CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-577

Generic Name:	Midodrine Hydrochloride Tablets 2.5mg, 5mg, and 10mg
Sponsor:	Mylan Pharmaceuticals, Inc.
Approval Date:	September 10, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

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76-577

APPROVAL LETTER

ANDA 76-577

SEP 10 2003

Mylan Pharmaceuticals, Inc.
Attention: S. Wayne Talton
781 Chestnut Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 17, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg, and 10 mg.

Reference is also made to your amendments dated June 10, June 11, and August 26, 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, 5 mg, and 10 mg, to be bioequivalent and therapeutically equivalent to the listed drug (ProAmatine® Tablets, 2.5mg, 5 mg, and 10 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.

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

9/10/2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-577

FINAL PRINTED LABELING(S)

MIDODRINE HYDROCHLORIDE TABLETS

2.5 mg, 5 mg and 10 mg

℞ only

WARNING: Because midodrine 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 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, principally improved ability to carry out activities of daily living, have not been verified.

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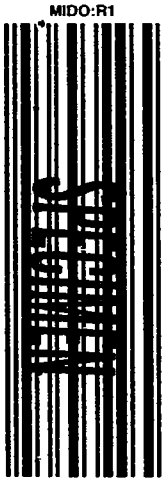
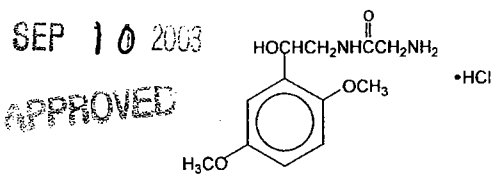


DESCRIPTION: Midodrine hydrochloride is a vasopressor/antihypotensive. The chemical name for midodrine hydrochloride is acetamide, 2-amino-*N*-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-, monohydrochloride, (±)-. The molecular weight of midodrine hydrochloride is 290.7. Its structural formula and molecular formula are:



$C_{12}H_{18}N_2O_4HCl$

Midodrine hydrochloride is an odorless, white, crystalline powder. It is soluble in water and sparingly soluble in methanol and has a pKa of 7.8 (0.3% aqueous solution) and a pH of 3.5 to 5.5 (5% aqueous solution). It has a melting range of 200 to 203°C.

Each midodrine hydrochloride tablet for oral administration contains 2.5 mg, 5 mg or 10 mg of midodrine hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, pregelatinized starch and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY: Mechanism of Action: Midodrine 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 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 has no clinically significant effect on standing or supine pulse rates in patients with autonomic failure.

Pharmacokinetics: Midodrine 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 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 tablets 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 tablets' 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 tablets, 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 tablets. After initiation of treatment, midodrine hydrochloride tablets 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 should not be used in patients with persistent and excessive supine hypertension.

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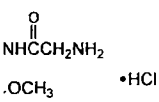

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CONTRAINDICATIONS: Midodrine hydrochloride tablets are contraindicated in patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma or thyrotoxicosis. Midodrine should not be used in patients with persistent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

WARNINGS: Supine Hypertension: The most potentially serious adverse reaction associated with midodrine therapy is marked elevation of supine arterial blood pressure (supine hypertension). Systolic pressures of about 200 mmHg were 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 in such patients is not recommended. Sitting blood pressures were also elevated by midodrine therapy. It is essential to monitor supine and sitting blood pressures in patients maintained on midodrine.

PRECAUTIONS: General: The potential for supine and sitting hypertension should be evaluated at the beginning of midodrine 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 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, primarily due to vagal reflex. Caution should be exercised when midodrine 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 and should be re-evaluated.

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

Midodrine use has not been studied in patients with hepatic impairment. Midodrine 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, as they may enhance or potentiate the pressor effects of midodrine (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 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, 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. Therefore, caution should be used when midodrine is administered concomitantly with agents that cause vasoconstriction.

Midodrine 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. Alpha-adrenergic blocking agents, such as prazosin, terazosin, and doxazosin, can antagonize the effects of midodrine.

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 interactions 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. Studies investigating the mutagenic potential of midodrine 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 on fertility.

Pregnancy: ***Pregnancy Category C:*** Midodrine 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 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 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

Event	Placebo n=88 # of reports	Placebo n=88 % of patients	Midodrine n=82 # of reports	Midodrine n=82 % 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 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, 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 tablets 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 tablets 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 tablets 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 Tablets are available containing 2.5 mg, 5 mg or 10 mg of midodrine hydrochloride.

The 2.5 mg tablets are white beveled edge, scored tablets d score and 1 below the score on c the other side. They are available

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bottles of 1(
NDC 0378·
bottles of 5(

The 5 mg tablets are white beveled edge, scored tablets d score and 2 below the score on c the other side. They are available

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bottles of 1(
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bottles of 5(

The 10 mg tablets are white beveled edge, scored tablets c score and 3 below the score on c the other side. They are available

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bottles of 1(
NDC 0378·
bottles of 5(

Store at controlled room temper with excursions permitted betw [See USP].

Dispense in a tight, light-resist USP using a child-resistant closu

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Mylan Pharma
Morgantown,

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 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, 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 tablets 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 tablets 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 tablets 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 Tablets are available containing 2.5 mg, 5 mg or 10 mg of midodrine hydrochloride.

The 2.5 mg tablets are white to off-white, round, flat-faced, beveled edge, scored tablets debossed with **MH** above the score and **1** below the score on one side of the tablet and **M** on the other side. They are available as follows:

NDC 0378-1901-01
bottles of 100 tablets
NDC 0378-1901-05
bottles of 500 tablets

The 5 mg tablets are white to off-white, round, flat-faced, beveled edge, scored tablets debossed with **MH** above the score and **2** below the score on one side of the tablet and **M** on the other side. They are available as follows:

NDC 0378-1902-01
bottles of 100 tablets
NDC 0378-1902-05
bottles of 500 tablets

The 10 mg tablets are white to off-white, round, flat-faced, beveled edge, scored tablets debossed with **MH** above the score and **3** below the score on one side of the tablet and **M** on the other side. They are available as follows:

NDC 0378-1903-01
bottles of 100 tablets
NDC 0378-1903-05
bottles of 500 tablets

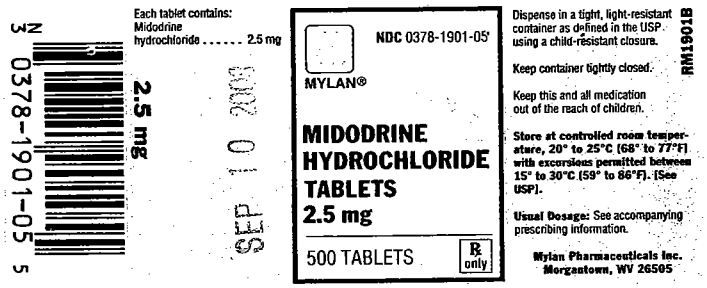
Store at controlled room temperature, 20° to 25°C (68° to 77°F) with excursions permitted between 15° to 30°C (59° to 86°F). [See USP].

