)	15 Apr 2004
Amendment Date(s)	none
Reviewer	J. Lee
First Generic	no
File Location	v:\\firmsam\Eon\ltrs&rev\76514S404.doc

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 midrodrine 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.

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

RD INITIALED GJPSINGH
FT INITIALED GJPSINGH Gurjeet Singh 6-22-04

Concur: Barbara M. Davit Date: 6/22/04

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

Sampling Times (Minutes)	Test Product: Lot No.: RDW00211 Strength: 10 mg			Ref Product: Lot No.: 214911 (exp. 12/03) Strength: 10 mg		
	Mean (%)	Range	% CV	Mean (%)	Range	% CV
5	98.5	___	2.4	98.7	___	2.6
10	99.6	___	1.9	100.8	___	2.3
15	99.9	___	1.7	101.3	___	2.3
20	100.0	___	1.7	101.8	___	2.7

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.

APPEARS THIS WAY
ON ORIGINAL

Midodrine HCl Dissolution Stability Data					
Tablets	3 Months, Accelerated		3 Months, Room Temperature		
	Tablet Count per Bottle 100	Tablet Count per Bottle 500	Tablet Count per Bottle 100	Tablet Count per Bottle 500	Tablet Count per Bottle Bulk
1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Average, %	100.5	96.8	97.8	98.5	98.0
Range, %	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
RSD, %	2.1	1.9	4.0	1.5	0.9

Reference: TJM 0608-052, 053 and DLC 0608-046.

APPEARS THIS WAY
ON ORIGINAL

COMPARISON OF COMPOSITION FOR MIDODRINE HYDROCHLORIDE TABLETS, 2.5 MG, 5 MG AND 10 MG

	Midodrine Hydrochloride Tablets, 2.5 mg		Midodrine Hydrochloride Tablets, 5 mg		Midodrine Hydrochloride Tablets, 10 mg	
Component	**Amount per tablet (mg)**	**% w/w**	**Amount per tablet (mg)**	**%w/w**	**Amount per Tablet (mg)**	**% w/w**
Midodrine Hydrochloride	2.5	1.92	5.0	3.85	10.0	7.69
Pregelatinized Starch 1500, NF						
FD&C Yellow # 6 Aluminum Lake						
FD&C Red # 40 Aluminum Lake						
FD&C Blue #2 Aluminum Lake						
Microcrystalline Cellulose, NF						
Colloidal Silicon Dioxide, NF						
Magnesium Stearate, NF						
Total Tablet Weight	**130.0**	**100.0**	**130.0**	**100.0**	**130.0**	**100.0**

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 DBE's dissolution method and specification as follows:

The dissolution testing should be conducted in [redacted]

The test product should meet the following specifications:

Not less than [redacted] (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,

/s/ Barbara M Davit

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

APPEARS THIS WAY
ON ORIGINAL

/

JUN 22 2004

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

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

PRIMARY REVIEWER : J. Lee BRANCH : II

INITIAL : K-L. DATE : 6/22/04

TEAM LEADER : GJP Singh BRANCH : II

INITIAL : GJP Singh DATE : 6-22-04

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

INITIAL : BMC DATE : 6/22/04

CC: ANDA 76-514/SCQ-001
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

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Endorsements: R.F. 6/22/04
HFD-655/ Reviewer
HFD-655/ Bio team Leader 6-22-04
HFD-650/ D. Conner BW 6/22/04

BIOEQUIVALENCE - ACCEPTABLE submission date: 15 April 2004

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).

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

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

PRIMARY REVIEWER : J. Lee BRANCH : II

INITIAL : R-L. DATE : 6/22/04

TEAM LEADER : GJP Singh BRANCH : II

INITIAL : GJP Singh DATE : 6-22-04

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

INITIAL : BNC DATE : 6/22/04

COMPARISON OF COMPOSITION FOR MIDODRINE HYDROCHLORIDE TABLETS, 2.5 MG, 5 MG AND 10 MG

	Midodrine Hydrochloride Tablets, 2.5 mg		Midodrine Hydrochloride Tablets, 5 mg		Midodrine Hydrochloride Tablets, 10 mg	
Component	**Amount per tablet (mg)**	**% w/w**	**Amount per tablet (mg)**	**%w/w**	**Amount per Tablet (mg)**	**% w/w**
Midodrine Hydrochloride	2.5	1.92	5.0	3.85	10.0	7.69
Pregelatinized Starch 1500, NF						
FD&C Yellow # 6 Aluminum Lake						
FD&C Red # 6 Aluminum Lake						
FD&C Blue #2 Aluminum Lake						
Microcrystalline Cellulose, NF						
Colloidal Silicon Dioxide, NF						
Magnesium Stearate, NF						
Total Tablet Weight	**130.0**	**100.0**	**130.0**	**100.0**	**130.0**	**100.0**

