CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-514

Generic Name:	Midodrine Hydrochloride Tablets 2.5mg and 5 mg
Sponsor:	Eon Labs, Inc.
Approval Date:	September 11, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 76-514

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter(s)	
Final Printed Labeling(s)	X
CSO Labeling Review(s)	X
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-514

APPROVAL LETTER

ANDA 76-514

SEP 11 2003

Eon Labs, Inc.
Attention: Sadie M. Ciganek
227-15 N. Conduit Avenue
Laurelton, NY 11413

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 26, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg.

Reference is also made to your amendments dated June 20, and August 8, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg, to be bioequivalent and therapeutically equivalent to the listed drug (ProAmatine® Tablets, 2.5mg and 5 mg, respectively, 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.

As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", the Orphan Drug Exclusivity (ODE) granted to Shire's ProAmatine Tablets under NDA 19-815 expired on September 6, 2003.

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 postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use of the drug product after marketing demonstrates that the postmarketing restrictions are inadequate to assure the safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing 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 341.150 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.

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

FDA's field staff has not completed its validation of the regulatory methods submitted in your application. It is the policy of the Office to proceed with approval while this process is ongoing. We acknowledge your commitment to cooperate with the agency to resolve satisfactorily any deficiencies which may be identified during the validation process.

Sincerely yours,

/S/

Gary Buehler
Director 9/11/03
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-514

FINAL PRINTED LABELING(S)

Iss. 02/03

0040

Midodrine Hydrochloride Tablets Rx only

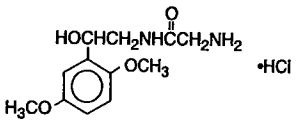
Midodrine Hydrochloride Tablets

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:



Each tablet for oral administration contains 2.5 mg, or 5 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.

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.

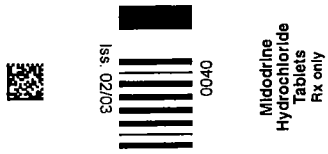
Midodrine hydrochloride should be used cautiously in patients with urinary retention problems, as desglymidodrine acts on the alpha-adrenergic receptors of the bladder neck.

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 (goosebumps), 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 and 5-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.

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

Issued 02/03
MF0040ISS02/03
OS8009
MG #18357

Exp. Date:

Lot No.:

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, with a child-resistant closure, as required.

Issued 02/03
L8056

NDC 0185-0040-01

Midodrine Hydrochloride Tablets

2.5 mg

Rx only

100 Tablets

SEP 11 2003

Eon Labs

Each tablet contains:
Midodrine HCl . . . . 2.5 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

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

Exp. Date:

Lot No.:

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 02/03
L8063

NDC 0185-0040-05

Midodrine Hydrochloride Tablets

2.5 mg

Rx only

500 Tablets

SEP 11 2003

Eon Labs

Each tablet contains:
Midodrine HCl . . . . . 2.5 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

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

Exp. Date:

Lot No.:

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, with a child-resistant closure, as required.

Issued 02/03
L8070

NDC 0185-0043-01

Midodrine Hydrochloride Tablets

5 mg

Rx only

100 Tablets

Eon Labs

Each tablet contains:
Midodrine HCl . . . . . 5 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

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

Exp. Date:

Lot No.:

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 02/03
L8077

NDC 0185-0043-05

Midodrine Hydrochloride Tablets

5 mg

Rx only

500 Tablets

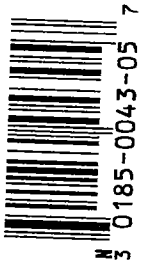
Eon Labs

Each tablet contains:
Midodrine HCl . . . . . 5 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

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



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-514

CSO LABELING REVIEW(S)

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-514
Date of Submission: March 14, 2003
Applicant's Name: Eon Laboratories, Inc.
Established Name: Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg

---

APPROVAL SUMMARY:

1. **Do you have 12 Final Printed Labels and Labeling? Yes**

2. **CONTAINER Labels**: Bottles of 100 and 500 tablets
   Satisfactory in **final print** as of the March 14, 2003 submission
   (See blue jacket volume 2.1)

3. **PROFESSIONAL PACKAGAGE INSERT Labeling**:
   Satisfactory in **final print** as of the March 14, 2003 submission
   (See blue jacket volume 2.1)

4. **Revisions needed post-approval**; None

5. **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

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: ProAmatine®
NDA Number: N 19-815
NDA Drug Name: ProAmatine®
NDA Firm: Wyeth-Ayerst Labs; N 19-815; Approved October 29, 1996
Date of Approval of NDA Insert and supplement: October 29, 1996; NDA 19-815
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, and ProAmatine®

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. 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.

2. **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

3. 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).

4. Product Line:
   The innovator markets their product in two strengths (2.5 mg and 5 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.

5. 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 0615 and 0621 in volume B. 1.3)**

6. 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.

7. Container/Closure (See page 0555 in Vol. B. 1.3)
   Containers: HDPE
   Closure: CRC closures for 100 count bottles and non-CRC for the 500 count bottles.

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

9. **The drug products submitted for this ANDA are both scored as is the RLD.**

Date of Review: 4/2/03 Date of Submission: 3/14/03
Primary Reviewer: Jim Barlow Date: 4/3/03

Team Leader: John Grace /S/ Date: 4/8/2003

---

cc:
ANDA: 76-514
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\EON\LTRS&REV\76514ap.s.doc
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-514
Date of Submission:	September 26, 2002
Applicant's Name:	Eon Laboratories, Inc.
Established Name:	Midodrin Hydrochloride Tablets, 2.5 mg and 5 mg

---

Labeling Deficiencies:

1. **CONTAINER – Bottles of 100 and 500 tablets**
   - **a.** We note that the contrasting colors that were utilized to differentiate between the two different strength tablets are very dark and very similar. To avoid any safety issues, we encourage you to increase the readability of these container labels. Please revise and/or comment.

   - **b.** Please revise your temperature/storage statement to read as follows:

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

2. **PACKAGE INSERT**
   - **a.** INDICATIONS AND USAGE
     Midodrine hydrochloride tablets are…

   - **b.** CONTRAINDICATIONS
     Midodrine hydrochloride tablets are…

   - **c.** DOSAGE AND ADMINISTRATION
     First paragraph, first sentence -

     The recommended dose of midodrine hydrochloride tablets is…

   - **d.** HOW SUPPLIED

     Please revise your temperature/storage statement to read as follows:

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

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Sincerely Yours

_____

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

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTE TO THE CHEMIST: Do you concur with the request to revise the storage temperature? This was requested as per Dr. Richard Adams and the committee associated with controlled room temperature.

FOR THE RECORD:

1. 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, 2002 for the RLD, NDA 19-815.
2. **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

3. Storage/Dispensing Conditions:
   NDA: Store from 15 to 25°C (59 to 77°F).
   ANDA: Store at controlled room temperature 15 to 30°C (59 to 86°F) (See USP). Protect from light and moisture. **{See comments above for requested revisions]**

   NDA: Dispense in a well-closed container as defined in the USP.
   ANDA:This is a bulk package. Dispense in tight, light-reisitant containers as defined in the USP. With a child-resistant closure, (as required).

   Note that requested revisions to the storage/temp conditions were made to be in accord with comments from Dr. Rich Adams.

4. Product Line:
   The innovator markets their product in two strengths (2.5 mg and 5 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.

5. 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 0615 and 0621 in volume B. 1.3)**

6. 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.

7. Container/Closure (See page 0555 in Vol. B. 1.3)
   Containers: HDPE
   Closure: CRC closures for 100 count bottles and non-CRC for the 500 count bottles.

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

9. **The drug products submitted for this ANDA are both scored as is the RLD.**

Date of Review: 11/22/02 Date of Submission: 9/26/02
Primary Reviewer: Jim Barlow 11/25/02

Team Leader: John Grace Date: 12/9/2002

---

cc:
ANDA: 76-514
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\EON\LTRS&REV\76514na1.l
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-514

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

ANDA 76-514

Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg

Eon Laboratories, Inc

Raj Bykadi, Ph.D
Division of Chemistry I

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. ANDA : 76-514

2. REVIEW #: 1

3. REVIEW DATE: December 26, 2002

4. REVIEWER: Raj Bykadi, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	26-Sept-2002
FDA Acknowledgement letter	19-Nov-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	26-Sept-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Eon Laboratories Inc
Address:	227-15 N. Conduit Avenue Laurelton, NY 11413
Representative:	Sadie M. Ciganek Vice President, Regulatory Affairs
Telephone:	Tel: (718) 276-8600 Fax: (718) 276-1735

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Midodrine Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION:

The legal basis for this ANDA submission is ProAmatine ® Tablets (NDA 19-815), reference listed drug (RLD) for Midodrine HCl tablets. The RLD is manufactured by Roberts Labs, Inc., a wholly owned subsidiary of Shire Pharmaceuticals. This drug is referenced on page 3-245 of the "Approved Drug Products With Therapeutic Equivalence Evaluations" (22nd edition) (Orange Book).

It is noted that the Shire Pharmaceuticals has listed a new dosage form, 10 mg tablet in supplement #7 of the Orange Book. Eon Laboratories is not pursuing the development or marketing of this formulation at present.

The firm certified that there are no patents for NDA 19-815 in the Orange book. However, there is an Orphan Drug exclusivity (for symptomatic orthostatic hypotension) which expires on September 6, 2003. The NCE exclusivity has expired on September 6, 2001. The firm acknowledged that it will not market the drug until after the expiration of the exclusivity.

10. PHARMACOL. CATEGORY:

Midodrine HCl is a blood pressure medication used in orthostatic hypotension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2.5 mg and 5 mg (Note: The 10 mg dosage form is not included)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

Chemistry Review Data Sheet

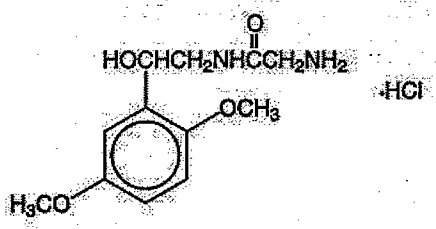
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT ETC.:

Midodrine hydrochloride (Brand Name: ProAmatine ®):



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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF file

Redacted 1

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

Chemistry Review Data Sheet

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application Number	Description
NDA for ProAmatine	19-815	Reference listed drug

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Microbiology	N/A		--
EES	Pending	-	Office of Compliance
Methods Validation	Pending	--	D. O'Brien
Labeling	Deficient	Dec 24, 02	J. Barlow
Bioequivalence	Pending	--	TBD
EA	N/A	--	--
Radiopharmaceutical	N/A	--	--

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes __X__ No If no, explain reason(s) below:

CHEMISTRY REVIEW

Chemistry Review Data Sheet

The Chemistry Review for ANDA 76-514

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry manufacturing and controls are not approvable. It is recommended that a "Not Approvable, MINOR letter" be sent to the applicant.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug is ProAmatine® Tablets manufactured by Shire Pharmaceuticals, Inc. (NDA no. 19-815). The active ingredient in ProAmatine Tablets is Midodrine HCl which is an anti-hypotensive drug. The molecular formula of Midodrine HCl is $C_{12}H_{18}N_2O_4HCl$; Molecular Weight: 290.7. Each 2.5 mg tablet of Midodrine HCl is a white (or reddish orange for 5 mg) round, flat face, with a beveled edge, and is scored. The tablet contains the following inactive ingredients: Pregelatinized starch 1500, Microcrystalline cellulose, Colloidal Silicon Dioxide, Magnesium stearate. Similarly, the 5 mg tablet contains all the above inactive ingredients and two coloring agents (FD&C Yellow #6 Aluminum Lake and FD&C Red #40 Aluminum Lake).

The package insert provides the information on labeling of the product. The dosage form, route of administration, indications and usage, active ingredient, potency and labeling for Midodrine HCl tablets are same as the ProAmatine tablets tablets. The firm has provided data on randomized, single-dose, two-way cross over bioequivalence study to compare Eon's as well as the reference listed Midodrine HCl 5 mg tablet under fasting conditions and fed conditions. Both bioequivalence and labeling reviews are pending.

The manufacturing, packaging and testing of the tablets are done at the applicant's facility at [redacted]. Size of the commercial batch is [redacted] for each strength of the product [redacted] tablets for each 2.5 mg and 5 mg strengths). The manufacturing process for the both strengths are the same. The manufacturing of Midodrine HCl Tablets involves [redacted] completion, the tablets (100's and 500's) are packaged in 60cc or 100 cc white HDPE bottle with plastic cap/liner and cotton as a filler. The packaged samples were evaluated for stability by storing at room temperature and at accelerated storage conditions.

The stability studies were conducted under a stability protocol that is conformance with the FDA stability guidance. At this time of the review, only up to three-month room temperature and accelerated stability data are available and the data are satisfactory. The firm has proposed a two-year expiration for the product.