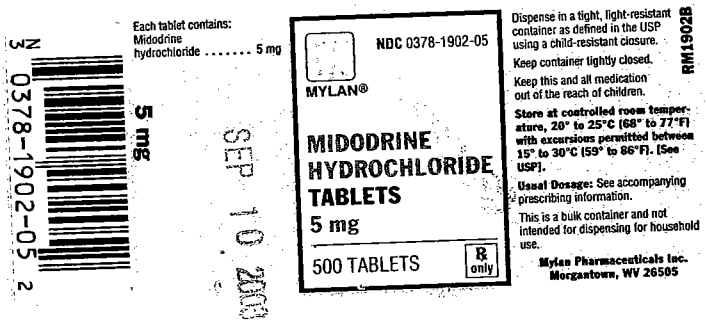
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

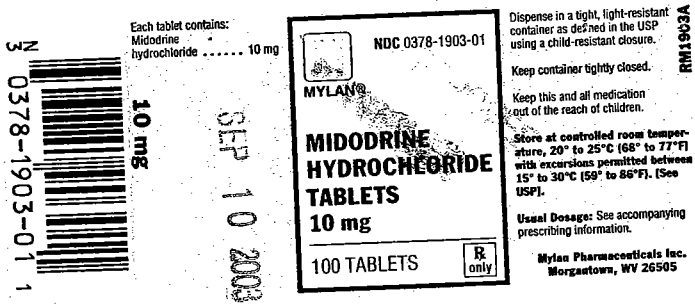
MYLAN®

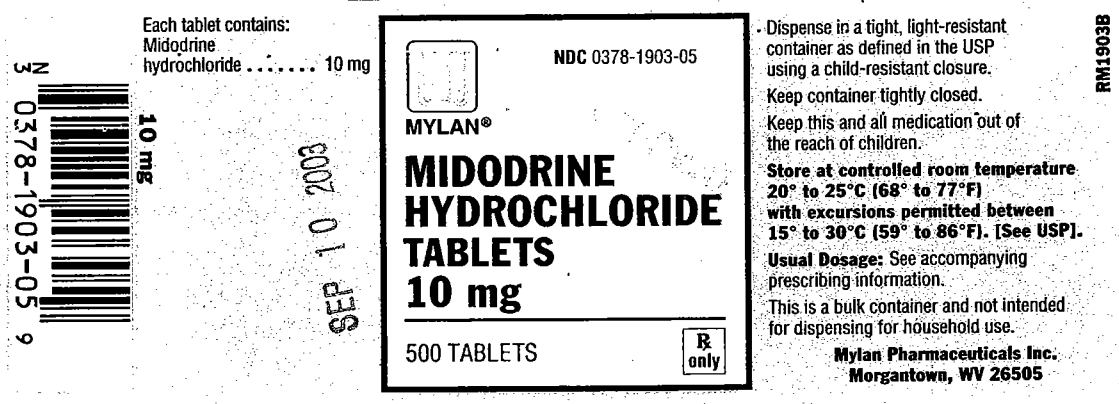
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED MAY 2003
MIDO:R1


Each tablet contains:
Midodrine
hydrochloride ..... 2.5 mg
NDC 0378-1901-05
MYLAN®
MIDODRINE
HYDROCHLORIDE
TABLETS
2.5 mg
500 TABLETS
Rx only
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
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].
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM1901B
0378-1901-05
2.5 mg
SEP 10 2003


Each tablet contains:
Midodrine
hydrochloride ..... 5 mg
NDC 0378-1902-05
MYLAN®
MIDODRINE
HYDROCHLORIDE
TABLETS
5 mg
500 TABLETS
Rx only
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
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].
Usual Dosage: See accompanying prescribing information.
This is a bulk container and not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM1902B
0378-1902-05
5 mg
SEP 10 2003


Each tablet contains:
Midodrine
hydrochloride ..... 10 mg
NDC 0378-1903-01
MYLAN®
MIDODRINE
HYDROCHLORIDE
TABLETS
10 mg
100 TABLETS
Rx only
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
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].
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM1903A
0378-1903-01
10 mg
SEP 10 2003


Each tablet contains:
Midodrine
hydrochloride ..... 10 mg
NDC 0378-1903-05
MYLAN®
MIDODRINE
HYDROCHLORIDE
TABLETS
10 mg
500 TABLETS
Rx only
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
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].
Usual Dosage: See accompanying prescribing information.
This is a bulk container and not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM1903B
0378-1903-05
10 mg
SEP 10 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-577

CSO LABELING REVIEW(S)

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

ANDA Number: 76-577
Date of Submission: June 11, 2003
Applicant's Name: Mylan Pharmaceuticals, Inc.
Established Name: Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

---

APPROVAL SUMMARY:

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

2. **CONTAINER – Bottles of 100 and 500 tablets**
   Satisfactory in **final print** as of the June 11, 2003 submission
   (See blue jacket volume 2.1)

3. **PACKAGE INSERT**
   Satisfactory in **final print** as of the June 11, 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.			

FIRST GENERIC ********

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 to 86°F). (See USP)."
   NDA: Dispense in a well-closed container as defined in the USP.

ANDA:Dispense in tight, light-reisitant container as defined in the USP, using a child-resistant closure. Keep container tightly closed.

4. Product Line:
   The innovator markets their product in three strengths (2.5 mg, 5 mg and 10 mg). They are packaged in bottles of 100 tablets.
   The applicant proposes to market their product as 2.5 mg, 5 mg and 10 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 **pg 5131, 5134 and 5137 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** 4549, Vol B. 1.2.

7. Container/Closure (See page 5031 in Vol. B. 1.2)
   Containers: HDPE
   Closure: CRC closures for 2.5 mg, 5 mg and 10 mg bottles of 100 and for the 2.5 mg bottles of 500 (ONLY)
   Non-CRC closures for the 5 mg and 10 mg bottles of 500 tablets.

8. All manufacturing will be done by Mylan Pharmaceuticals, Inc See page 4703 in vol. B. 1.2

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

Date of Review: 6/25/03 Date of Submission: 6/11/03
Primary Reviewer: Jim Barlow Date: 6/25/03

Team Leader: John Grace Date: 6/25/2003

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cc:
ANDA: 76-577
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
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Review

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

ANDA Number:	76-577
Date of Submission:	December 17, 2002
Applicant's Name:	Mylan Pharmaceuticals, Inc.
Established Name:	Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

---

Labeling Deficiencies:

1. **CONTAINER – Bottles of 100 and 500 tablets**
   Please revise your storage recommendation 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. PRECAUTIONS
   Revise subsection heading to read as follows -

   Pregnancy: *Pregnancy Category C:*

   b. DOSAGE AND ADMINISTRATION
   Second sentence; revise to read as follows -

   ...of daily life.

   c. HOW SUPPLIED

   Please revise your storage recommendation 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)."

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

/s/

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

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, 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	N/A	None

			product in the Orange Book Database.		

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:Dispense in tight, light-reisitant container as defined in the USP, using a child-resistant closure. Keep container tightly closed.

   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 three strengths (2.5 mg, 5 mg and 10 mg). They are packaged in bottles of 100 tablets.
   The applicant proposes to market their product as 2.5 mg, 5 mg and 10 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 **pg 5131, 5134 and 5137 in volume B. 1.3)**

6. Inactive Ingredients:
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7. Container/Closure (See page 5031 in Vol. B. 1.2)
   Containers: HDPE
   Closure: CRC closures for 2.5 mg, 5 mg and 10 mg bottles of 100 and for the 2.5 mg bottles of 500 (ONLY)
   Non-CRC closures for the 5 mg and 10 mg bottles of 500 tablets.

8. All manufacturing will be done by Mylan Pharmaceuticals, Inc See page 4703 in vol. B. 1.2

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

Date of Review: 2/10/03 Date of Submission: 12/17/02
Primary Reviewer: Jim Barlow Date: 3/6/03

Team Leader: John Grace Date:

/S/ 3/6/2003

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cc:
ANDA: 76-577
DUP/DIVISION FILE
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-577

CHEMISTRY REVIEW(S)

ANDA 76-577

Midodrine Hydrochloride Tablets
2.5 mg, 5 mg and 10 mg

Mylan Pharmaceuticals, Inc.