All levels are held the same for 2.5 mg, 5 mg and 10 mg.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-514
Drug Product Name	**Midodrine HCl tablet**
Strength	10 mg
Applicant Name	Eon Labs
Address	**Wilson, North Carolina**
Submission Date(s)	11 Sept 2003
Amendment Date(s)	none
Reviewer	**J. Lee**
First Generic	**no**
File Location	v:\\firmsam\Eon\ltrs&rev\76514S903.doc

I. Executive Summary

This submission is a supplement to the sponsor's approved application for the 2.5 and 5 mg strengths of midrodrine 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:

[redacted]

specification: NLT [redacted] in 30 min

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

[redacted]

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

Recommendation:

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

The sponsor should address comment #1.

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

RD INITIALED SNERURKAR
for FT INITIALED SNERURKAR Mhaswal. 3/30/04

Concur: Barbara M Davit Date: 3/31/04

for 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

Method Ref.:	sponsor's in-house	Medium:	[redacted]
USP 27 Apparatus:	II	Volume:	[redacted]
RPM:	[redacted]	Tolerance:	Q= [redacted], in 30 min. (sponsor's specification)
No. Units Tested:	12		
Reference Drug:	ProAmatine® 10 mg tablet	Assay Method:	[redacted]

Sampling Times (Minutes)	Test Product: Lot No.: RDW00211 Strength: 10 mg			Ref Product: Lot No.: 214911 (exp. 12/03) Strength: 10 mg		
	Mean (%)	Range	% CV	Mean (%)	Range	% CV
5	100.1	[redacted]	2.1	97.1	[redacted]	4.1
10	101.0	[redacted]	2.2	99.4	[redacted]	3.3
15	100.9	[redacted]	2.4	100.2	[redacted]	2.7
20	101.0	[redacted]	2.5	100.5	[redacted]	2.8
30	101.3	[redacted]	2.3	101.1	[redacted]	2.5

APPEARS THIS WAY
ON ORIGINAL

COMPARISON OF COMPOSITION FOR MIDODRINE HYDROCHLORIDE TABLETS, 2.5 MG, 5 MG AND 10 MG

	Midodrine Hydrochloride Tablets, 2.5 mg		Midodrine Hydrochloride Tablets, 5 mg		Midodrine Hydrochloride Tablets, 10 mg	
Component	**Amount per tablet (mg)**	**% w/w**	**Amount per tablet (mg)**	**%w/w**	**Amount per Tablet (mg)**	**% w/w**
Midodrine Hydrochloride	2.5	1.92	5.0	3.85	10.0	7.69
Pregelatinized Starch 1500, NF						
FD&C Yellow # 6 Aluminum Lake						
FD&C Red # 40 Aluminum Lake						
FD&C Blue #2 Aluminum Lake						
Microcrystalline Cellulose, NF						
Colloidal Silicon Dioxide, NF						
Magnesium Stearate, NF						
Total Tablet Weight	**130.0**	**100.0**	**130.0**	**100.0**	**130.0**	**100.0**

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:

   [redacted]

   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,

/s/

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

CC: ANDA 76-514
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655 /Reviewer E.S. 3/30/04
for HFD-655 /Bio Team Leader [signature] 3/30/04
HFD-617/Project Manager
for HFD-650/Dale Conner [signature] 3/31/04

V:\firmsam\Eon\ltrs&rev\76514S903.doc

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.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

ADMINISTRATIVE DOCUMENTS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application: ANDA 76514/003 Action Goal:

Stamp: 29-DEC-2004 District Goal: 29-MAY-2005

Regulatory Due: Brand Name:

76514

Applicant: EON LABS Estab. Name: MIDODRINE HYDROCHLORIDE

4700 EON DR Generic Name:

WILSON, NC 27893

Priority: Dosage Form: (TABLET)

Org Code: 600 Strength: 2.5 MG 5 MG AND 10 MG

Application Comment: ESTING LAB

ING.

SPONSOR ALSO USES EON LABS CFN 2431929 TO DO TESTING ON R.

MATERIAL/COMPONENTS, IN-PROCESS, FINISHED PRODUCT, AND OR

STABILITY TESTING. THANKS. (SIMON 1/11/05) (on 11-JAN-2005 by S.