Both the drug product and the drug substance are non-compendial items therefore require method validation by the FDA District Laboratory.

This ANDA is found to be deficient and the deficiencies are highlighted in bold letters in the text. Additionally, the DMF is found deficient. The deficiencies noted will be communicated to the applicant.

B. Description of How Drug Product is Intended for Use:

The recommended dose of Midodrine HCl is 10 mg, three times a day. The dosing should take place during day time when the patient needs to be upright, pursuing the activities of daily life. Single doses as high as 20 mg have been given to patients, severe and persistent systolic supine hypertension occurs at a high rate at this dose.

C. Basis for Approvability or Not-Approval Recommendation:

The Drug Master File for Midodrine HCl is deficient. Additionally, firm needs to resolve issues related to drug substance and drug product specifications and other deficiencies noted in the deficiency letter.

III. Administrative

A. Reviewer's Signature

/S/ Feb 14, 2003

B. Endorsement Block

Raj Bykadi, Ph.D./Chemist/ 1/27/03

Al Mueller, Ph.D./Chemistry Team Leader/1/28/03 /S/ Feb 14, 2003

C. Kiester, PM/ /S/ 2-14-03

\\CDS013\OGDS11\FIRMSAM\EON\LTRS&REV\76514CR01.doc

Redacted 36

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

ANDA 76-514

Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg

Eon Laboratories, Inc

Raj Bykadi, Ph.D
Division of Chemistry I

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. ANDA : 76-514
   (Note: First Generic Drug)

2. REVIEW #: 2

3. REVIEW DATE: April 25, 2003

4. REVIEWER: Raj Bykadi, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	26-Sept-2002
FDA Acknowledgement letter	19-Nov-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	14-Mar-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Eon Laboratories Inc
Address:	227-15 N. Conduit Avenue Laurelton, NY 11413
Representative:	Enna Krivitsky Manager Regulatory Affairs
Telephone:	Tel: (718) 276-8607, ext. 235 Fax: (718) 276-8635

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A

Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Midodrine Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION:

The legal basis for this ANDA submission is ProAmatine ® Tablets (NDA 19-815), reference listed drug (RLD) for Midodrine HCl tablets. The RLD is manufactured by Roberts Labs, Inc., a wholly owned subsidiary of Shire Pharmaceuticals. This drug is referenced on page 3-245 of the "Approved Drug Products With Therapeutic Equivalence Evaluations" (22nd edition) (Orange Book).

It is noted that the Shire Pharmaceuticals has listed a new dosage form, 10 mg tablet in supplement #7 of the Orange Book. Eon Laboratories is not pursuing the development or marketing of this formulation at present.

The firm certified that there are no patents for NDA 19-815 in the Orange book. However, there is an Orphan Drug exclusivity (for symptomatic orthostatic hypotension) which expires on September 6, 2003. The NCE exclusivity has expired on September 6, 2001. The firm acknowledged that it will not market the drug until after the expiration of the exclusivity.

10. PHARMACOL. CATEGORY:

Midodrine HCl is a blood pressure medication used in orthostatic hypotension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2.5 mg and 5 mg (Note: The 10 mg dosage form is not included)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

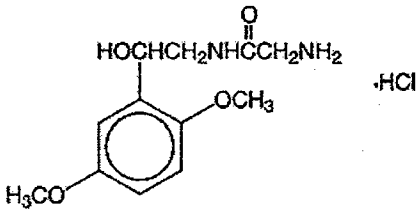
_____SPOTS product – Form Completed

___X__Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT ETC.:

Midodrine hydrochloride (Brand Name: ProAmatine ®):



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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF#	Type	Holder	Item referenced	Code[1]	Status[2]	Date review completed	Comments
[redacted]	II	[redacted]	[redacted]	1	Inadequate	25-April-2003	R. Bykadi
[redacted]	III	[redacted]	[redacted]				
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			

Chemistry Review Data Sheet

DMF#	Type	Holder	Item referenced	Code[1]	Status[2]	Date review completed	Comments
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application Number	Description

Chemistry Review Data Sheet

NDA for ProAmatine	19-815	Reference listed drug

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Microbiology	N/A		--
EES	Acceptable	12-Feb-2003	Office of Compliance
Methods Validation	Pending	--	D. O'Brien
Labeling	Satisfactory	April 8, 2003	J. Barlow
Bioequivalence	Satisfactory	Feb 21, 2003	H. Nguyen
EA (exclusion requested)	Acceptable	--	G. Bykadi
Radiopharmaceutical	N/A	--	--

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
Yes __X__ No If no, explain reason(s) below:

Chemistry Review Data Sheet

The Chemistry Review for ANDA 76-514

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Chemistry manufacturing and controls are not approvable. It is recommended that a "Not Approvable, MINOR letter" be sent to the applicant.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s) See review #1

B. Description of How Drug Product is Intended for Use:

The recommended dose of Midodrine HCl is 10 mg, three times a day. The dosing should take place during day time when the patient needs to be upright, pursuing the activities of daily life. Single doses as high as 20 mg have been given to patients, severe and persistent systolic supine hypertension occurs at a high rate at this dose.

C. Basis for Approvability or Not-Approval Recommendation:

The Drug Master File for Midodrine HCl is deficient. Additionally, firm needs to resolve issues related to drug substance and drug product specifications and other deficiencies noted in the deficiency letter.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
Raj Bykadi, Ph.D./Chemist/ April 25, 2003 /S/ 6-3-03
Al Mueller, Ph.D./Chemist/ Team Leader/ /S/ 6-6-03
C. Kiester, PM/ /S/ 6/6/03
\\CDS013\OGDS11\FIRMSAM\EON\LTRS&REV\76514CR02.doc

Redacted 26

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

ANDA 76-514

Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg

Eon Laboratories, Inc

Raj Bykadi, Ph.D
Division of Chemistry I

Chemistry Review Data Sheet

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. ANDA : 76-514
   (Note: First Generic Drug)

2. REVIEW #: 3

3. REVIEW DATE: July 15, 2003

4. REVIEWER: Raj Bykadi, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	26-Sept-2002
FDA Acknowledgement letter	19-Nov-2002
Minor Amendment	14-Mar-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	**June 20, 2003**
Telephone Amendment	**August 8, 2003**

7. NAME & ADDRESS OF APPLICANT:

Name:	Eon Labs, Inc.
Address:	227-15 N. Conduit Avenue Laurelton, NY 11413
Representative:	Sadle M. Ciganek Vice president Regulatory Affairs
Telephone:	Tel: (718) 276-8607, ext. 330 Fax: (718) 276-8635

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Midodrine Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION:

   The legal basis for this ANDA submission is ProAmatine ® Tablets (NDA 19-815), reference listed drug (RLD) for Midodrine HCl tablets. The RLD is manufactured by Roberts Labs, Inc., a wholly owned subsidiary of Shire Pharmaceuticals. This drug is referenced on page 3-245 of the "Approved Drug Products With Therapeutic Equivalence Evaluations" (22nd edition) (Orange Book).

   It is noted that the Shire Pharmaceuticals has listed a new dosage form, 10 mg tablet in supplement #7 of the Orange Book. Eon Laboratories is not pursuing the development or marketing of this formulation at present.

   The firm certified that there are no patents for NDA 19-815 in the Orange book. However, there is an Orphan Drug exclusivity (for symptomatic orthostatic hypotension) which expires on September 6, 2003. The NCE exclusivity has expired on September 6, 2001. The firm acknowledged that it will not market the drug until after the expiration of the exclusivity.

10. PHARMACOL. CATEGORY:

    Midodrine HCl is a blood pressure medication used in orthostatic hypotension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2.5 mg and 5 mg (Note: The 10 mg dosage form is not included)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

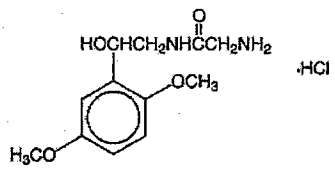
    _____SPOTS product – Form Completed

    ___X__Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT ETC.:

Midodrine hydrochloride (Brand Name: ProAmatine ®):
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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF#	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
	II			1	Adequate	17-July-2003	R. Bykadi
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

Chemistry Review Data Sheet

DMF#	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application Number	Description
NDA for ProAmatine	19-815	Reference listed drug

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Microbiology	N/A		--

Chemistry Review Data Sheet

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
EES	Acceptable	12 Feb, 2003	Office of Compliance
Methods Validation	Requested (memo sent on July 18, 2003)	July 18, 2003	D. O'Brien
Labeling	Satisfactory	April 8, 2003	J. Barlow
Bioequivalence	Satisfactory	Feb 21, 2003	H. Nguyen
EA (exclusion requested)	Acceptable	--	G. Bykadi
Radiopharmaceutical	N/A	--	--

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
Yes __X__ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

The Chemistry Review for ANDA 76-514

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry manufacturing and controls are approvable. It is recommended that an "Approvable letter" be sent to the applicant.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug is ProAmatine® Tablets manufactured by Shire Pharmaceuticals, Inc. (NDA no. 19-815). The active ingredient in ProAmatine Tablets is Midodrine HCl which is an anti-hypotensive drug. The molecular formula of Midodrine HCl is $C_{12}H_{18}N_2O_4HCl$; Molecular Weight: 290.7. Each 2.5 mg tablet of Midodrine HCl is a white (or reddish orange for 5 mg) round, flat face, with a beveled edge, and is scored. The tablet contains the following inactive ingredients: Pregelatinized starch 1500, Microcrystalline cellulose, Colloidal Silicon Dioxide, Magnesium stearate. Similarly, the 5 mg tablet contains all the above inactive ingredients and two coloring agents (FD&C Yellow #6 Aluminum Lake and FD&C Red #40 Aluminum Lake).

The package insert provides the information on labeling of the product. The dosage form, route of administration, indications and usage, active ingredient, potency and labeling for Midodrine HCl tablets are same as the ProAmatine tablets. The firm has provided data on randomized, single-dose, two-way cross over bioequivalence study to compare Eon's as well as the reference listed Midodrine HCl 5 mg tablet under fasting conditions and fed conditions.

The manufacturing, packaging and testing of the tablets are done at the applicant's facility at [redacted] Size of the commercial batch is [redacted] for each strength of the product ([redacted] tablets for each 2.5 mg and 5 mg strengths). The manufacturing processes for the both strengths are the same. The manufacturing of Midodrine HCl Tablets involves [redacted] Upon completion, the tablets (100's and 500's) are packaged in 60cc or 100 cc white HDPE bottle with plastic cap/liner and cotton as a filler. The packaged samples were evaluated for stability by storing at room temperature and at accelerated storage conditions.

The stability studies were conducted under a stability protocol that is conformance with the FDA stability guidance. The accelerated and room temperature stability data generated are satisfactory. The firm has proposed a two-year expiration for the product.

B. Description of How Drug Product is Intended for Use

The recommended dose of Midodrine HCl is 10 mg, three times a day. The dosing should take place during day time when the patient needs to be upright, pursuing the activities of daily life. Single doses as high as 20 mg have been given to patients, severe and persistent systolic supine hypertension occurs at a high rate at this dose.

C. Basis for Approvability or Not-Approval Recommendation

The firm addressed all the CMC issues and the CMC section is complete. There are no issues with Drug Master File. Bioequivalence and Labeling are satisfactory. Overall recommendation for EER is acceptable. The 12-month room temperature stability data are with out any issues. The firm intends to increase the exhibit batch size (———) for future commercial production. The manufacturing procedure and components for the bio-batch and the scale-up batches are the same.

III. Administrative

A. Reviewer's Signature /S/ Aug 29, 2003

B. Endorsement Block

HFD-623/Raj Bykadi, Ph.D./Chemistry Reviewer/8/15/03 /S/ Aug 29, 2003
HFD-623/Al Mueller, Ph.D./Team Leader/8/15/03 FOR /S/ 8/29/03
HFD-617/C. Kiester, Project Manager/8/29/03 /S/ 9/3/03

V:\FIRMSAM\EON\LTRS&REV\76514.REV3.doc

Redacted 14

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-514

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-514 SPONSOR : Eon Laboratories
DRUG AND DOSAGE FORM : Midodrine HCl Tablets
STRENGTH(S) : 2.5 mg & 5 mg
TYPES OF STUDIES : Fasting Study & Non-Fasting Study (5 mg)
CINICAL STUDY SITE(S) : ———
ANALYTICAL SITE(S) : ———

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable
WAIVER REQUEST: Acceptable

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : hn DATE : 2/7/03

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 2/10/2003

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

INITIAL : BNC DATE : 2/21/03

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-514
Drug Product Name	Midodrine HCl Tablets
Strength	2.5 mg & 5 mg
Applicant Name	Eon Laboratoreis
Address	Laurelton, NY
Submission Date(s)	September 26, 2002
Amendment Date(s)	N/A
Reviewer	Hoainhon Nguyen
File Location	c:\firmsam\eon\ltrs&rev\76514n0902.doc

I. Executive Summary

The firm has submitted a single-dose fasting bioequivalence study and a single-dose nonfasting bioequivalence study comparing the firm's Midodrine HCl Tablets, 5 mg, with the RLD product, ProAmatine Tablets, 5 mg, manufactured by Shire Pharmaceuticals. The firm has also submitted comparative dissolution data for all strengths of the test and reference products, and a biowaiver request for the lower strength, 2.5 mg, based on the formulation proportionality and comparable dissolution profiles. The studies and dissolution data were found acceptable. The submitted formulations of the test product were found acceptable. The biowaiver request is granted. The test product, 5 mg, is deemed bioequivalent to the RLD product, 5 mg, under fasting and nonfasting conditions. The test product, 2.5 mg, is also deemed bioequivalent to the RLD product, 2.5 mg.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product Eon's Midodrine HCl Tablets, 5 mg Lot# RDW00062
Reference Product ProAmatine (NDA # 19-815, Shire Pharmaceuticals, Approved 09/06/96) Lot # 210541
Indication indicated in the treatment of symptomatic orthostatic hypotension.