Roslyn F. Powers, Ph.D.
Office Of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-577 **FIRST GENERIC**

2. REVIEW # 1

3. REVIEW DATE: 30-MAR-2003

4. REVIEWER: Roslyn F. Powers, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	17-DEC-2002
Telecom	17-JAN-2003
Patent Amendment	22-JAN-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals, Inc.
Address:	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Representative:	Frank Sisto
Telephone:	304-599-2595 FAX: 304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Midodrine Hydrochloride
c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only): N/A

9. LEGAL BASIS FOR SUBMISSION: The basis for the ANDA submission is Shire Pharmaceutical Development, Inc.'s ProAmatine® Tablets (Midodrine Hydrochloride Tablets 2.5 mg, 5 mg and 10 mg), NDA 19815.

   Pursuant to Section 505(j)(2)(a)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, according to the patent information published by the FDA in that document entitled, "Approved Drug Products With Therapeutic Equivalence Evaluations" (22nd Edition through the 'Electronic Orange Book', Cumulative Supplement 10), there are no patents that claim the listed drug referred to in this application.

   Mylan further certifies that according to the exclusivity information published by the FDA in that document entitled, "Approved Drug Products With Therapeutic Equivalence Evaluations" (22nd Edition through the 'Electronic Orange Book', Cumulative Supplement 10), the 2.5 mg, 5 mg and 10 mg strengths of the referenced product are covered by Orphan Drug Exclusivity ("ODE") which expires September 6, 2003.

   Mylan will market its Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg upon approval of this application and expiration of the above-referenced exclusivity.

10. PHARMACOL. CATEGORY: Indicated for the treatment of symptomatic orthostatic hypotension (OH).

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 2.5 mg, 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __X___Rx ___OTC

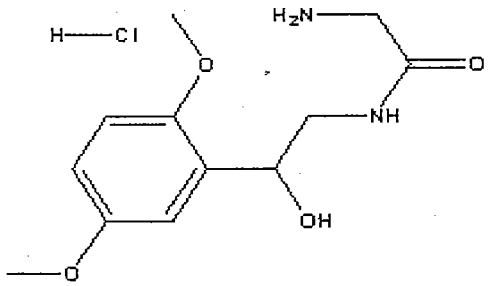
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    ___X__Not a SPOTS product

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

    Chemical Name: Acetamide, 2-amino-N-[2-(2,5-dimeth oxyphenyl)-2-hydroxyethyl] Hydrochloride; 2-amino-N-(β-Hydroxy-2,5-dimethoxyphenethyl)-Acetamide Hydrochloride
    Established Name: Midodrine Hydrochloride
    Molecular Formula: $C_{12}H_{18}N_2O_4 \cdot HCl$

Molecular Weight: 245.29
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Not Adequate	01-APR-2003	RPowers - reviewer
	III			4			
	III						
	III			4			
	III						
	III			4			
	III						
	III			4			

		Brockway				
	III		4			
			DMF			
	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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Pending		
Labeling	Deficient	06-MAR-2003	JBarlow

Bioequivalence	Pending		
EA	Adequate	08-APR-2003	R.Powers
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. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-354

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable- Minor

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

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

Drug Substance: The drug substance is a white to off-white powder with a melting range between 192°C and 193°C. It is soluble in water and has a pH between 4.0 and 5.0 for a 5 g sample dissolved in 100 mL of water.

Drug Product: The 2.5 mg strength of the drug product is white to off white, round, flat-faced, beveled edge, scored tablet debossed with **MH** above the score and **1** below the score on one side of the tablet and **M** on the other side. This strength is packaged in bottles of 100 and 500 tablets.

The 5 mg strength of the drug product is white to off white, round, flat-faced, beveled edge, scored tablet debossed with **MH** above the score and **2** below the score on one side of the tablet and **M** on the other side. This strength is packaged in bottles of 100 and 500 tablets.

The 10 mg strength of the drug product is white to off white, round, flat-faced, beveled edge, scored tablet debossed with **MH** above the score and **3** below the score on one side of the tablet and **M** on the other side. This strength is packaged in bottles of 100 and 500 tablets.

The drug product is manufactured from the drug substance and the following inactive ingredients: Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate. Microcrystalline Cellulose, Pregelatinized Starch and Sodium Lauryl Sulfate.

B. Description of How the Drug Product is Intended to be Used:

See package insert

C. Basis for Approvability or Not-Approval Recommendation

Drug Substance: DMF — has been found deficient. We are recommending that the firm reduce the related substances, limit of ——— and ———, and OVI acceptance criteria to agree more closely with the reported data and report ——— and ———, and OVI results as numerical values, and not as "LT numbers". We are requesting that the firm provide drug substance method validation for the assay and related compounds methods.

Excipients: We are requesting clarification of the following statement: "...that each test described in the inactive ingredient specification is performed on each and every lot of inactive ingredient either by the supplier or Mylan prior to its release for use. Mylan does not use the vendor's COA as the sole basis for release".

Manufacturing: We are requesting a clarification for the description for each strength shown on the ——— In-Process specifications as the description noted on the specifications are the same as final drug product descriptions.

Drug Product: We are requesting that the identity of "Impurity A" be added to the to the drug product release and stability specifications and to report the Related Compounds release and stability test results for the drug product as a numerical value and not as "LT —. We are also recommending that the firm reduce the related compounds release and stability specifications to agree more closely with the reported data and to provide a summary of the evaluation of the related compounds for your different strengths of the drug product versus the data obtained from the evaluation of the different strengths of the related compounds in the reference listed drug.

Standards: We are requesting data for the characterization of the in-house drug substance reference standard. Clarification is needed for a spot described as ——— -In- house standard shown on a ———. A list of reference standard used in the method validation studies for the drug substance and drug product is requested.

III. Administrative

A. Reviewer's Signature /S/

B. Endorsement Block

HFD-623/RPowers, Ph.D./08-APR-2003 Revised: 23-APR-2003 /S/ 5/21/03
HFD-623/AMueller, Ph.D./ /S/ 5-21-03

HFD-617/CKiester, PM./

C. CC Block

Original ANDA/ANDA 76-577
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Page(s) of trade secret and /or confidential commercial information

ANDA 76-577

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

Mylan Pharmaceuticals, Inc.

Roslyn F. Powers, Ph.D.
Office Of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-577 **FIRST GENERIC**

2. REVIEW # 2

3. REVIEW DATE: 23-JUL-2003

4. REVIEWER: Roslyn F. Powers, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	17-DEC-2002
Telecom	17-JAN-2003
Patent Amendment	22-JAN-2003
Amendment	**11-JUN-2003**
Telephone Amendment	**26-AUG-2003**

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals, Inc.
Address:	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Representative:	S. Wayne Talton
Telephone:	304-599-2595 FAX: 304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

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

c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only): N/A

9. LEGAL BASIS FOR SUBMISSION: The basis for the ANDA submission is Shire Pharmaceutical Development, Inc.'s ProAmatine® Tablets (Midodrine Hydrochloride Tablets 2.5 mg, 5 mg and 10 mg), NDA 19815.

   Pursuant to Section 505(j)(2)(a)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, according to the patent information published by the FDA in that document entitled, "Approved Drug Products With Therapeutic Equivalence Evaluations" (22nd Edition through the 'Electronic Orange Book', Cumulative Supplement 10), there are no patents that claim the listed drug referred to in this application.

   Mylan further certifies that according to the exclusivity information published by the FDA in that document entitled, "Approved Drug Products With Therapeutic Equivalence Evaluations" (22nd Edition through the 'Electronic Orange Book', Cumulative Supplement 10), the 2.5 mg, 5 mg and 10 mg strengths of the referenced product are covered by Orphan Drug Exclusivity ("ODE") which expires September 6, 2003.

   Mylan will market its Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg upon approval of this application and expiration of the above-referenced exclusivity.