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 Leader

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

9049

Establishment: CFN 2431929 FEI 2431929

EON LABORATORIES MANUFACTURING INC

227-15 NORTH CONDUIT AVE

LAURELTON, NY 114133134

DMF No: AADA:

ponsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CTL OAI Status: NONE

EMilestone Name reator	Date	Type	Insp. Date	Decision & Reason	C
SUBMITTED TO OC ENGS	11-JAN-2005				
SUBMITTED TO DO ERGUSONS	12-JAN-2005	GMP			F
DO RECOMMENDATION LFARINA	13-JAN-2005			ACCEPTABLE BASED ON FILE REVIEW	
OC RECOMMENDATION ERGUSONS	14-JAN-2005			ACCEPTABLE DISTRICT RECOMMENDATION	F

Establishment: CFN [redacted] FEI [redacted]

DMF No: AADA:

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

›file: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	C reator
SUBMITTED TO OC ENGS	11-JAN-2005				
SUBMITTED TO DO ERGUSONS	12-JAN-2005	GMP			F
DO RECOMMENDATION LANDREWS	15-MAR-2005			ACCEPTABLE BASED ON FILE REVIEW	
EI OF 3/05 WAS VAI. PROFILE CLASS IS ACCEPTABLE.					
OC RECOMMENDATION MBROGIOJ	15-MAR-2005			ACCEPTABLE DISTRICT RECOMMENDATION	DA

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

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019815	001	ODE	SEP 06,2003

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.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019815	002	ODE	SEP 06,2003

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 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

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019815	003	ODE	SEP 06,2003

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 Appl No 019815 Product 001 in the OB_Rx list.

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

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019815	001	ODE	SEP 06,2003

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."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
019815	AB	No	MIDODRINE HYDROCHLORIDE	TABLET; ORAL	10MG	PROAMATINE	SHIRE PHARM
019815	AB	No	MIDODRINE HYDROCHLORIDE	TABLET; ORAL	2.5MG	PROAMATINE	SHIRE PHARM
019815	AB	Yes	MIDODRINE HYDROCHLORIDE	TABLET; ORAL	5MG	PROAMATINE	SHIRE PHARM

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

Return to Electronic Orange Book Home Page

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

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)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Eon Labs, Inc.	December 22, 2004
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(252) 234-2222	(252) 234-2323
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
4700 Eon Drive Wilson, NC 27893 CFN 1062246	

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)*	PROPRIETARY NAME *(trade name)* IF ANY
Midodrine Hydrochloride Tablets	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	2.5 mg, 5 mg and 10 mg	Oral

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

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*

☐ 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, BMFs, and DMFs referenced in the current application)

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(f)(1), 21 CFR 601.2)
☐	12. Case report forms (e.g. 21 CFR 314.50(f)(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.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
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	TYPED NAME AND TITLE	DATE
Steven W. Brown	**Steven W. Brown, R.Ph.** **Director, Regulatory Affairs**	22 December 2004

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
4700 Eon Drive, Wilson, NC 27893	(252) 234-2224

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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

CORRESPONDENCE

Eon Labs
The Pharmacy Drug Company

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

NDA NO. 76-514 REF NO. SCB-003-AT
NDA SUPPL FOR Facility Add

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** [redacted]. 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 [redacted] is:

[redacted]

CFN [redacted]

EOR Submitted 1/11/05

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

RECEIVED
DEC 29 2004
OGD / CDER

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

In support of this request, enclosed are cGMP and GDEA certifications, along with a list of tests that may be performed by [redacted] The change in the [redacted] 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.

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

F:\DEPTS\RA\PAC_ATLS\TEMPLATE.WPD

Eon Labs
The Pharmacy Drug Company

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

Eon Labs
The Pharmacy Drug Company

Archival Copy

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

BIOEQUIVALENCY AMENDMENT

SUPPLEMENT AMENDMENT
SCQ-001-AB

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,

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

RECEIVED
APR 16 2004
OGD / CDER

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

Eon Labs
The Pharmacy Drug Company

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

MINOR AMENDMENT

SUPPLEMENT AMENDMENT
SCQ-001
SC-002 /AM

FPL

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

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

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JAN 2 0 2004
OGD/CDER

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

ANDA 76-514/ S-001 and S-002

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 [redacted] 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 [redacted] 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,

12-15-03

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

Eon Labs
The Pharmacy Drug Company

11/3/03

October 21, 2003

NEW CORRESP
NC

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 Debarrment 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

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

RECEIVED
OCT 22 2003
OGD/CDER

10/24 nc

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

Eon Labs
The Pharmacy Drug Company

September 11, 2003

ANDA Supplement

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

NDA NO. 76-514 REF. NO. SCE-001/1
NDA SUPPL FOR (New Strength)

NDA NO. _____ REF. NO. SL-002
NDA SUPPL FOR Labeling Rev.

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.

SEP 12 2003

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

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

APPEARS THIS WAY
ON ORIGINAL