PK/PD Information

Bioavailability: 93% (measured as desglymidodrine)

Metabolism: Midodrine is a prodrug. Deglycination of midodrine to desglymidodrine takes place in many tissues, and both compounds are metabolized in part by the liver.

Half Life: approximately 25 minutes for midodrine, and 3 to 4 hours for desglymidodrine

Tmax: 30 minutes for midodrine, and 1 to 2 hours for desglymidodrine

Excretion: insignificant renal elimination for midodrine, and active renal secretion for desglymidodrine

Food Effect: The bioavailability of desglymidodrine is not affected by food.

Relevant DBE History: This is not the **First Generic** product. However, there is currently no other ANDA review for the drug product on file. The reviews for both Control Documents # 01-195 (Bioassay; 04/16/01) and 01-266 (Upsher-Smith; 05/04/01) recommended that a single-dose fasting and a single-dose nonfasting bio studies be conducted for the drug product, that a biowaiver be granted based on formulation proportionality and dissolution comparability, and that only the parent midodrine be measured for the studies. Control Document #02-174 (Barr; 08/08/02) raised the question of whether midodrine should be classified as a BCS Class I drug. The review of this Control Document is pending.

B. Contents of Submission

			How many?
Single-dose fasting study	X		1
Single-dose fed study	X	1	
In vitro dissolution testing	X		1
Waiver requests	X		1

C. Bioanalytical Method Validation (Pre-Study, Vol. C1.2 Pages. 2191-2281)

[ ]

D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study No. R01-921
Study Design randomized, 2-way crossover
No. of subjects enrolled 30
No. of subjects completing 30
No. of subjects analyzed 30
Subjects
Sex(es) included (how many?) Male 20 Female 10
Test product Eon's Midodrine HCl Tablets, 5 mg, Lot # RDW00062
Reference product Shire's ProAmatine Tablets , 5 mg, Lot # 210541
Strength tested 5 mg
Dose 2x5 mg

Summary of Statistical Analysis

Parameter	Point Estimate	90% Confidence Interval
LAUCt	97.0	92.5-102
LAUCi	97.0	92.6-102
LCmax	101	89.7-115

The study is acceptable.

2. Single-dose Fed Bioequivalence Study

Study No. R01-922
Study Design randomized, 2-way crossover
No. of subjects enrolled 24
No. of subjects completing 23
No. of subjects with samples analyzed 23
Subjects
Sex(es) included (how many) Male 12 Female 12
Test product Eon's Midodrine HCl Tablets, 5 mg, Lot # RDW00062
Reference product Shire's ProAmatine Tablets, 5 mg, Lot # 210541
Strength tested 5 mg
Dose 2x5 mg

Summary of Statistical Analysis:

Parameter	Point Estimate	90% Confidence Interval
AUCt	98.8	94.5-103
AUCi	98.8	94.7-103
Cmax	105	89.6-122

The study is acceptable

E. Formulation

The test product formulation is shown in the Appendix.
Inactive Ingredients within IIG limits Yes
The formulation is acceptable Yes

F. In Vitro Dissolution

Methods Submitted FDA's Method (NDA 19-815 submission dated 04/12/01)
Medium 0.1 N HCl
Volume (mL) 900 mL
USP Apparatus Type II (paddle)
Rotation (rpm) 50
FDA-recommended specifications —› dissolved in 15 minutes
F2- value (s): not determined due to fast dissolution rate
In vitro dissolution is acceptable.

G. Waiver Request

The applicant requests a waiver of in vivo bioequivalence testing under 21 CFR 320.22(b)(2) for the following strength: 2.5 mg

The formulation is proportionally similar to that of the 5 mg strength which underwent acceptable in vivo testing.

Dissolution testing of all strengths is acceptable.

H. Deficiency Comments None

I. Recommendations

1. The single-dose, fasting bioequivalence study and the single-dose nonfasting bioequivalence study conducted by Eon Laboratories on the test product, Midodrine HCl Tablets, 5 mg, lot # RDW00062, comparing it with the reference product, Shire's ProAmatine Tablets, 5 mg, lot # 210541, have been found **acceptable** by the Division of Bioequivalence. The test product, Eon's Midodrine HCl Tablets, 5 mg, is deemed bioequivalent to the reference product, Shire's ProAmatine Tablets, 5 mg, under fasting and nonfasting conditions.

2. The in-vitro dissolution testing conducted by Eon Laboratories on its Midodrine HCl Tablets, 5 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 NHCl at 37°C using USP apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

Not less than '—› of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

3. The in-vitro testing conducted by Eon Laboratories on its Midodrine HCl Tablets, 2.5 mg, has been found acceptable. The formulation of the 2.5 mg strength of the test product has been shown to be proportionally similar to the 5 mg strength which underwent acceptable in-vivo bioequivalence testing. The biowaiver request for the 2.5 mg strength of the test product is granted. The test product, Eon's

Midodrine HCl Tablets, 2.5 mg, is deemed bioequivalent to the reference product, Shire's ProAmatine Tablets, 2.5 mg.

/S/ 2/7/03
Hoainhon Nguyen, Review Branch I

/S/ 2/10/2003
Yih Chain Huang
Team Leader, Review Branch I

/S/ 2/12/03
for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Hnguyen/01-30-03/W#76514n0902.doc/Final 02-07-03

APPEARS THIS WAY
ON ORIGINAL

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study (R01-921): A Relative Bioavailability Study of 5 mg Midodrine HCl Tablets Under Fasting Conditions

Study Information

Study Number R01-921
Clinical Site [redacted]
Principal Investigator [redacted]
Study/Dosing Dates 05/26/02 to 06/02/02
Analytical Site [redacted]
Analytical Director [redacted]
Analysis Dates 06/14/02 to 07/16/02
Storage Period 51 days (between the day the first sample was collected and the day the last sample was analyzed).

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Midodrine HCl Tablets	ProAmatine Tablets
Manufacturer	Eon	Shire
Batch/Lot No.	RDW00062	210541
Manufacture Date	04/2002	
Expiration Date	N/A	02/2004
Strength	5 mg	5 mg
Dosage Form	Tablets	Tablets
Batch Size	[redacted]	
Production Size	[redacted]	
Potency	98.7%	100.1%
Content Uniformity	98.7%(RSD=1.2%)	99.4%(RSD=2.3%)
Formulation	See Appendix	
Dose Administered	2x5 mg	
Route of Administration	Oral	

No. of Sequences		2	
No. of Periods		2	
No. of Treatments	2	**Balanced**	yes
No. of Groups/Sequence	1	**Washout Period**	7 days
Randomization Scheme		Yes	
Blood Sampling Times		Predose, 5, 10, 15, 20, 30 and 45 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 hours	
Blood Volume Collected/Sample		7 mL/sample	
Blood Sample Processing/Storage		In EDTA vacutainers, plasma separated after centrifuging, and stored at –20C	

IRB Approval Yes
Informed Consent Yes
Subjects Demographics See below
Length of Fasting 10 hours predose until 4 hours postdose
Length of Confinement 10 hours predose until 5 hours postdose
Safety Monitoring Vital signs (sitting blood pressure and radial heart rate) measured prior to dosing and at 2, 3, 4, and 5 hours postdose.

Subjects Demographics

Age		Age Groups		Gender		Race		Weight (kg)	
		Range	%	Sex		Category	%		
		<18	0			Caucasian	93		
Mean	22.7	18-40	97	Male	20	Afr. Amer.	0	Mean	72.2
SD	5.0	41-64	3	Female	10	Hispanic	0	SD	11.4
Range	18-47	65-75	0			Asian	0	Range	49-93
		>75	0			Others	7		

Study Results

Clinical: The firm's clinical summary is provided on Pages 1003-1016, Vol. C1.4

Dropout Information No dropouts

Adverse Events # Total events possibly/probably drug related: 8 (paresthesia (tingling head))
received Treatment A: 4
received Treatment B: 4
All others unrelated to study medication: 7
For additional information see Vol. C1.3, pages # 2670-2671

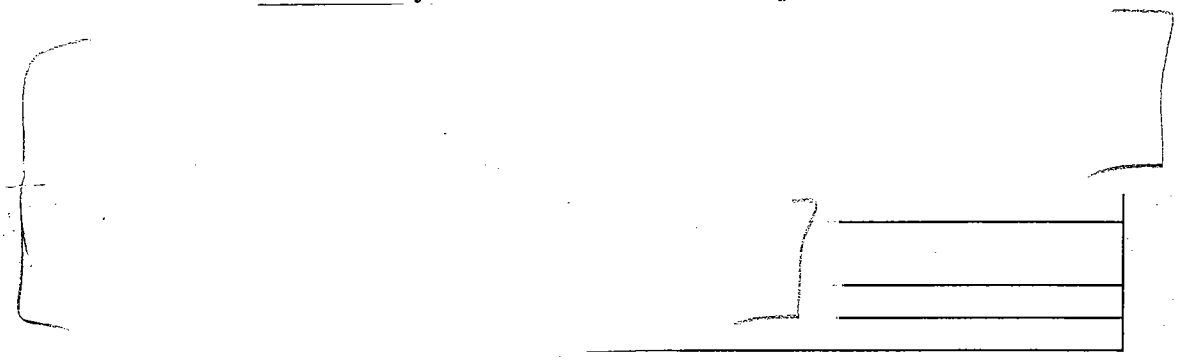
Protocol Deviations

Deviations in blood sampling times: 13 samples with deviated sampling times (not greater than ±4 minutes) Corrections were made in the calculations for the few deviations that were more than ±2 minutes from the target times as reported by the clinic (5 deviations).

Other Deviations: Repeat vital sign measurements were requested for 6 subjects. Hematology laboratory test results were outside the reference range at screening for 4 subjects, and at exit for 4 subjects. Chemistry laboratory test results were outside the reference range at screening for 4 subjects, and at exit for 16 subjects. None of the above deviations were judged clinically significant by the study investigator.

Comments: None of the above adverse events or protocol deviations were judged clinically significant by the study investigator.

Assay Validation - Within Study



Repeat Assays:

SOPs (Vol. C1.2, Pages 2301-2304) The SOP #L200.107 specified reasons for reassaying of samples. The reason of "Unknown Processing Error" is not well defined. There were 15 samples reassayed for "Unknown Processing Error" in addition to samples that were reassayed for valid analytical reasons. The data were reanalyzed by the reviewer using the original values of these reassay samples of "Unknown Processing Error". The results of the reanalysis showed that the reassay of these samples had no significant impact on the study outcome, as seen in the 90% confidence intervals calculated by the reviewer.

Number of Samples Re-assayed: 64 (6.3%, for analytical reasons), 15 (for other reasons)

Number of Pharmacokinetic Repeats: None

Impact of Repeat-assays on the study outcome: Not significant (See PK parameter summary table)

Chromatograms: No significant interfering peaks observed.

Comments: (on analytical study) The highest observed CMAX was [redacted]. Selection of concentration range of QCs (including diluted QCs) and standard curves was therefore acceptable.

Conclusion: Analytical method is acceptable.

Pharmacokinetic/Statistical Analysis

Mean Plasma Concentrations	Table #1&2, Figure #1 (Attachments)
AUCt/AUCi ratio	Tables # 3& 4 (Attachments)

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

A. Arithmetic Mean Pharmacokinetic Parameters

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	40.15	26	41.31	25	0.97
AUCi	Ng.hr/mL	40.60	25	41.76	24	0.97
Cmax	ng/mL	50.61	36	49.49	34	1.02
Tmax	Hrs	0.549	55	0.535	50	1.03
T1/2	hrs	0.433	22	0.458	26	0.94
Kel	hrs^{-1}	1.66	15	1.58	18	1.05

B. Geometric Mean and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	38.92	40.14	0.97	92.5-102
AUCi	39.39	40.60	0.97	92.6-102
Cmax	47.16	46.55	1.01	89.7-115

C. Total SD and within-subject error (root MSE): Values are shown below (for ln-transformed AUCt and Cmax only)

	lnCmax	lnAUCt
Root MSE, test & ref combined	0.27861	0.10729

Individual Subject AUCt, AUCi and Cmax data with Per and SEQ: Tables # 5&6 (Attachments)

Comments: (on pharmacokinetic analysis)

ALWAYS include the comments below. Other comments may be listed if appropriate.