10. PHARMACOL. CATEGORY: Indicated for the treatment of symptomatic orthostatic hypotension (OH).

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 2.5 mg, 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __X__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    ___X__Not a SPOTS product

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

Executive Summary Section

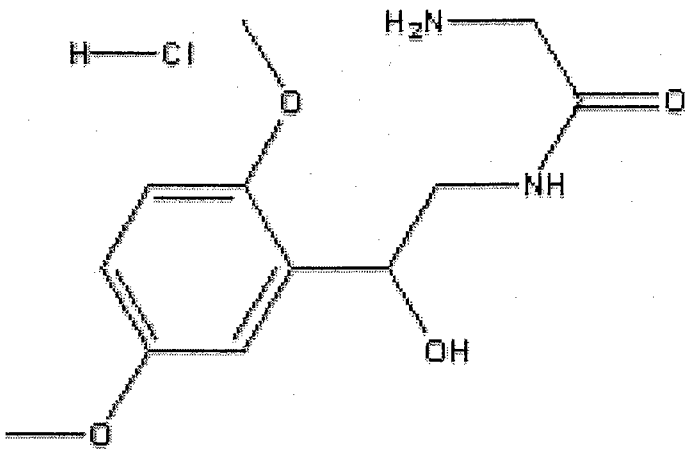
Chemical Name: Acetamide, 2-amino-N-[2-(2, 5-dimeth oxyphenyl)-2-hydroxyethyl] Hydrochloride; 2-amino-N-(β-Hydroxy-2, 5-dimethoxyphenethyl)-Acetamide Hydrochloride

Established Name: Midodrine Hydrochloride

Molecular Formula: $C_{12}H_{18}N_2O_4 \cdot HCl$

Molecular Weight: 290.7

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II				Adequate	22-AUG-2003	RPowers - reviewer
	III			1			
	III						
	III			4			
	III						

Executive Summary Section

	III			4			
	III						
	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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	15-AUG-2003	SFerguson
Methods Validation	Pending		Method Validation Package sent to D. Bargo on 28-JUL-2003.
Labeling	Acceptable	25-JUN-2003	JBarlow
Bioequivalence	Acceptable	27-JUN-2003	MHMakary
EA	Adequate	08-APR-2003	R.Powers
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:

This is a Minor Amendment review.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-577

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

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

Drug Substance: The drug substance is a white to off-white powder with a melting range between 192°C and 193°C. It is soluble in water and has a pH between 4.0 and 5.0 for a 5 g sample dissolved in 100 mL of water.

Drug Product: The 2.5 mg strength of the drug product is white to off white, round, flat-faced, beveled edge, scored tablet debossed with **MH** above the score and **1** below the score on one side of the tablet and **M** on the other side. This strength is packaged in bottles of 100 and 500 tablets.

The 5 mg strength of the drug product is white to off white, round, flat-faced, beveled edge, scored tablet debossed with **MH** above the score and **2** below the score on one side of the tablet and **M** on the other side. This strength is packaged in bottles of 100 and 500 tablets.

The 10 mg strength of the drug product is white to off white, round, flat-faced, beveled edge, scored tablet debossed with **MH** above the score and **3** below the score on one side of the tablet and **M** on the other side. This strength is packaged in bottles of 100 and 500 tablets.

The drug product is manufactured from the drug substance and the following inactive ingredients: Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate. Microcrystalline Cellulose, Pregelatinized Starch and Sodium Lauryl Sulfate.

B. Description of How the Drug Product is Intended to be Used:

See package insert

C. Basis for Approvability or Not-Approval Recommendation

CMC section is acceptable.

Labeling is acceptable.

Bioequivalence is acceptable.

EES is acceptable.

Method Validation is Pending.

III. Administrative

A. Reviewer's Signature /S/ , Ph.D.

B. Endorsement Block

HFD-623/RPowers, Ph.D./27 AUG 2003 /S/ 8/27/03
HFD-623/AMueller, Ph.D /S/ 8-27-03
HFD-617/CKiester, PM./ /S/ 8/27/03

C. CC Block

Original ANDA/ANDA 76-577
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ON ORIGINAL

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-577

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 76-577 SPONSOR : Mylan Pharmaceuticals Inc.
DRUG AND DOSAGE FORM : Midodrine Hydrochloride Tablets
STRENGTH(S) :2.5 mg, 5 mg and 10 mg
TYPES OF STUDIES : Fasting Study & Non-Fasting Study (5 mg)
CINICAL STUDY SITE(S) : ———
ANALYTICAL SITE(S) : Mylan Pharmaceuticals Inc.

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable
WAIVER REQUEST: Waivers for the 2.5 mg and 10 mg strengths are granted

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 :Moheb H. Makary, Ph.D BRANCH : III
INITIAL : MHM DATE : 6/27/03

TEAM LEADER : GJP SINGH, Ph.D BRANCH : III
INITIAL : /S/ DATE : 6-27-03

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

INITIAL : /S/ DATE : 6/27/03

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-577
Drug Product Name	Midodrine Hydrochloride Tablets
Strength	2.5 mg, 5 mg and 10 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Address	Morantown, WV
Submission Date(s)	December 17, 2002
Reviewer	Moheb H. Makary
File Location	V:\FIRMSAM\MYLAN\LTRS&REV\76577N1202.doc

I. Executive Summary

This submission consisted of two BE studies, one under fasting and the other nonfasting conditions and dissolution data on all strengths of the test and reference products. As recommended by DBE, the studies conducted on the 5 mg strength comparing it with ProAmatine^{R} tablet, 5 mg, of Shire US Inc. The study design for each of the BE studies is a two-way, crossover study in normal male and female subjects (n=36 and n=38 for the fasting and nonfasting studies, respectively). Statistical analyses of the plasma concentration data for midodrine for both studies demonstrate bioequivalence.

For the fasting BE study, midodrine results are (point estimate, 90% CI): $LAUC_t$ of 96, 92-100%; $LAUC_i$ of 96, 92-99% and LCmax of 94, 87-102%. For the nonfasting BE study, midodrine results are (point estimate, 90% CI): $LAUC_t$ of 97, 92.0-101.4%; $LAUC_i$ of 98, 94.1-102.4% and LCmax of 86, 77.9-95.9%. The ratios of the geometric means are within the acceptable 0.8-1.25 range for AUCt, AUCi and Cmax for midodrine.It is noted that the study was initiated on October 26, 2002, and meets the FDA criteria in place at that time. The product meets the FDA dissolution specifications. Waivers of in vivo study requirements are granted for the 2.5 mg and 10 mg strengths. The application is acceptable with no deficiencies.

APPEARS THIS WAY
ON ORIGINAL

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product:
Midodrine hydrochloride tablets 2.5 mg, 5 mg and 10 mg, are white to off-white, round, flat-faced edge, beveled edge, scored tablets.

Reference Product:
ProAmatine® (midodrine hydrochloride) tablets are available in three strengths: 2.5 mg, 5 mg and 10 mg. The Orange Book (Electronic 2003) lists ProAmatine® 5 mg tablet manufactured by Shire US Inc. as the reference listed drug (NDA 19815, approved in September 6, 1996). Lot #213531 (EXP. 8/04) of the 5 mg ProAmatine^{R} tablet was used in the BE studies.

Indication:
The RLD is indicated for the treatment of symptomatic orthostatic hypotension.

PK/PD Information

Bioavailability:	Midodrine hydrochloride has an absolute bioavailability of about 93%.
Metabolism:	ProAmatine® (midodrine hydrochloride) tablets are prodrug, i.e., the therapeutic effect of orally administered midodrine is due to its major metabolite desglymidodrine, formed by deglycination of midodrine.

Half Life:	25 minutes
Tmax:	0.5 hour
Excretion:	Renal elimination of midodrine is insignificant. The renal clearance of desglymidodrine is of the order of 385 mL/minute, about 80%, by active renal secretion. The actual mechanism of active secretion has not been studied.
Food Effect:	The bioavailability of desglymidodrine is not affected by food. Approximately the same amount of desglymidodrine is formed after intravenous and oral administration of midodrine.