- Ke and AUCi were determined for all subjects.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as Tmax: None
  c. first measurable drug concentration as Cmax: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations: Yes. Reviewer's 90% CI for lnAUCT, lnAUCI and lnCMAX were [0.92; 1.01], [0.91; 1.01], and [0.90;1.15], respectively.
- Were there statistically significant sequence or period effects? No
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%: Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect: N/A

Conclusion: The single-dose fasting bioequivalence study is acceptable.

2. Single-dose Nonfasting Bioequivalence Study (R01-922): A Relative Bioavailability Study of 5 mg Midodrine HCl Tablets Under Nonfasting Conditions

Study Information

Study Number R01-922
Clinical Site [redacted]
Principal Investigator [redacted]
Study/Dosing Dates 07/16/02 to 07/23/02
Analytical Site [redacted]
Analytical Director [redacted]
Analysis Dates 08/05/02 to 08/21/02
Storage Period 36 days (between the day the first sample was collected and the day the last sample was analyzed).

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Midodrine HCl Tablets	ProAmatine Tablets
Manufacturer	Eon	Shire
Batch/Lot No.	RDW00062	210541
Manufacture Date	04/2002	
Expiration Date		02/2004
Strength	5 mg	5 mg
Dosage Form	Tablets	Tablets
Batch Size	[redacted]	
Production Size	[redacted]	
Potency	98.7%	100.1%
Content Uniformity	98.7%(RSD=1.2%)	99.4%(RSD=2.3%)
Formulation	See Appendix	
Dose Administered	2x5 mg	
Route of Administration	Oral	
No. of Sequences	2	
No. of Periods	2	
No. of Treatments	2	**Balanced** yes
No. of Groups/Sequence	1	**Washout Period** 7 days
Randomization Scheme	Yes	
Blood Sampling Times	Predose, 5, 10, 15, 20, 30 and 45 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 hours	
Blood Volume Collected/Sample	7 mL/sample	
Blood Sample Processing/Storage	In EDTA vacutainers, plasma separated after centrifuging, and stored at –20C	
IRB Approval	Yes	
Informed Consent	Yes	
Subjects Demographics	See below	

Length of Fasting 10 hours prior to a standardized breakfast* which was given 30 minutes predose.

Length of Confinement 10 hours predose until 5 hours postdose

Safety Monitoring Vital signs (sitting blood pressure and radial heart rate) measured prior to dosing and at 2, 3, 4, and 5 hours postdose.

*Standardized breakfast included one buttered English muffin, one slice of American cheese, one serving of hash brown potatoes, one fried egg, one slice of Canadian bacon, 240 mL of whole milk and 180 mL of orange juice.

Subjects Demographics

Age		Age Groups		Gender		Race		Weight (kg)	
		Range	%	Sex		Category	%		
		<18	0			Caucasian	100		
Mean	29.5	18-40	79	Male	12	Afr. Amer.	0	Mean	75.6
SD	10.7	41-64	21	Female	12	Hispanic	0	SD	12.9
Range	18-50	65-75	0			Asian	0	Range	59-98
		>75	0			Others	0		

Study Results

Clinical: The firm's clinical summary is provided on Pages 3793-38-06, Vol. C1.5

Dropout Information Subject #16 withdrew for personal reasons prior to Period II

Adverse Events

Total events possibly/probably drug related: 3 (backache, fatigue and scalp tingling)
received Treatment A: 3
received Treatment B: 0
All others unrelated to study medication: 4
For additional information see Vol. C1.5, pages # 3873-3874

Protocol Deviations

Deviations in blood sampling times: 12 samples with deviated sampling times (not greater than ±4 minutes) Corrections were made in the calculations for the few deviations that were more than ±2 minutes from the target times as reported by the clinic (2 deviations).

Other Deviations: Repeat blood pressure and heart rate measurements were requested for 1 subject. Hematology laboratory test results were outside the reference range at screening for 2 subjects, and at exit for 3 subjects. Chemistry laboratory test results were outside the reference range at screening for 9 subjects, and at exit for 6 subjects. None of the above deviations were judged clinically significant by the study investigator.
One subject was given topical Anti-Itch Lotion on Study Days 4, 5, 6 and 7 for Poison Ivy Rash.

Comments: None of the above adverse events or protocol deviations were judged clinically significant by the study investigator.

Assay Validation - Within Study

Repeat Assays:

SOPs (Vol. C1.4, Pages 3569-3570) The SOP #L200.107 specified reasons for reassaying of samples. The reason of "Unknown Processing Error" is not well defined. However, no samples were reassayed for "Unknown Processing Error".

Number of Samples Re-assayed: 11 (for analytical reasons)

Number of Pharmacokinetic Repeats: None

Impact of Repeat-assays on the study outcome: None

Chromatograms: No significant interfering peaks observed.

Comments: (on analytical study) The highest observed CMAX was [redacted]. Selection of concentration range of QCs (including diluted QCs) and standard curves was therefore acceptable.

Conclusion: Analytical method is acceptable.

Pharmacokinetic/Statistical Analysis

Mean Plasma Concentrations Table #7 & 8, Figure #2 (Attachments)

AUCt/AUCi ratio Tables # 9 & 10 (Attachments)

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

A. Arithmetic Mean Pharmacokinetic Parameters

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	47.42	24	48.43	24	0.98
AUCi	Ng.hr/mL	48.88	24	49.58	24	0.99
Cmax	Ng/mL	33.00	44	30.49	31	1.08
Tmax	Hrs	0.859	57	1.109	59	0.77
T1/2	hrs	0.643	23	0.672	24	0.96
Kel	hrs^{-1}	1.125	20	1.076	19	1.05

B. Geometric Mean and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	46.41	46.97	0.99	94.5-103
AUCi	47.52	48.08	0.99	94.7-103
Cmax	30.22	28.89	1.05	89.6-122

C. Total SD and within-subject error (root MSE): Values are shown below (for ln-transformed AUCt and Cmax only)

	LnCmax	lnAUCt
Root MSE, test & ref combined	0.30462	0.08682

Individual Subject AUCt, AUCi and Cmax data with Per and SEQ: Tables #11 & 12 (Attachments)

Comments: (on pharmacokinetic analysis)

ALWAYS include the comments below. Other comments may be listed if appropriate.

- Ke and AUCi were determined for all subjects.
- Indicate the number of subjects with the following:
  d. measurable drug concentrations at 0 hr: None
  e. first scheduled post-dose sampling time as Tmax: None
  f. first measurable drug concentration as Cmax: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations: Yes. Reviewer's 90% CI for lnAUCT, lnAUCI and lnCMAX were[0.95; 1.04], [0.94; 1.03] and [0.90;1.22], respectively.
- Were there statistically significant sequence or period effects? No
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%: Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect: N/A

Conclusion: The single-dose nonfasting bioequivalence study is acceptable.

Dissolution Data

Sampling Time (min.)	Test Product, Eon's Strength 5 mg Lot No. RDW00062			Reference Product, ProAmatine Strength 5 mg Lot No. 210541		
	Mean	%CV	Range	Mean	%CV	Range
5	98.7	0.8		97.0	1.8	
10	99.2	0.8		98.7	1.7	
15	99.1	0.8		99.4	1.7	
20	99.2	0.8		99.7	1.7	

Sampling Time (min.)	Test Product, Eon's Strength 2.5 mg Lot No. RDW00063			Reference Product, ProAmatine Strength 2.5 mg Lot No. 210221		
	Mean	%CV	Range	Mean	%CV	Range
5	96.4	2.4		79.4	6.6	
10	97.8	2.1		87.7	2.9	
15	98.0	2.1		90.0	2.4	
20	98.0	2.1		90.9	2.6	

APPEARS THIS WAY
ON ORIGINAL

B. Attachments

Table I
Comparative Mean Plasma Levels of Midodrine
Dose=2x5 mg; n=30
ng/mL
Fasting/Single-Dose Study

MIDODRINE HCl 5 MG TABLET FASTING STUDY
EON R01-921
MIDODRINE DATA
ARITHMETIC MEANS BY PRODUCT

PRODUCT=A:TEST

The MEANS Procedure

Variable	Label	N	Mean	Std Dev	Coeff of Variation
AUCTLQC		30	40.148	10.272	25.586
AUCINF		30	40.605	10.282	25.323
CMAX		30	50.613	18.055	35.672
TMAX		30	0.549	0.303	55.176
KELM		30	1.655	0.258	15.598
THALF		30	0.433	0.096	22.279
LAUCTLQC		30	3.662	0.253	6.911
LAUCINF		30	3.674	0.250	6.811
LCMAX		30	3.854	0.402	10.435
C1	0.00 HR	30	0.000	0.000	.
C2	0.083 HR	30	1.257	2.030	161.521
C3	0.167 HR	30	12.571	13.374	106.387
C4	0.25 HR	30	28.316	21.484	75.872
C5	0.333 HR	30	37.584	22.618	60.181
C6	0.50 HR	30	41.768	21.383	51.194
C7	0.75 HR	30	30.255	12.239	40.451
C8	1.00 HR	30	20.553	8.989	43.736
C9	1.25 HR	30	14.216	7.233	50.884
C10	1.50 HR	30	9.136	4.825	52.819
C11	2.00 HR	30	4.264	2.494	58.474
C12	2.50 HR	30	2.049	1.404	68.507
C13	3.00 HR	30	0.842	0.628	74.611
C14	3.50 HR	30	0.242	0.359	148.317
C15	4.00 HR	30	0.051	0.195	380.852
C16	4.50 HR	30	0.017	0.091	547.723
C17	5.00 HR	30	0.000	0.000	.

Table II

Comparative Mean Plasma Levels of Midodrine
Dose=2x5 mg; n=30
ng/mL

Fasting/Single-Dose Study

MIDODRINE HCl 5 MG TABLET FASTING STUDY
EON R01-921
MIDODRINE DATA
ARITHMETIC MEANS BY PRODUCT

PRODUCT=B:REFERENCE

The MEANS Procedure

Variable	Label	N	Mean	Std Dev	Coeff of Variation
AUCTLQC		30	41.306	10.199	24.691
AUCINF		30	41.761	10.235	24.508
CMAX		30	49.490	16.986	34.322
TMAX		30	0.535	0.270	50.503
KELM		30	1.582	0.278	17.557
THALF		30	0.458	0.121	26.376
LAUCTLQC		30	3.692	0.242	6.554
LAUCINF		30	3.704	0.240	6.480
LCMAX		30	3.840	0.364	9.490
C1	0.00 HR	30	0.000	0.000	.
C2	0.083 HR	30	3.166	5.201	164.293
C3	0.167 HR	30	17.437	18.790	107.758
C4	0.25 HR	30	28.458	21.718	76.317
C5	0.333 HR	30	36.017	21.908	60.826
C6	0.50 HR	30	39.085	18.364	46.986
C7	0.75 HR	30	30.572	11.243	36.775
C8	1.00 HR	30	20.957	8.290	39.559
C9	1.25 HR	30	15.409	8.318	53.979
C10	1.50 HR	30	10.356	6.123	59.124
C11	2.00 HR	30	4.587	2.832	61.743
C12	2.50 HR	30	2.186	1.432	65.517
C13	3.00 HR	30	0.992	0.740	74.656
C14	3.50 HR	30	0.387	0.472	121.865
C15	4.00 HR	30	0.108	0.246	229.011
C16	4.50 HR	30	0.018	0.099	547.723
C17	5.00 HR	30	0.000	0.000	.

Figure 1

Fasting Study No. R01-921

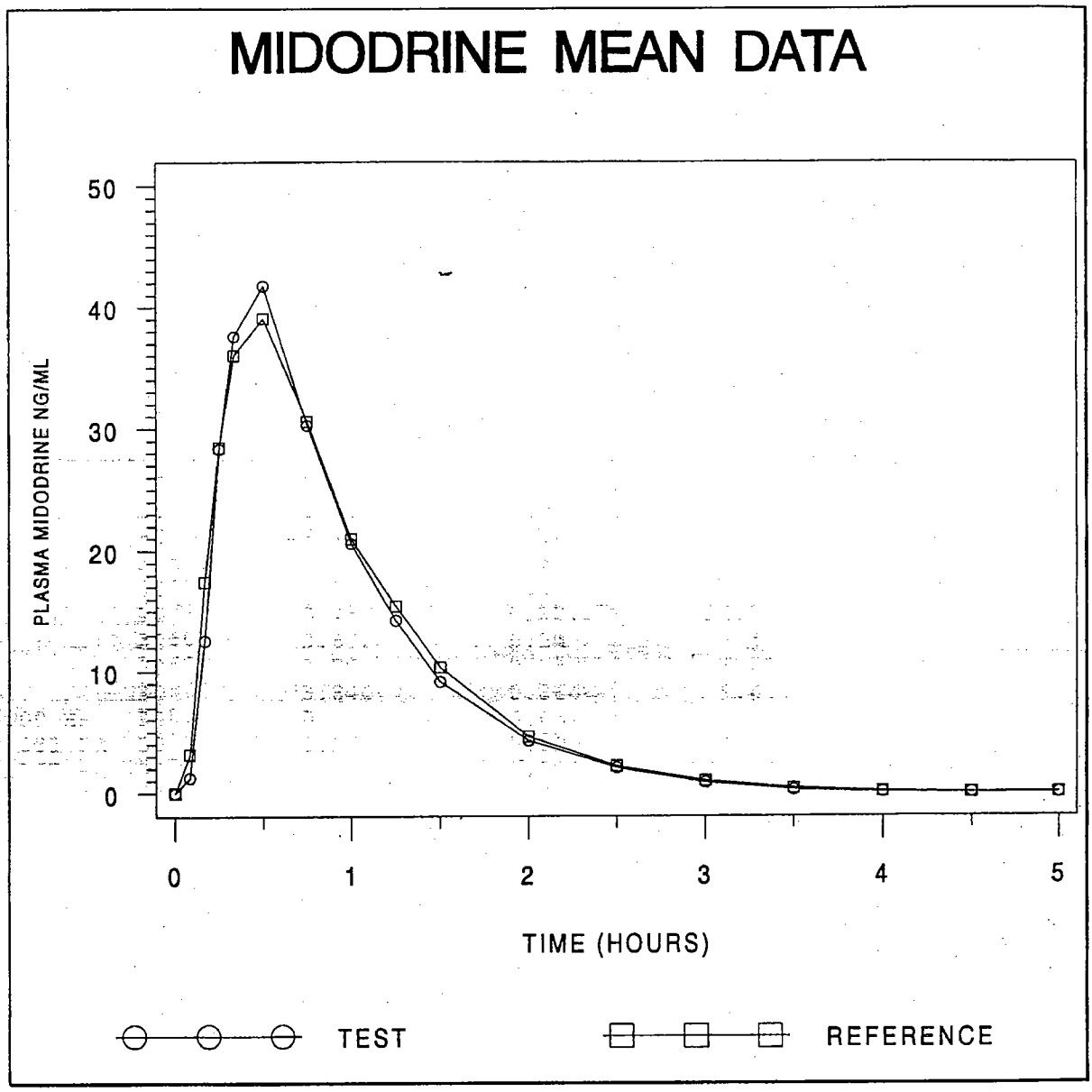


Table III

Test Product's Individual AUCT/AUCI Ratios

Fasting Study No. R01-921

SUBJECT	AUCT Ng.hr/mL	AUCI Ng.hr/mL	AUCT/AUCI
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
MEAN	40.15	40.61	0.99
SDEV	10.27134	10.279	0.00434
CV%	25.58455	25.314	0.43927
MIN			
MAX			

Table IV
Reference Product's Individual AUCT/AUCI Ratios
Fasting Study No. R01-921

SUBJECT	AUCT Ng.hr/mL	AUCI Ng.hr/mL	AUCT/AUCI
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
MEAN	41.31	41.76	0.99
STDEV	10.204304	10.2344	0.003198989
CV%	24.701778	24.5058	0.323567995
MIN			
MAX			

Table V
Fasting Study No. R01-921
Individual AUCT, AUCI & CMAX
Test Product

SUBJECT	PERIOD	SEQUENCE	AUCT Ng.hr/mL	AUCI Ng.hr/mL	CMAX Ng/mL
1	1	1			
2	2	2			
3	1	1			
4	1	1			
5	2	2			
6	1	1			
7	2	2			
8	2	2			
9	1	1			
10	2	2			
11	1	1			
12	2	2			
13	1	1			
14	2	2			
15	2	2			
16	2	2			
17	1	1			
18	1	1			
19	1	1			
20	2	2			
21	1	1			
22	2	2			
23	2	2			
24	2	2			
25	1	1			
26	2	2			
27	1	1			
28	1	1			
29	2	2			
30	1	1			

Table VI
Fasting Study No. R01-921
Individual AUCT, AUCI & CMAX
Reference Product

SUBJECT	PERIOD	SEQUENCE	AUCT Ng.hr/mL	AUCI Ng.hr/mL	CMAX Ng/mL
1	2	1			
2	1	2			
3	2	1			
4	2	1			
5	1	2			
6	2	1			
7	1	2			
8	1	2			
9	2	1			
10	1	2			
11	2	1			
12	1	2			
13	2	1			
14	1	2			
15	1	2			
16	1	2			
17	2	1			
18	2	1			
19	2	1			
20	1	2			
21	2	1			
22	1	2			
23	1	2			
24	1	2			
25	2	1			
26	1	2			
27	2	1			
28	2	1			
29	1	2			
30	2	1			

Table VII
Comparative Mean Plasma Levels of Midodrine
Dose=2x5 mg; n=23
ng/mL
Nonfasting/Single-Dose Study

MIDODRINE HCl 5 MG TABLET FOOD STUDY
EON R01-922
MIDODRINE DATA
ARITHMETIC MEANS BY PRODUCT

---------- PRODUCT=A:TEST FED ----------

The MEANS Procedure

Variable	Label	N	Mean	Std Dev	Coeff of Variation
AUCTLQC		23	47.724	11.311	23.700
AUCINF		23	48.880	11.610	23.752
CMAX		23	33.004	14.542	44.060
TMAX		23	0.859	0.486	56.553
KELM		23	1.125	0.220	19.509
THALF		23	0.643	0.150	23.354
LAUCTLQC		23	3.838	0.241	6.287
LAUCINF		23	3.861	0.244	6.313
LCMAX		23	3.413	0.411	12.044
C1	0.00 HR	23	0.000	0.000	.
C2	0.083 HR	23	0.216	0.620	287.707
C3	0.167 HR	23	3.586	5.163	143.958
C4	0.25 HR	23	10.437	11.646	111.586
C5	0.333 HR	23	15.995	14.283	89.293
C6	0.50 HR	23	24.220	19.300	79.686
C7	0.75 HR	23	24.812	15.448	62.261
C8	1.00 HR	23	21.691	8.720	40.198
C9	1.25 HR	23	19.704	7.528	38.204
C10	1.50 HR	23	16.743	6.019	35.953
C11	2.00 HR	23	12.252	5.425	44.280
C12	2.50 HR	23	9.003	5.061	56.216
C13	3.00 HR	23	5.600	3.954	70.613
C14	3.50 HR	23	3.314	2.763	83.390
C15	4.00 HR	23	1.873	1.586	84.647
C16	4.50 HR	23	1.169	1.408	120.434
C17	5.00 HR	23	0.656	1.094	166.774

Table VIII
Comparative Mean Plasma Levels of Midodrine
Dose=2x5 mg; n=23
ng/mL
Nonfasting/Single-Dose Study

MIDODRINE HCl 5 MG TABLET FOOD STUDY
EON R01-922
MIDODRINE DATA
ARITHMETIC MEANS BY PRODUCT

PRODUCT=B:REFERENCE FED

The MEANS Procedure

Variable	Label	N	Mean	Std Dev	Coeff of Variation
AUCTLQC		23	48.432	11.809	24.383
AUCINF		23	49.576	12.118	24.443
CMAX		23	30.491	9.467	31.049
TMAX		23	1.109	0.656	59.203
KELM		23	1.076	0.202	18.777
THALF		23	0.672	0.162	24.076
LAUCTLQC		23	3.850	0.254	6.591
LAUCINF		23	3.873	0.256	6.604
LCMAX		23	3.366	0.341	10.127
C1	0.00 HR	23	0.000	0.000	.
C2	0.083 HR	23	0.959	1.826	190.352
C3	0.167 HR	23	6.767	11.988	177.147
C4	0.25 HR	23	11.674	16.691	142.976
C5	0.333 HR	23	12.962	15.796	121.861
C6	0.50 HR	23	14.662	13.120	89.482
C7	0.75 HR	23	16.882	9.872	58.480
C8	1.00 HR	23	18.750	7.765	41.415
C9	1.25 HR	23	19.190	7.616	39.688
C10	1.50 HR	23	18.951	8.073	42.599
C11	2.00 HR	23	15.169	6.926	45.662
C12	2.50 HR	23	11.594	6.340	54.686
C13	3.00 HR	23	7.268	4.637	63.803
C14	3.50 HR	23	4.237	2.822	66.611
C15	4.00 HR	23	2.359	1.603	67.922
C16	4.50 HR	23	1.587	1.531	96.520
C17	5.00 HR	23	0.915	0.916	100.111

Figure 2
Nonfasting Study No. R01-922

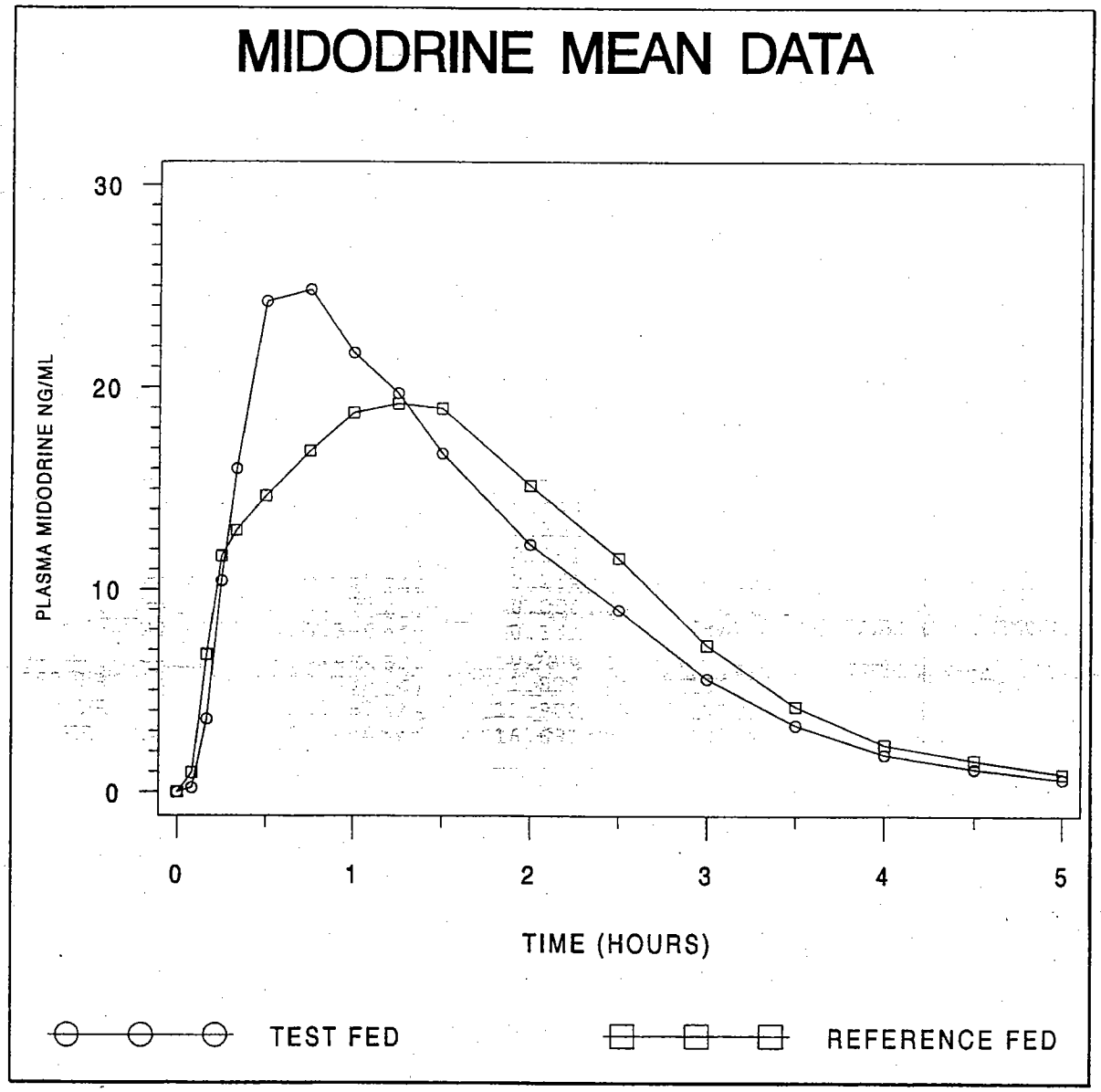


Table IX

Test Product's Individual AUCT/AUCI Ratios

Nonfasting Study No. R01-922

SUBJECT	PERIOD	SEQUENCE	AUCT Ng.hr/mL	AUCI Ng.hr/mL	AUCT/AUCI
1	2	2			
2	1	1			
3	2	2			
4	2	2			
5	1	1			
6	1	1			
7	2	2			
8	2	2			
9	1	1			
10	2	2			
11	2	2			
12	1	1			
13	2	2			
14	2	2			
15	2	2			
17	1	1			
18	1	1			
19	2	2			
20	1	1			
21	1	1			
22	1	1			
23	2	2			
24	1	1			
MEAN			47.72	48.88	0.97707
STDEV			11.3098	11.616	0.022781
CV%			23.6995	23.766	2.331564
MIN					
MAX					