Relevant DBE History

At the time this ANDA was submitted, the Division of Bioequivalence requested the following for documentation of bioequivalence of midodrine hydrochloride tablets (Control Documents: 01-195: 04/16/01, [redacted] and 01-266, 5/4/01, [redacted]

1). Both fasting and non-fasting studies on the 5 mg tablets to establish bioequivalence. Due to safety reasons, the Division of Bioequivalence has concluded that the 5 mg dose is more appropriate for bioequivalence studies in normal volunteers.
2). Plasma levels of only midodrine for bioequivalence assessment. Quantitation of the metabolite, desglymidodrine for the bioequivalence studies is not requested.
3). Biowaivers for the generic midodrine HCl tablets, 2.5 mg and 10 mg, may be considered if the following conditions are met:
   a. Results of both fasting and non-fasting bioequivalence studies conducted on the 5 mg tablets are acceptable.
   b. Dissolution testing conducted on all three strengths of the generic midodrine HCl tablets is acceptable.
   c. Formulations among the three strengths of generic tablets are proportionally similar.

Based on the NDA review of the biowaiver request for the 10 mg strength of ProAmatine^{R} Tablets, the DBE confirms that midodrine HCl has been classified as a BCS Class I drug substance by the Agency. As the results of this classification, the DBE presently requests the following for midodrine drug products (Control #02-174, dated 3/27/02, Barr):

1. Only dissolution testing for all strengths of the test and reference products in support of a BCS-based biowaiver request for the test product.

2. In addition, the firm is requested to demonstrate that the formulations of all strengths of the test product are proportionally similar, and the excipients used in the test product should be within the excipient concentration ranges of approved IR drug products.

B. Contents of Submission

		How many?	
Single-dose fasting study	Yes	1	
Single-dose fed study	Yes	1	
Steady-state study	No	0	
In vitro dissolution testing	Yes	3	(one for each strength)
Waiver requests	Yes	2	
BCS data	No		
Vasocontrictor studies	No		
Clinical endpoints	No		
Failed studies	No		
Amendments	No		

C. Bioanalytical Method Validation (Pre-Study, Vol.1.2, Page 562)

D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study No.	MIDO-0276
Study Design:	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	38
No. of subjects completing	36
No. of subjects analyzed	36
Sex(es) included (how many?)	Male (22) Female (16)
Test product	Midodrine HCl tablets
Reference product	ProAmatine® (midodrine HCl) tablets of Shire US Inc.
Strength tested	5 mg
Dose	1 x 5 mg tablet

Summary of Statistical Analysis

Parameter	Point Estimate	90% Confidence Interval
LnAUCt	0.96	92 – 100
LnAUCi	0.96	92 – 99
LnCmax	0.94	87 – 102

The study is acceptable. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCt, AUCi and Cmax for midodrine. The reviewer's calculations are similar to those submitted by the firm.

2. Single-dose Fed Bioequivalence Study

Study No.	MIDO-0299
Study Design:	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	38
No. of subjects completing	38
No. of subjects analyzed	38
Sex(es) included (how many?)	Male (11) Female (27)
Test product	Midodrine HCl tablets
Reference product	ProAmatine® (midodrine HCl) tablets of Shire US Inc.
Strength tested	5 mg
Dose	1 x 5 mg tablet

Summary of Statistical Analysis

Parameter	Point Estimate	90% Confidence Interval
LnAUCt	0.97	92 – 101
LnAUCi	0.98	94 – 102
LnCmax	0.86	77.9 – 95.9

The study is acceptable. For the test product, the ratios of the geometric means are within the acceptable 0.8-1.25 range for AUCt, AUCi and Cmax for midodrine. The reviewer's calculations are similar to those submitted by the firm. The study was initiated on October 26, 2002, and meets the FDA acceptance criteria in place at that time for fed bioequivalence studies.

E. Formulation

The test product formulations are shown in Table 1 of the Appendix.

Inactive Ingredients within IIG limits	Yes
The formulation is acceptable	Yes

F. In Vitro Dissolution (FDA Method)

Dissolution studies were conducted in 900 mL of 0.1N HCl at 37^{O}C using USP apparatus II (paddle) at 50 rpm. The dissolution testing conducted by Mylan Pharmaceuticals Inc. on its midodrine hydrochloride tablets, 2.5, 5 and 10 mg, is acceptable.

G. Waiver Requests

The applicant requests a waiver of in vivo bioequivalence testing under 21 CFR 320.22(d)(2) for the 2.5 mg and 10 mg tablets.

The formulations are proportionally similar to that of the strength, which underwent acceptable in vivo testing:	Yes
Acceptable dissolution testing, all strengths:	Yes
H. Deficiency Comment	None

I. Recommendations

1.The single-dose fasting and non-fasting bioequivalence studies conducted by Mylan Pharmaceuticals Inc. on its midodrine hydrochloride, 5 mg tablets, Lot # R1K2293, comparing it to ProAmatine^{R} 5mg tablets, Lot #213531, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Mylan Pharmaceuticals Inc.'s midodrine hydrochloride 5 mg tablets are bioequivalent to the reference product ProAmatine^{R} 5 mg tablets, manufactured by Shire US Inc.

2. The dissolution testing conducted by Mylan Pharmaceuticals Inc. on its midodrine hydrochloride, 2.5 mg, 5 mg and 10 mg, lots #R1K2292, R1K2293 and R1K2294, respectively, is acceptable. The formulations for the 2.5 mg and 10 mg midodrine hydrochloride tablet strengths are proportionally similar to that of the 5 mg midodrine hydrochloride tablet of the test product, which underwent acceptable bioequivalency testing. Waivers of in-vivo bioequivalence study requirements for the 2.5 mg and 10 mg tablets of midodrine hydrochloride are granted per 21 CFR 320.22(d)(2).

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37°C 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.

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

The firm should be informed of the above recommendations.

/S/

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

RD INITIALLED
FT INITIALLED GJP SINGH /S/ Date 6-27-03

Concur: /S/ Date: 6/27/03
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 6-28-03, 76577N1202.doc
cc: ANDA #76-577, original, HFD-658 (Makary), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information

Study Number: #MIDO-0276
Clinical Site:

Dosing Dates: period I: 8/17/2002
period II: 8/24/2002
Analytical Site: Mylan Pharmaceuticals Inc.
Morgantown, WV
Analysis Dates: 8/27/2002-9/13/2002
Storage Period: 26 days

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Midodrine HCl Tablets	ProAmatine® Tablets
Manufacturer:	Mylan Pharmaceuticals Inc.	Shire US Inc.
Manufacture Date:	6/02	N/A
Expiration Date:	N/A	8/04
Strength	5 mg	5 mg
Dosage Form	Tablets	Tablets
Bio Batch Size:	Tablets	N/A
Batch/Lot Number:	R1K2293	213531
Potency	99.7%	101.8%
Content Uniformity	98.5%	101.0%
Formulation	See Table #1	N/A
Dose Administered:	1x5 mg Tablet	1x5 mg Tablet
Route of Administration	Oral	Oral
Study Condition:	Fasting	Fasting

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
Washout Period	7 days
Randomization Scheme	AB for subjects #1, 3, 5, 8, 10, 12, 14, 16, 18, 20, 21, 23, 25, 26, 29, 32, 35, 36 and BA for the rest of subjects.
Blood Sampling Times	0, 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours

Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Under conditions with minimal UV exposure
IRB Approval	Yes, on 7/23/2002

Informed Consent	Yes, 7/23/2002
Subjects Demographics	See Table #3
Length of Fasting:	10 hours pre-dose and 4 hours post-dose.
Length of Confinement	From at least 11 hours pre-dose to 24 hours post-dose.
Safety Monitoring	Vital signs measurements were obtained prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 12 and 24 hours after dosing.