APPEARS THIS WAY
ON ORIGINAL

Table X

Reference Product's Individual AUCT/AUCI Ratios

Nonfasting Study No. R01-922

SUBJECT	PERIOD	SEQUENCE	AUCT Ng.hr/mL	AUCI Ng.hr/mL	AUCT/AUCI
1	1	2			
2	2	1			
3	1	2			
4	1	2			
5	2	1			
6	2	1			
7	1	2			
8	1	2			
9	2	1			
10	1	2			
11	1	2			
12	2	1			
13	1	2			
14	1	2			
15	1	2			
17	2	1			
18	2	1			
19	1	2			
20	2	1			
21	2	1			
22	2	1			
23	1	2			
24	2	1			
MEAN			48.43	49.57	0.97785
STDEV			11.809374	12.12764	0.024439
CV%			24.384199	24.46804	2.499253
MIN					
MAX					

APPEARS THIS WAY
ON ORIGINAL

Table XI
Nonfasting Study No. R01-922
Individual AUCT, AUCI & CMAX
Test Product

SUBJECT	PERIOD	SEQUENCE	AUCTLQC	AUCINF	CMAX
1	2	2			
2	1	1			
3	2	2			
4	2	2			
5	1	1			
6	1	1			
7	2	2			
8	2	2			
9	1	1			
10	2	2			
11	2	2			
12	1	1			
13	2	2			
14	2	2			
15	2	2			
17	1	1			
18	1	1			
19	2	2			
20	1	1			
21	1	1			
22	1	1			
23	2	2			
24	1	1			

Table XII
Nonfasting Study No. R01-922
Individual AUCT, AUCI & CMAX
Reference Product

SUBJECT	PERIOD	SEQUENCE	AUCTLQC	AUCINF	CMAX
1	1	2			
2	2	1			
3	1	2			
4	1	2			
5	2	1			
6	2	1			
7	1	2			
8	1	2			
9	2	1			
10	1	2			
11	1	2			
12	2	1			
13	1	2			
14	1	2			
15	1	2			
17	2	1			
18	2	1			
19	1	2			
20	2	1			
21	2	1			
22	2	1			
23	1	2			
24	2	1			

Table XII

Formulation of Eon's Midodrine HCl Tablets, 5 mg & 2.5 mg

Comparison of Composition for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg

Components	Midodrine Hydrochloride Tablets, 2.5 mg		Midodrine Hydrochloride Tablets, 5 mg	
	Amount per tablet (mg)	% W/W	Amount per tablet (mg)	% W/W
Midodrine Hydrochloride	2.5	1.92	5.0	3.85
Pregelatinized Starch 1500, NF				
FD&C Yellow # 6 Aluminum Lake	-	-		
FD&C Red # 6 Aluminum Lake	-	-		
Microcrystalline Cellulose, NF				
Colloidal Silicon Dioxide, NF				
Magnesium Stearate, NF				
Total Tablet Weight	130.0	100.0	130.0	100.0

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS

ANDA: 76-514 APPLICANT: Eon Laboratories

DRUG PRODUCT: Midodrine Hydrochloride Tablets, 2.5 mg & 5 mg

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

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

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

The dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37C using USP Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

Not less than ___(Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

for 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
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen HNE
HFD-652/ YHuang YH 2/10/2003
HFD-617/ A. Sigler
for HFD-650/ D. Conner BZD 2/21/03

V:\FIRMSAM\eon\ltrs&rev\76514n0902.doc
Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 09-26-02

1. FASTING STUDY (STF) olc Strength: 5 MG
   Clinical: **Outcome: AC**
   Analytical:

2. NON-FASTING STUDY (STP) olc Strength: 5 MG
   Clinical: **Outcome: AC**
   Analytical:

3. DISSOLUTION WAIVER (DIW) olc Strength: 2.5 MG
   Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-514

CORRESPONDENCE

Eon Labs
The Pharmacy Drug Company

Eon Labs, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 276-1735

August 8, 2003

Mr. Craig Kiester
Project Manager
Division of Chemistry I, HFD-620
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-02773

ORIG AMENDMENT
N/ANA

RECEIVED
AUG 11 2003
OGD/CDER

- TELEPHONE AMENDMENT -

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

Dear Mr. Kiester:

Pursuant to our telephone conversation on August 08, 2003, regarding our Abbreviated New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg, ANDA # 76-514, submitted herein is a **TELEPHONE AMENDMENT**.

We acknowledge your comment requesting Eon Labs to tighten its release and stability specification for potency to [redacted] However, based on a review of our current data, we will not be able to readily meet this limit without future problems. As such, we are proposing to maintain the current specification of [redacted] for the following reasons:

1. The stability data for the 3 months accelerated studies submitted in the original application show low assay results for both strengths as follows:

   2.5 mg strength: [redacted] (100 counts) and [redacted] (500 counts)
   5.0 mg strength: [redacted] (100 counts) and [redacted] (500 counts)

   For your convenience, copies of the corresponding pages 0807, 0808, 0811, 0812, 0828, 0829, 0832 and 0833 from the original ANDA are resubmitted, **ATTACHMENT 1**.

2. The stability data for the 12 months room temperature for 5 mg strength show a potency of [redacted] (100 counts) and [redacted] (500 counts), respectively. The long-term stability reports for Midodrine Hydrochloride 5 mg are provided, **ATTACHMENT 2**. Although these values are passing, they are close to FDA's proposed lower limit of [redacted] An analytical deviation of [redacted] could render the same sample out-of-specification. Therefore, setting a tight specification based on borderline results is not recommended.

3. Midodrine Hydrochloride Tablets 2.5 mg and 5 mg are low dose products. A tight specification for a low dose product is not recommended since small weight changes in the tablets (in-process specification of — can adversely affect the assay of the finished product. These same weight changes, which are typical during ——— , have much less impact on larger and higher concentration drug products.

Based on the above, we believe that our current specification of ——— is appropriate for our formulation and manufacturing process.

We hope our responses address satisfactorily all your comments. If you require further information or clarification, do not hesitate to call me at (718) 276-8607 extension 404.

Sincerely,
Eon Labs, Inc.

Zoita Titi

Zoita Titi
Sr. Regulatory Affairs Associate

Eon Labs

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

June 20, 2003

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I, HFD-620
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-02773

ORIG AMENDMENT
N/AM

- MINOR AMENDMENT -

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

Dear Dr. Patel:

In response to your correspondence dated June 09, 2003, regarding our Abbreviated New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg, ANDA # 76-514, submitted herein is a **MINOR AMENDMENT**, in accordance with the provisions outlined in the letter.

CHEMISTRY DEFICIENCY

A. Deficiencies

Comment 1

DMF [redacted] remains deficient. The deficiencies have been communicated to the DMF holder. Please do not respond to this deficiency letter until the DMF holder has informed you that all the deficiencies have been addressed.

Response:

Eon Labs has been advised by the DMF holder, [redacted] that they have responded to the agency's deficiencies. A written confirmation is provided, **ATTACHMENT 1**.

Comment 2

We note your statement regarding the drug substance limit for " [redacted] The Agency considers that your limit for [redacted] (NMT [redacted] is not acceptable. Please reduce the limit.

Response:

The specification in the drug substance for " [redacted] " was reduced per your request and in accordance with the API manufacturer's DMF amendment from **"NMT [redacted]"** to **"NMT [redacted]"**. This change has been included in the revised **Raw Material Specification and Analysis Report** form and analytical method **M59 -The Testing of Midodrine Hydrochloride Raw Material, ATTACHMENT 2.**

Comment 3

We reviewed your revised limits of "Known" and "Total Impurities" for the drug substance. These limits are not acceptable and should be reduced.

Response:

The limits for "Known" and "Total Impurities" for the drug substance have been reduced to be in conformance with manufacturer's DMF amendment. The revised limits for the known related compounds and total related compounds are as follow:

- [redacted] NMT [redacted]
- [redacted] NMT [redacted]
- [redacted] NMT [redacted]
- Total Related Compounds: NMT [redacted]

Please note that the specification for [redacted] NMT [redacted] remained the same. The API manufacturer made a commitment to the FDA to further monitor this impurity until sufficient data is available to reduce the specification.

The new limits have been included in the revised **Raw Material Specification and Analysis Report** form and analytical method **M59 -The Testing of Midodrine Hydrochloride Raw Material** (see **ATTACHMENT 2**).

Comment 4

We reviewed the information that you provided in the revised method validation report. The chromatograms that you provided for the selectivity study (Fig # 13, 14, and 15) have several extra peaks. Please explain the peaks at RT [redacted] in figure 13 (page 30 of 36) and provide their levels calculated as area percent. Additionally, please provide separate individual chromatograms for Midodrine, Rel compd. 2, Rel compd. 3, Rel compd. 4, and blank obtained at the same scale. Please include a representative calculation for total related substance in your response.

Response:

The raw material used for the method validation studies for selectivity and recovery of related compounds was from a R&D raw material, Lot # MID0801003 (Eon's Index # WD00040) containing a higher level of unknown related compounds than what is typically seen in the scale-up batches of

the API. For the rest of the validation study, a different lot was used, Lot # RSN-299-02, as mentioned on page 29 of the ARMR 288 submitted in the March 14, 2003 Minor Amendment (Attachment 12). This explains the high level of the total related compounds in the chromatograms for the selectivity study.

Review of Figure 13, in ARMR 288 from March 14, 2003 amendment has identified the following peaks with their level calculated as area percent:

Peak	RT	RRT	Area	Area Percent *
Midodrine	[redacted]	[redacted]	[redacted]	[redacted]

* Area Percent = Area of the related compound/ Area of the midodrine peak*100

The peak with the retention time of 18.254 has been identified as [redacted], a process related compound. The current specification for this related compound is NMT [redacted] The peaks with retention times of [redacted] are considered unknown related compounds. The current specification for any unknown related compounds is NMT [redacted]

As requested, we are providing herein individual chromatograms of Midodrine, Rel compd. 2, Rel compd. 3, Rel compd. 4, and blank obtained at the same scale, **ATTACHMENT 3.**

The total related compounds are calculated by summing the percentage of all individual known and unknown related compounds. We are providing a representative calculation for the total related compounds in midodrine hydrochloride raw material Lot # MID0202004 used in the manufacturing of the exhibit batch for Midodrine Hydrochloride Tablets, 5 mg. A copy of the HPLC chromatogram for related compounds determination (page 0144 of the original submission) and a copy of the chemist's notebook with the calculation for TRC, are included for your review, **ATTACHMENT 4.**

Comment 5

Please update your stability data to reflect the current stability specifications and any additional accrued room temperature stability data.

Response:

The most updated long-term stability reports for Midodrine Hydrochloride 2.5 mg and 5 mg, which reflect the current stability specifications are provided, **ATTACHMENT 5.**

Comment 6

We noted your comments regarding ' [redacted] as the release and stability specification for potency of your drug products. The Agency, however, cannot accept this as your potency specification. Please tighten the specification range for drug product stability.
Response:

After a thorough evaluation of all available data for both strengths of the finished product, we can agree to reduce the potency specification of the finished product from " [redacted] This new limit has also been adopted for the in-process blend uniformity testing. Subsequently, the **Quality Control Finished Tablet Specification & Report Forms**, **Quality Control In-Process Specification & Report Forms**, **Product Monograph M010QC**, and **Post-Approval Stability Commitment**, have been revised to reflect the tighter limit, **ATTACHMENT 6.**

B. Bioequivalence Defficiencies

In addition to responding to the above deficiencies, please note and acknowledge the following comments in your response:

1. **Division of Bioequivalence has recommended the following dissolution specifications:**

   The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

   Please revise your dissolution specification for release and stability. Also, provide your updated product specification and report.

   Response:

   Following your recommendations, we have revised the specifications for the dissolution testing, accordingly. The changes are reflected in the revised **Quality Control Finished Tablet Specification & Report Forms**, **Product Monograph M010QC**, and **Post - Approval Stability Commitment**, (see **ATTACHMENT 6**).

   In order to support the changes adopted, following the new specifications, we have performed dissolution testing for finished dosage product, Midodrine Hydrochloride Tablets, 2.5 mg, Lot # RDW00063 and 5 mg, Lot # RD00062, at 3 months accelerated, 3 months CRT and 12 months CRT conditions. The **Dissolution Testing Report**, provided in **ATTACHMENT 7**, shows that all samples met the new specifications for dissolution.

2. **Please supply currently available room temperature, long term stability data from your exhibit batches.**

Response:

Please refer to Comment # 5.

Also, please be advised that Eon Labs commits to providing any samples that FDA will require for method validation testing and to addressing any deficiencies found by the District Laboratory relating to our analytical methods for the drug products post approval.

We hope our responses address satisfactorily all your comments. If you require further information or clarification, do not hesitate to call me at (718) 276-8607 extension 404.

Sincerely,
Eon Labs, Inc.

_____
Zoita Titi
Sr. Regulatory Affairs Associate

Eon Labs
The Pharmacy Drug Company

Eon Labs, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 276-1735

March 14, 2003

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
NDA

- MINOR AMENDMENT -

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

Dear Dr. Patel:

In response to your correspondence dated February 19, 2003, regarding our Abbreviated New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg, ANDA # 76-514, submitted herein is a **MINOR AMENDMENT**, in accordance with the provisions outlined in the letter.

CHEMISTRY DEFICIENCY

A. Deficiencies

Comment 1

You indicated in the FDA form 356h that the strength of Midodrine HCl Tablets as 2.5 mg and 50 mg. Apparently there is a typographical mistake. Please resubmit a corrected copy.

Response:

We are resubmitting a revised FDA form 356h, corrected to the 5 mg dosage strength, **ATTACHMENT** 1.

Comment 2

Please provide a cGMP certification from the Drug Substance manufacturer certifying that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug substance are in conformity with current Good Manufacturing Practice, 21 CFR, Parts 210-211.

RECEIVED
MAR 1 8 2003
OGD / CDER

3/27/03

Response:

A cGMP certification statement from [redacted] the [redacted] of midodrine hydrochloride, the [redacted]; is provided, **ATTACHMENT 2**.

Comment 3

The Drug Master File (DMF) has been reviewed and found to be deficient. The deficiencies have been communicated to the DMF holder. Please do not respond to this deficiency letter until the DMF holder has informed you that all deficiencies have been addressed.

Response:

Eon Labs has been advised by the DMF holder, [redacted], that they have responded to the agency's deficiencies. A written confirmation is provided, **ATTACHMENT 3**.

Comment 4

Please update specifications for the drug substance to include an identification test for [redacted]

Response:

Eon Labs has updated the **Raw Material Specification and Analysis Report** form and the analytical method **M59 -The Testing of Midodrine Hydrochloride Raw Material**, to include the identification test " [redacted] for midodrine hydrochloride, the active pharmaceutical ingredient, **ATTACHMENT 4**.

Comment 5

Please tighten the limits for [redacted] **and** [redacted] **in your drug substance specifications based on the observed values.**

Response:

The original limits for [redacted] and [redacted] in the active pharmaceutical ingredient, midodrine hydrochloride, were set in accordance with the recommendations from the ICH-Guidance: Residual Solvents. However, we have reduced our limits per your request, as follows:

- [redacted] NMT [redacted]
- [redacted] NMT [redacted]

These limits are in accordance with the API manufacturer's DMF amendment which was recently submitted. These changes have been included in the revised **Raw Material Specification and Analysis Report** form and analytical method **M59 -The Testing of Midodrine Hydrochloride Raw Material** (see **ATTACHMENT 4**).

Comment 6

Your drug substance specifications for "pH", "Residue on Ignition" and "[redacted]" are not acceptable. Please tighten the specifications.

Response:

The specifications in the drug substance for "pH", and "Residue on Ignition" were changed to be in agreement with manufacturer's DMF amendment, as detailed below:

- The specification for the "pH" test has been tightened from "[redacted]" to "[redacted]". Since this new specification was adopted based on the observed values, we consider that they are appropriate. Moreover, they are in conformance with the manufacturer's specifications for the drug substance.

- The specification for the "Residue on Ignition" test has been revised based on the observed values and in conformance with manufacturer's specifications for the drug substance from "NMT [redacted] to "NMT [redacted]

The changes for pH and Residue on Ignition were included in the revised **Raw Material Specification and Analysis Report** form and analytical method **M59-The Testing of Midodrine Hydrochloride Raw Material** (see **ATTACHMENT 4**).

The specification for "[redacted]" of "NMT [redacted]. (NMT [redacted] is in accordance with general USP test requirements for most raw materials. Eon Labs considers that this limit is appropriate since it follows accepted compendial standards. Accordingly, we are proposing to maintain the current specification submitted in the original application.

Comment 7

What are the known impurities in the drug substance? Please include their names in the drug substance specifications and certificates of analysis. Additionally, your drug substance specifications of NMT [redacted] for "Known Impurities" and NMT [redacted] for "Total impurities" are not acceptable. Please reduce their limits based on the observed values.

Response:

We have identified the known impurities as:

a) [redacted]
b) [redacted]
c) [redacted]

Initially, only two known impurities [redacted] and [redacted] were listed in the analytical method **M-59**. We are now adding impurity C and Impurity A as known related substances, and will test for them accordingly. The identification of these impurities, previously classified as unknown, permitted us to tighten the limit for the "Unknown Impurities" as described below.

Based on the observed values and in conformance with manufacturer's DMF amendment, the revised limits for the related compounds, known and unknown, in the drug substance, are:

- [redacted] NMT [redacted].
- [redacted] NMT [redacted].
- [redacted] NMT [redacted].
- Individual Unknown Related Compound: NMT [redacted].
- Total Related Compounds: NMT [redacted].

A reference standard for [redacted]) is not available. Therefore, this impurity will be monitored based on the relative retention time (RRT). Impurity [redacted] (listed initially in the analytical test method) is a process related impurity. However, based on the information from the API's manufacturer, this impurity has never been detected in the raw material. Therefore, impurity [redacted] is now classified as an unknown related compound with a specification of NMT [redacted].

The revised related compounds specifications were included in the **Raw Material Specification and Analysis Report** and analytical method **M59 -The Testing of Midodrine Hydrochloride Raw Material** (see **ATTACHMENT 4**).

Comment 8

Your submitted data does not support your limit of NMT [redacted] for the "Unknown Impurity" in the drug substance. Please consider tightening the limit.

Response:

Please refer to Comment # 7.

Comment 9

We recommend that you include the following specifications for your drug substance: Particle size distribution, Bulk density and Tapped density.

Response:

Particle size distribution profiles, bulk and tap density are extensively evaluated throughout the early stages of product development and later in our pre-validation studies of the exhibit batches. They are further evaluated during the process validation studies of the first three commercial batches following ANDA approval. Data from all the studies are compared and summarized in the final validation report providing a comprehensive analysis of the physical attributes of the API. Because of this, Eon Labs does not routinely set a QC release criteria for particle size distribution and bulk and tap density of incoming APIs.

We do, however, set a particle size specification for all incoming APIs. The specification is based on either a one point or two point measurement depending on the critical nature of particle size to the manufacturing process. The currently proposed particle size specification of "NLT [redacted] (one point) for midodrine hydrochloride, was derived after first evaluating particle size profiles of three different lots of API and further evaluating particle size profiles of the lots used to manufacture

the exhibit batches. Based on the good blend uniformity data in the exhibit batches, refer to pages 328 (2.5 mg) and 401 (5 mg) of the original application, it can be concluded that our proposed particle size specification for midodrine hydrochloride is adequate for the finished drug product, and that bulk and tap density are not required as a QC release criteria.

Comment 10

The IR spectra of standard and sample provided in pages 132 and 133 do not appear to be concordant. Please comment.

Response:

The IR spectrum of the standard (page 132 in the original application) appears to have some noise disturbance not seen in the sample spectrum (page 133), but both show IR absorptions at the same wavelengths. New IR spectra for the standard and the sample were recorded to confirm original results. The new spectra are provided, **ATTACHMENT 5**.

Comment 11

We recommend that you include [redacted] test as an in-process control on the [redacted] tablets.

Response:

Eon Labs routinely performs [redacted] tests as an in-process control on the [redacted] tablets. This is a standard procedure in the manufacturing process for all our products and is conducted as stated in our internal SOP T-016. The [redacted] test is performed at least once at the commencement of [redacted] process and as directed in the formulation manufacturing record (FMR).

In regards to Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg, the subject of this discussion, the [redacted] test was submitted in the original application as part of the Executed Batch Records. Copies of the corresponding pages 321 and 395, respectively, are re-submitted for your convenience, **ATTACHMENT 6**.

Comment 12

You have specified the percent yield for the [redacted] in step #9 (page 314) as NLT [redacted] and NMT [redacted]. Similarly, the yield tolerance for [redacted] in step #2 (page #316) is NLT [redacted] and NMT [redacted]. The lower limit that you established is not acceptable. Please tighten these limits based on the observed value.

Response:

Eon Labs has revised its master **Formulation Manufacturing Record** (FMR) for the 2.5 mg (MF # 0040) and the 5 mg (MF # 0043) to tighten the lower limit of the yield tolerance for [redacted] and [redacted] steps as follows:

- After [redacted] in Step # 9 (MF # 0040) and Step # 10 (MF # 0043): from **"NMT** [redacted] to **"NMT** [redacted] **NLT** [redacted].
- After [redacted] in Step # 2 (both products): **"NMT** [redacted] **NLT** [redacted]" to **"NMT** [redacted]**, NLT** [redacted].
- In **"Summary"** reconciliation, step # 5 (both products): **"NMT** [redacted]**, NLT** [redacted]**"** to **"NMT** [redacted]**, NLT** [redacted]**"**.

These limits are our general specifications for all our commercial batches. The revised FMR documents are provided, **ATTACHMENT 7**.

Comment 13

Please provide justification for the [redacted] **specifications for Midodrine HCl tablets by providing the** [redacted]**, data at the upper and lower end of the proposed** [redacted] **limits.**

Response:

Extensive evaluation on [redacted] is done as part of our pre-validation studies for the finished product. The [redacted] data at the upper and lower end of the proposed [redacted] range justify our limits. The data in tabular form are provided for your evaluation, **ATTACHMENT 8**.

Comment 14

You have indicated that you have removed samples for [redacted] **and other tests. However, there is no record of having removed the samples in your percent yield calculations in step #10 and step #2 of MFC. Please comment and include location of sampling sites in the** [redacted] **prior to** [redacted]

Response:

With regards to including the removed [redacted] samples in the percent yield calculations, we consider the amount removed (1-3 unit doses (grams)) insignificant compared to the overall batch size of [redacted]. We have included the sample amount in the general waste, expressed in the yield calculation formula, as " [redacted]

With regards to the location of the sampling sites of the [redacted], this information was provided in the original application, on page 463, in the **In-Process Control** section.

Comment 15

On page 463 you indicated that you will perform [redacted] **testing on both exhibit and commercial batches. However, it is not clear from the scale-up master formula card (page 269) that this test will be performed. We recommend that you perform the** [redacted] **analysis on the** [redacted] **for the commercial batches. Please acknowledge.**

Response:

Eon Labs routinely performs [redacted] testing for both the exhibit and commercial batches. It is our standard procedure to include instructions to collect [redacted] sample. Inadvertently, this information was omitted in the master **Formulation Manufacturing Records**. Therefore, we have revised our **Formulation Manufacturing Record** masters for 2.5 mg (MF # 0040) and the 5 mg (MF # 0048) to include instructions for the operator to collect [redacted] samples (see **ATTACHMENT 7**).

Comment 16

Please provide a comparison of the ANDA exhibit batch and proposed Scale-up batch with equipment specified and list of changes if any in the tabular form.

Response:

A comparison of the ANDA exhibit batch and proposed Scale-up batch with the equipment list for Midodrine HCl Tablets, 2.5 mg and 5 mg, was provided in the original application, pages 296 and 297, respectively.

Comment 17

We recommend that you include the following specifications in your drug product release specifications and report: (1) Appearance/description (2) Identification by IR, and (3) [redacted] (KF).

Response:

(1) **Appearance/description**: The **Quality Control Finished Tablet Specification & Report Forms** for both, Midodrine HCl Tablets, 2.5 mg and 5 mg, have already included the specifications related to Appearance/description, on top of the first page, under **TABLET DESCRIPTION, MARKING/IMPRINT, COLOR** and **SHAPE**.