Study Results

Clinical: The firm's clinical summary is provided on Page 86, Vol. 1.5).

Dropout Information	
Subject Nos.	26 and 29
Reason	Subject #26 dropped out of the study during period 1 due to the length of the study confinement. Subject #29 was discontinued from the study during period 1 due to an adverse event (vomiting).
Adverse Events	A total of 20 adverse events were reported. No serious adverse events occurred during the study. 13 following administration of Treatment A 7 following administration of Treatment B For additional information see Vol. 1.5, page #9
Protocol Deviations	No significant deviations from the protocol were documented.

Comments:
The adverse events occurred with greater frequency following treatment A.

DURING STUDY ASSAY VALIDATION (Vol.1.2, page 16)

Parameter	
QC Conc. (ng/mL)	1.5, 5, 30
Standard Curve Conc. (ng/mL)	0.5, 1, 1.5, 2.5, 5, 10, 20, 30, 40, 50
Between-Batch Precision for Standards (%CV)	2.8-7.4
Between-Batch Accuracy for Standards (% Actual)	95.9-103.9
Between-Batch Precision for QC (%CV)	6.5-7.3
Between-Batch Accuracy for QC (% Actual)	95.1-99.9

Repeat Assays
The total number of re-assays represented 1.1% of the overall number of samples analyzed. There were no pharmacokinetic repeats.

Chromatograms: Acceptable

Comments: The analytical method and data for midodrine are acceptable.

Pharmacokinetic/Statistical Analysis for Midodrine

Mean Plasma Concentrations	Table #4, Figure #1

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

a. Arithmetic Mean Pharmacokinetic Parameters (N=36)

PK Parameter	Test Treatment A	Reference Treatment B	T/R
AUCt [ng-hr/mL]	21.50 (23%)	22.82 (44%)	0.94
AUCi [ng-hr/mL]	22.02 (22%)	23.35 (46%)	0.94
Cmax [ng/mL]	26.66 (33%)	28.36 (44%)	0.94
Tmax [hr]	0.486	0.578	
K_{el} [1/hr]	1.597	1.603	
$T_{½}$ [hr]	0.45	0.45	

b. 90% Confidence Intervals (N=36)

Parameter	RMSE	Point Estimate	90% Confidence Interval
LnAUCt	0.099	0.96	92 – 100
LnAUCi	0.095	0.96	92 – 99
LnCmax	0.198	0.94	87 – 102

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for all 36 subjects
- Measurable drug concentrations at 0 hr: None
- First scheduled post-dose sampling time as Tmax: 3
- First measurable drug concentration as Cmax: 3

- Cmax is the first measurable concentration for subject Nos. 14, 19 and 35, after excluding these subjects from the statistical analysis, the 90% confidence intervals remained within the acceptable limits of 80-125% for AUCt, AUCi and, Cmax.
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for AUCt, AUCi, Cmax are within the acceptable limits of 80-125%.

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

2. Single-dose Fed Bioequivalence Study

Study Information

Study Number: # MIDO-0299
Clinical Site: [redacted]

Dosing Dates: period I: 10/26/2002
period II: 11/2/2002
Analytical Site: Mylan Pharmaceuticals Inc.
Morgantown, WV
Analysis Dates: 11/13/2002-11/22/2002
Storage Period: 26 days

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Midodrine HCl Tablets	ProAmatine® Tablets
Manufacturer:	Mylan Pharmaceuticals Inc.	Shire US Inc.
Manufacture Date:	6/02	N/A
Expiration Date:	N/A	8/04
Strength	5 mg	5 mg
Dosage Form	Tablets	Tablets
Bio Batch Size:	[redacted] Tablets	N/A
Batch/Lot Number:	R1K2293	213531
Potency	99.7%	101.8%
Content Uniformity	98.5%	101.0%
Formulation	See Table #1	N/A
Dose Administered:	1x5 mg Tablet	1x5 mg Tablet
Route of Administration	Oral	Oral
Study Condition:	Fed	Fed

No. of Sequences	2
No. of Periods	2

No. of Treatments	2
Washout Period	7 days
Randomization Scheme	AB for subjects #1, 2, 6, 7, 9, 11, 14, 15, 17, 18, 21, 23, 25, 26, 30, 31, 33, 36 and 38 and BA for the rest of subjects.
Blood Sampling Times	0, 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Under conditions with minimal UV exposure
IRB Approval	Yes, on 7/23/2002
Informed Consent	Yes, 7/23/2002
Subjects Demographics	See Table #4
Length of Fasting:	10 hours pre-dose until 30 minutes prior to dosing when a standard breakfast (same as the one recommended by the DBE) was given.
Length of Confinement	From at least 11 hours pre-dose to 24 hours post-dose.
Safety Monitoring	Vital signs measurements were obtained prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 12 and 24 hours after dosing.

Study Results

Clinical: The firm's clinical summary is provided on Page 9, Vol. 1.9).

Dropout Information	
Subject Nos.	None
Adverse Events	A total of 29 adverse events were reported. No serious adverse events occurred during the study. 14 following administration of Treatment A 15 following administration of Treatment B For additional information see Vol. 1.4, page #1270
Protocol Deviations	No significant deviations from the protocol were documented.

Comments:
The adverse events occurred with same frequency for both treatments.

DURING STUDY ASSAY VALIDATION (Vol.1.7, page 17)

Parameter	
QC Conc. (ng/mL)	1.5, 5, 30
Standard Curve Conc. (ng/mL)	0.5, 1, 1.5, 2.5, 5, 10, 20, 30, 40, 50
Between-Batch Precision for Standards (%CV)	3.2-8.3
Between-Batch Accuracy for Standards (% Actual)	96.7-103.8

Between-Batch Precision for QC (%CV)	4.8-7.4
Between-Batch Accuracy for QC (% Actual)	92.5-97.4

Repeat Assays
There were no miscellaneous repeats.

Chromatograms: Acceptable

Comments: The analytical method and data for midodrine are acceptable.

Pharmacokinetic/Statistical Analysis for Midodrine

Mean Plasma Concentrations	Table #6, Figure #2

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

a. Arithmetic Mean Pharmacokinetic Parameters (N=38)

PK Parameter	Test Treatment A	Reference Treatment B	T/R
AUCt [ng-hr/mL]	26.35 (23%)	27.23 (22%)	0.97
AUCi [ng-hr/mL]	27.72 (21%)	28.21 (22%)	0.98
Cmax [ng/mL]	15.78 (20%)	19.09 (36%)	0.83
Tmax [hr]	1.101	1.05	
K_{el} [1/hr]	1.134	1.145	
$T_{½}$ [hr]	0.65	0.65	

b. 90% Confidence Intervals (N=38)

Parameter	RMSE	Point Estimate	90% Confidence Interval
LnAUCt	0.124	0.97	92 – 101
LnAUCi	0.107	0.98	94 – 102
LnCmax	0.268	0.86	77.9 – 95.9

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for 37 subjects
- Measurable drug concentrations at 0 hr: None
- First scheduled post-dose sampling time as Tmax: None
- First measurable drug concentration as Cmax: None.
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The geometric mean ratios for AUC and Cmax are within the acceptable limits of 80-125%.

Conclusion:

The post-prandial bioequivalence study is acceptable.

B. Attachments
Fig I - Fasting Study

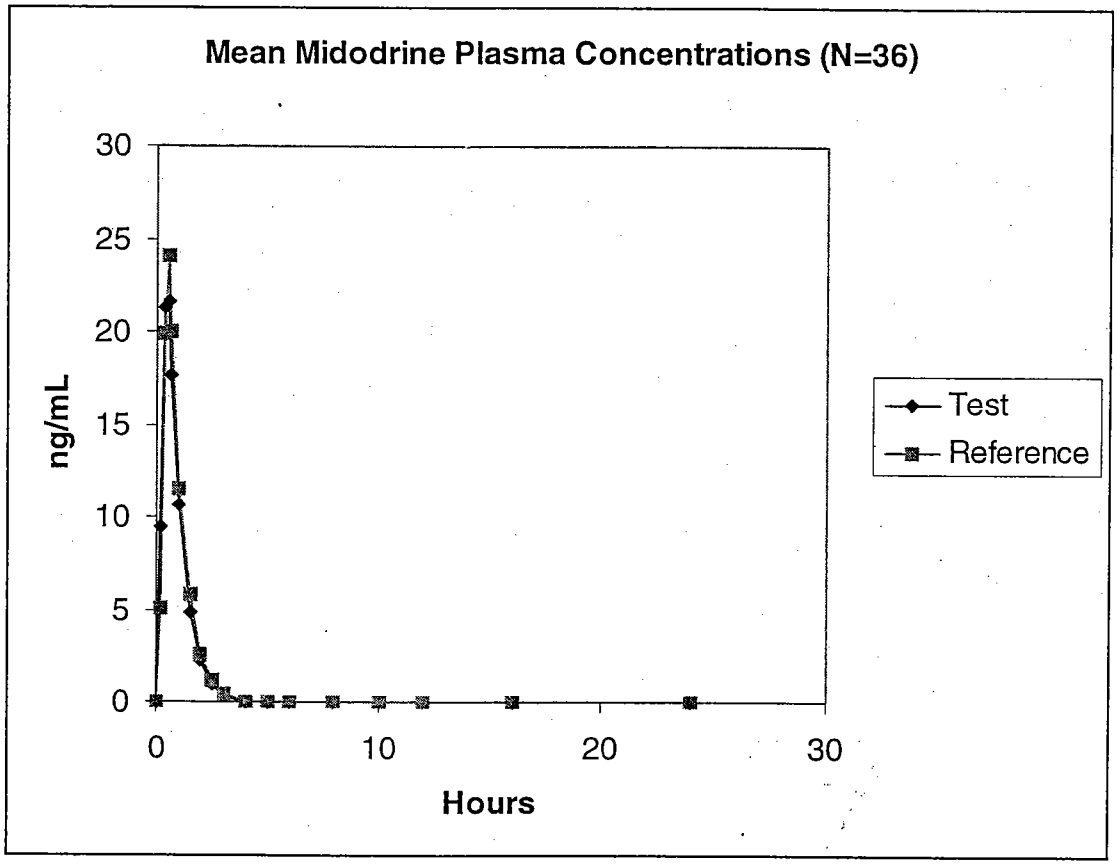

Fig II- Fed Study

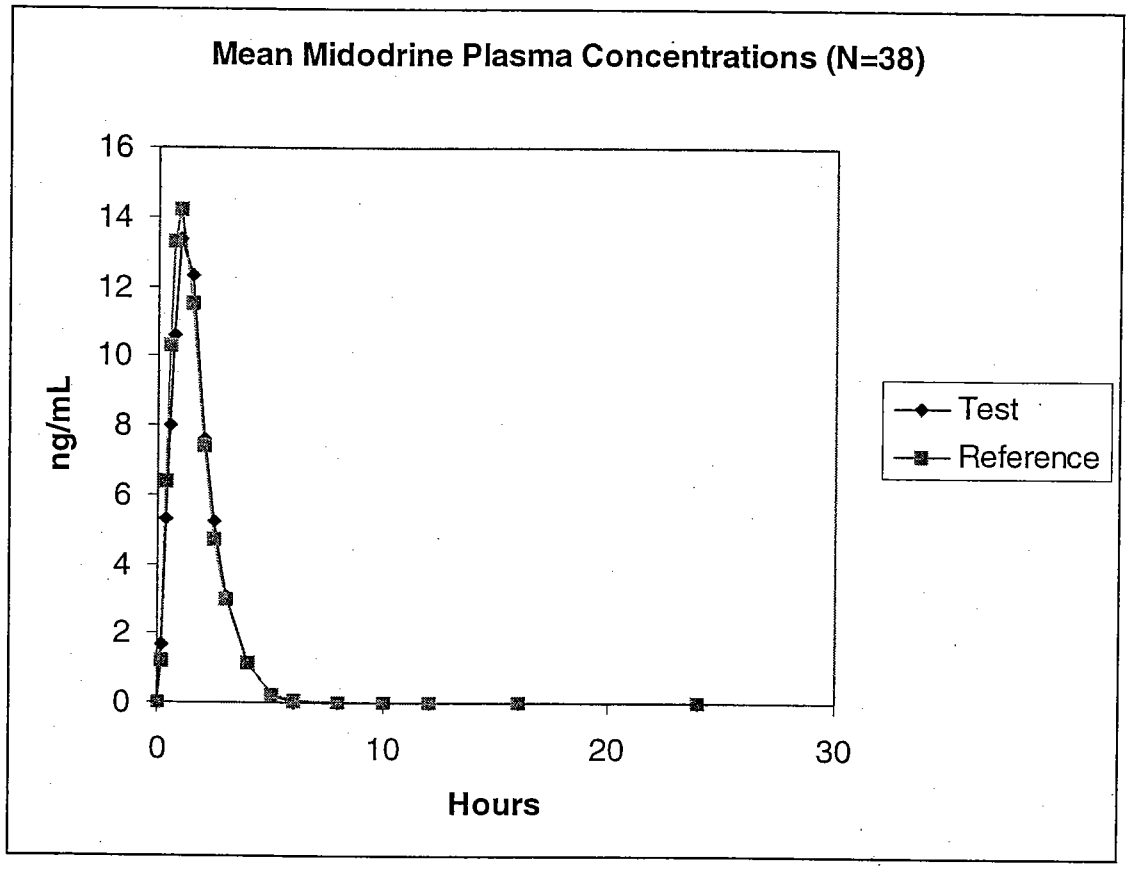

TABLE 1: Formulation - Not to be released under FOI

Formula Ingredients	2.5 mg tablet	5 mg tablet	10 mg tablet
	mg/tab	mg/tab	mg/tab
Midodrine Hydrochloride	2.50	5.00	10.00
Colloidal Silicon Dioxide NF			
Magnesium Stearate/Sodium Lauryl Sulfate			
Microcrystalline Cellulose, NF			
Pregelatinized Starch, NF			
Croscarmellose Sodium, NF			
Total	**125.0**	**250.0**	**500.0**

Table II

Test Products: Midodrine Hydrochloride Tablets
Dose strengths: 2.5 mg, 5 mg and 10 mg
Reference Products: ProAmatine® Tablets, 2.5 mg, 5 mg and 10 mg
900 mL of 0.1N HCl, apparatus 2 (paddle) at 50 rpm, NLT (Q) in 15 minutes

Results of dissolution testing (% dissolved in minutes)

Sampling time (min)	Test product Midodrine HCl Tablets **2.5 mg**, Lot # R1K2292			Reference Product ProAmatine® Tablets **2.5 mg**, Lot # 212811		
	Mean	Range	%CV	Mean	Range	%CV
5	89		7.1	98		5.4
10	96		3.6	100		5.6
15	97		1.9	100		5.4
Sampling time (min)	Test product Midodrine HCl Tablets **5 mg**, Lot # R1K2293			Reference Product ProAmatine® Tablets **5 mg**, Lot # 213531		
	Mean	Range	%CV	Mean	Range	%CV
5	90		7.2	98		1.9
10	95		3.9	99		1.7
15	97		2.3	100		1.6
Sampling time (min)	Test product Midodrine HCl Tablets **10 mg**, Lot # R1K2294			Reference Product ProAmatine® Tablets **10 mg**, Lot # 214911		
	Mean	Range	%CV	Mean	Range	%CV
5	86		9.4	97		4.1
10	95		4.8	100		2.5
15	99		2.7	101		1.9