(2) **Identification by IR**: Eon labs has performed IR tests for the finished product Midodrine Tablets 2.5 mg and 5 mg. Due to the interference of the color ingredient, we have determined that this test is not conclusive. As an alternative, an identification test by [redacted] was performed with favorable results for both strengths. Therefore, the [redacted] identification test, along with the HPLC identification test, will be included in our release specifications for the finished product, **ATTACHMENT 9**. We believe that this will satisfy the requirement for the identification test.

(3) [redacted] **(KF)**: [redacted] determination for the drug product was evaluated prior to the submission of this application, by using a [redacted] Since a [redacted] process is used to manufacture the product, we did not consider necessary to set a [redacted] specification for the finished product. However, we have now included the LOD test in our release specification and stability requirements for the finished product. We propose a limit of "NMT [redacted], which we consider justified for our product for the following reasons. First, Midodrine Hydrochloride Tablets is a [redacted] manufacturing process. Because of this,

from the excipients will play a major roll in determining in the finished product. Second, the LOD specification was determined based on the 2.5 mg dosage strength since it contains the highest ratio of excipients to the API, representing a worse case scenario.

The product formulation contains by weight of ingredients with limits (LOD):

-
-
-
-
-

Based on the actual percentage of each ingredient in the 2.5 mg strength formulation, the drug product may contain as much as depending on the content of the specific raw material lots used, see table as **ATTACHMENT 10**. For the exhibit batch of 2.5 mg, Lot # RDW00063, the , content, calculated based on the actual excipients lots used was Considering that the experimental values can be higher than the nominal amount, we believe that the value of content (by this LOD method) is appropriate.

Comment 18

Your release and stability specifications for "Individual Unknown Related Compound" are not acceptable. Please tighten the specification for based on the observed values.

Response:

The specification for "Individual Unknown Related Compound" for product release and stability has been revised from "NMT ' to "NMT . The lower limit for the unknown impurities was possible due to the identification of Impurity C and Impurity A (see response to Comment #7). Subsequently, the **Quality Control Finished Tablet Specification & Report Forms** (see **ATTACHMENT 9**), **Monograph M010QC**, and **Post-Approval Stability Commitment**, **ATTACHMENT 11,** have been revised to reflect the tighter limit.

Comment 19

Your release and stability specification for potency is not acceptable. Please consider reducing the potency limit.

Response:

Eon Labs considers a potency limit of " an appropriate specification for a low dose product such as Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg. Furthermore, this specification is in accordance with the USP general recommendations for most tablet products. As such, we are proposing to maintain our current specification.

Comment 20

What are the known related compounds present in the drug product? Please include the names of the known related compounds in your Certificate of Analysis, Product Release Specifications and Stability Reports. Please consider reducing the release specification for "Known Related Compounds" to be consistent with your submitted data.

Response:

We have now identified four known impurities in both, the drug substance and the drug product (refer to Comment # 7). They are as follows:

a)
b)
c)
d)

Based on the observed values for all related compounds, we have adopted the following specifications for the finished product:

- Related Compound – NMT
- Individual Other Known Related Compound: NMT
- Individual Unknown Related Compound: NMT
- Total Related Compounds: NMT

Related compound 2 (the main degradation product) and the new specifications adopted for the related compounds were included in the following documents: **Quality Control Finished Tablet Specification & Report Forms** (see **ATTACHMENT 9**) and **Post-Approval Stability Commitment** (see **ATTACHMENT 11**).

The names and the RRT for the other known related compounds, along with the new specifications adopted for the related compounds were included in the **Product Monograph M010QC** (see **ATTACHMENT 11**).

Comment 21

Please consider reducing "Total Impurities Specification" on release to a value consistent to your data.

Response:

The total impurities specification has been reduced from "NMT to "NMT (refer to comment 20).

Comment 22

The related compound 3 is one of the known impurities you listed in the validation report. This compound elutes at as can be seen from the chromatograph in page 662.

However, this peak is fused with the Midodrine HCl peak as shown in the typical chromatograms for the sample preparation in page 663. Please comment on this impurity peak being accurately quantitated in the drug substance.

Response:

A selectivity study, which inadvertently was not included in the method validation report, was performed for all related compounds by spiking the active pharmaceutical ingredient with the related compounds at a concentration of about ——of the sample preparation. The chromatograms obtained showed that related compounds and midodrine hydrochloride are well resolved from each other and are quantitatable at the level of —— These also apply for the related compound 3, which is the subject of this comment. The data with the chromatograms obtained, are included in the revised ARMR 288, **ATTACHMENT 12**.

Comment 23

We could not find the validation of the "accuracy" performance characteristic in your validation report for related compounds. Please provide the data by following USP 26 <1225> for method validation.

Response:

An **"Accuracy/Recovery"** study for the related compounds was performed. The complete study with data was included in the revised validation report ARMR 288 (see **ATTACHMENT 12**).

B. OTHER COMMENTS

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. **The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.**

   Response:

   We acknowledge that a satisfactory cGMP compliance status relative to the manufacturing and testing of the product is required for all referenced firms listed in our ANDA before the approval of our application.

2. **The bioequivalence information which you have provided is under review. Upon completion of this review, any deficiencies found will be communicated to you under a separate cover.**

   Response:

   We commit to responding to any deficiencies found in our bioequivalence study upon receipt of a separate letter.

3. **Labeling portion of your application is deficient and the comments are being communicated to you along with facsimile. Your response must be complete and incorporate all deficiencies.**

Response:

Our responses to the labeling deficiencies follow immediately after this section.

4. **To facilitate the review process, all changes (chemistry/manufacturing/ controls, labeling, etc.) should be identified and itemized in your cover letter.**

Response:

We acknowledge your request and will comply accordingly.

5. **Please update your stability data tables and provide the long-term stability data generated whenever you respond to the deficiency letter.**

Response:

The most updated long-term stability reports for Midodrine Hydrochloride 2.5 mg and 5 mg, are provided, **ATTACHMENT 13**.

6. **We will request the appropriate FDA District Laboratory to obtain samples of the new drug substance and finished dosage form for method validation, when the method validation issues have been resolved.**

Response:

We will provide the FDA District Laboratory with samples upon request.

7. **Please commit to updating your raw material specifications to most current USP or NF specification requirements.**

Response:

All appropriate **"Raw Material Specification And Analysis Report"** forms have been updated to USP 26-NF 21. The revised documents are provided, **ATTACHMENT 14**.
In the future, we commit to updating all raw material specifications to the most current compendial standards when published.

In addition to responding the deficiency letter, we are submitting herein the analytical method **S-39 – Foreign Particles in** recently updated to the manufacturer's procedure for the testing of foreign particles in **ATTACHMENT 15**.

In addition, we are responding to the Labeling Deficiencies FDA letter, received on February 19, 2003. The following are your comments:

LABELING DEFICIENCIES

1. **CONTAINER – Bottles of 100 and 500 tablets**

   a. **We note that the contrasting colors that were utilized to differentiate between the two different strength tablets are very dark and very similar. To avoid any safety issues, we encourage you to increase the readability of these container labels. Please revise and/or comment.**

   b. **Please revise your temperature/storage statement to read as follows:**

      "Store at controlled room temperature, 20 to 25°C (68 to 77°F) with excursions permitted between 15 to 30°C (59 to 86°F). (See USP)."

2. **PACKAGE INSERT**

   a. **INDICATIONS AND USAGE**
      Midodrine hydrochloride tablets are...

   b. **CONTRAINDICATIONS**
      Midodrine hydrochloride tablets are...

   c. **DOSAGE AND ADMINISTRATION**
      First paragraph, first sentence

      The recommended dose of midodrine hydrochloride tablets is...

   d. **HOW SUPPLIED**

      Please revise your temperature/storage statement to read as follows:

      "Store at controlled room temperature, 20 to 25°C (68 to 77°F) with excursions permitted between 15 to 30°C (59 to 86°F). (See USP)."

We have made all the necessary changes to the container labels and package insert in accordance with your comments. In regards to the color-coding, the proofs provided in the original application were computer-generated and did not show a true representation of the color. We are now submitting the Final Printed Container Labels, which shows a sufficient contrast to differentiate the two strengths and to avoid a safety issue. Provided herein are the following:

- Twelve copies of the Final Printed Container Labels. A side-by-side comparison of our current container labels versus the revised container labels along with a table of annotation is also included, **ATTACHMENT 16**.

- Twelve copies of the Final Printed Labeling Insert. A side-by-side comparison of our current labeling versus the revised labeling insert, is also included, **ATTACHMENT 17**.

We hope our responses address satisfactorily all your comments. If you require further information or clarification, do not hesitate to call me at (718) 276-8607 extension 404.

Sincerely,
Eon Labs, Inc.

Zoita Titi

Zoita Titi
Sr. Regulatory Affairs Associate

ANDA 76-514

NOV 18 2002

Eon Labs, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Madam:

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

Reference is made to the telephone conversation dated November 6, 2002 and to your correspondence dated November 7, 2002.

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

DATE OF APPLICATION: September 26, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 3, 2002

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

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

Should you have questions concerning this application, contact:

Craig Kiester
Project Manager
(301) 827-5848

Sincerely yours,

/S/

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

Eon Labs
The Pharmacy Drug Company

Eon Labs, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 276-1735

November 07, 2002

NEW CORRESP

NC

George Paras Patel
Project Manager
Regulatory Support Branch
Office of Generic Drugs, HFD-615
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

- GENERAL CORRESPONDENCE -

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

Dear Mr. Patel:

Pursuant to your telephone conversation with Ms. Sadie Ciganek of Eon Labs, on November 6, 2002, we are submitting herein a revised **Exclusivity Statement (Attachment 1)** for our Abbreviated New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg, ANDA 76-514.

If there are any comments or questions regarding this submission, please feel free to contact me at (718) 276-8607, extension 404.

Sincerely,
Eon Labs, Inc.

Zoita Titi

Zoita Titi
Sr. Regulatory Affairs Associate

RECEIVED
NOV 0 8 2002
OGD / CDER

Eon Labs
The Pharmacy Drug Company

Eon Labs, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 276-1735

October 10, 2002

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

NEW CORRESP
NC

76-574

Re: Original ANDA
Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg

Dear Mr. Buehler:

Reference is made to the telephone conversation on October 07, 2002, between Mr. Greg Davis of the FDA and myself. At that time, we were informed that part of our original Abbreviated New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg was lost in transit and was not received by the FDA. Therefore, we are hereby resubmitting the missing volumes, which include:

- Volumes 2 and 3, in red folders (review copy), and
- Volumes 4 through 7, in orange folders (pharmacokinetic section)

The content of the volumes submitted consists of:

Volume 2 Raw material control data, manufacturing and packaging records including **Executed Batch Records**.

Volume 3 Container/closure information, finished product controls, methods validation, stability data, debarment statement, and environmental impact statement.

Volume 4-7 Bioequivalence study summary and test results.

According to Mr. Greg Davis, the archival copies were received.

We want to apologize for any inconvenience this may have caused. If there are any comments or questions about this application, please contact me at (718) 276-8607, extension 404, or via facsimile at (718) 276-8635.

Sincerely,
Eon Labs, Inc.

Zoita Titi

Zoita Titi
Sr. Regulatory Affairs Associate

9/10/03

RECEIVED
OCT 11 2002
OGD / CDER

Eon Labs
The Pharmacy Drug Company

Eon Labs, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 276-1735

September 26, 2002

505(j)(2)(A) OK
18-NOV-2002

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: Original ANDA
Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, enclosed is an original Abbreviated New Drug Application for Midodrine Hydrochloride Tablets, 2.5 mg and 5 mg. This application consists of the following volumes:

Volume 1	Patent and exclusivity certifications, Section 505(j)(2)(A) information, labeling, dissolution profiles, signed disclosure statement, Certificates of Analysis, and components and composition statements.
Volume 2	Raw material control data, manufacturing and packaging records including **Executed Batch Records**.
Volume 3	Container/closure information, finished product controls, methods validation, stability data, debarment statement, and environmental impact statement.
Volume 4-7	Bioequivalence study summary and test results. Also included are two diskettes containing bioequivalence data and information in electronic format.

A full table of contents precedes each appropriately paginated volume.

We have also enclosed three (03) copies of analytical methods validation package in a separate volume.

In addition to the archival and review copies, we are submitting a certified true copy of the chemistry, manufacturing and controls data to the District Field Office, Atlanta, Georgia. Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Field Office.

Please note that Eon has officially changed its corporate name from "Eon Labs Manufacturing, Inc." (Laurelton, NY) and "Eon Pharma, LLC" (Wilson, NC) to "Eon Labs, Inc." References to either "Eon Labs manufacturing, Inc." and/or 'Eon Pharma, LLC" throughout this ANDA should be construed to mean "Eon Labs, Inc." The corporate headquarters are located at Laurelton, NY.

If there are any comments or questions about this application, please contact me at (718) 276-8607, extension 330, or via facsimile at (718) 276-8635.

Sincerely,
Eon Labs, Inc.

Sadie M. Ciganek
Vice President, Regulatory Affairs