Table 3 : Subject Demographics for Fasting Study									
Age		Age Groups		Gender		Race		Weight (lbs)	
		Range	%	Sex	%	Category	%		
		<18	0			Caucasian	73.7		
Mean	30.1	24-40	76.3	Male	57.9	Black.	10.5	Mean	165.0
SD	10.1	41-64	23.7	Female	42.1	Asian	10.5	SD	26.0
Range	19-52	65-75	0			Other	2.6	Range	115-238
		>75	0			Hispanic	2.6		

Table 4: Subject Demographics for Fed Study									
Age		Age Groups		Gender		Race		Weight (lbs)	
		Range	%	Sex	%	Category	%		
		<18	0			Caucasian	65.8		
Mean	24.7	18-40	100	Male	28.9	Black.	18.4	Mean	146.9
SD	5.4	41-64	0	Female	71.1	Asian	2.6	SD	22.6
Range	19-40	65-75	0			Hispanic	7.8	Range	115-202
		>75	0			Other	5.3		

Table 5: Mean Plasma Concentration (ng/mL) of Midodrine – Fasting Study

Time (Hrs)	Test Treatment A	Test Treatment B	Ratio (A vs B)
pre-dose	0.00 .	0.0 .	.
0.17	9.43 (95)	5.10 (101)	1.85
0.33	21.29 (54)	19.94 (62)	1.07
0.5	21.62 (40)	24.08 (52)	0.90
0.67	17.61 (37)	20.03 (46)	0.88
1.0	10.61 (48)	11.54 (45)	0.92
1.5	4.79 (51)	5.79 (57)	0.83
2.0	2.23 (62)	2.53 (49)	0.88
2.5	0.96 (65)	1.17 (71)	0.82
3.0	0.33 (143)	0.41 (141)	0.80
4.0	0.00 .	0.03 (600)	0.00
5.0	0.00 .	0.00 .	.
6.0	0.00 .	0.00 .	.
8.0	0.00 .	0.00 .	.
10.0	0.00 .	0.00 .	.
12.0	0.00 .	0.00 .	.
16.0	0.00 .	0.00 .	.
24.0	0.00 .	0.00 .	.

Table 6: Mean Plasma Concentration (ng/mL) of Midodrine – Fed Study

Time (Hrs)	Test Treatment A	Test Treatment B	Ratio (A vs B)
pre-dose	0.00 .	0.0 .	.
0.17	1.68 (151)	1.19 (270)	1.41
0.33	5.32 (85)	6.38 (137)	0.83
0.5	7.99 (60)	10.32 (90)	0.77
0.67	10.59 (47)	13.32 (65)	0.80
1.0	13.34 (31)	14.24 (34)	0.94
1.5	12.29 (29)	11.52 (42)	1.07
2.0	7.62 (39)	7.41 (58)	1.03
2.5	5.22 (60)	4.71 (70)	1.11
3.0	3.05 (62)	3.02 (82)	1.01
4.0	1.13 (106)	1.14 (116)	0.99
5.0	0.22 (218)	0.24 (243)	0.92
6.0	0.02 (616)	0.03 (616)	0.67
8.0	0.00 .	0.00 .	.
10.0	0.00 .	0.00 .	.
12.0	0.00 .	0.00 .	.
16.0	0.00 .	0.00 .	.
24.0	0.00 .	0.00 .	.

BIOEQUIVALENCY COMMENTS

ANDA: 76-577 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg

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

We acknowledge that the following dissolution testing has been incorporated in 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 #76-577
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

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Printed in final on 6/27/03

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM
HFD-658/ Bio team Leader G. Singh GSPS 6-27-03
HFD-650/ D. Conner BNO 6/27/03

BIOEQUIVALENCY - ACCEPTABLE submission date: 12-17-02

1. **FASTING STUDY** (STF) Strengths: 5 mg
Clinical:: [redacted] **Outcome: AC**
Analytical: Mylan Pharmaceuticals Inc.

2. **FOOD STUDY** (STF) Strengths: 5 mg
Clinical: [redacted] **Outcome: AC**
Analytical: Mylan Pharmaceuticals Inc.

3. **DISSOLUTION WAIVER** (DIW) Strengths: 2.5 mg
Outcome: AC

4. **DISSOLUTION WAIVER** (DIW) Strengths: 10 mg
Outcome: AC

Outcome Decisions: **AC** – Acceptable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-577

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

1. We called the firm and asked them to tighten their drug product release and stability specification for Assay. Currently it is [redacted]

2. We also asked them to tighten their drug product specification for Any Unknown Impurity. Currently it is at NMT [redacted]

This application is an approval pending the expiration of the Orphan Drug Exclusivity on September 6, 2003.

The firm is to submit the response via fax to Craig Kiester, and follow up with a hard copy.

DATE: 8/25/2003
ANDA NUMBER 76-577
TELECON INITIATED BY FDA
PRODUCT NAME: Midodrine HCl Tablets, 2.5mg, 5mg, 10 mg
FIRM NAME: Mylan Pharmaceuticals
FIRM REPRESENTATIVES: Wayne Talton
TELEPHONE NUMBER: 304.599.2595
FDA REPRESENTATIVES: Roslyn Powers Al Mueller Craig Kiester
SIGNATURES:

Orig: ANDA
Cc: Division File
Chem. I Telecon Binder

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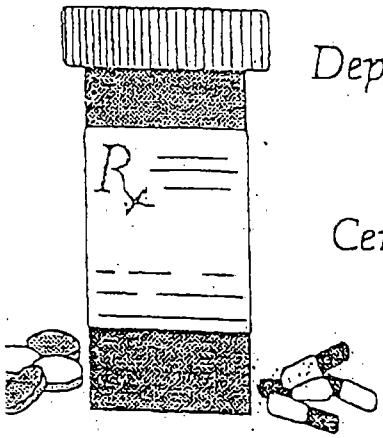
FAX COVER SHEET



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: 9/1/03

To: Emma Kravitsky

Phone: _____ Fax: _____

From: Craig Kleeb

Phone: (301) 827-5848 FAX: (301) 594-0180

Number of pages: 4
(Including Cover Sheet)

Comments: Congrats!

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : January 3, 2003

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

/S/ 03-JAN-2003

SUBJECT: Examination of the bioequivalence study and waiver submitted with an ANDA for Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg **(the 10 mg is a new strength)** to determine if the application is substantially complete for filing.

Mylan Pharmaceuticals Inc. has submitted ANDA 76-577 for Midodrine Hydrochloride Tablets, 2.5 mg, 5 mg and 10 mg **(the 10 mg is a new strength)**. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study and waiver submitted by Mylan on December 17, 2002 for its Midodrine Hydrochloride product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-577

CORRESPONDENCE

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

FAX COVER

ORIG AMENDMENT

N/AM

DATE: August 26, 2003

TO: Mr. Craig Kiester
OGD, CDER, FDA
Fax 301-594-0180

FROM: Wayne Talton, Executive Director
Regulatory Affairs Department
Mylan Pharmaceuticals Inc.

RE: Midodrine Hydrochloride Tablets, 2.5mg, 5mg and 10mg
ANDA 76-577

Mr. Keister:

In response to your telephone call received on August 25, 2003, attached is a copy of our Telephone Amendment being sent by express mail for delivery on Wednesday, August 27, 2003.

Regards,

S. Wayne Talton

PHONE - (800) 826-9526 Ext. 6551

FAX - (304) 285-6407

Number of pages including this sheet 21

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Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

August 26, 2003

TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MIDODRINE HYDROCHLORIDE TABLETS, 2.5MG, 5MG AND 10MG
ANDA 76-577
(Response to FDA Telephone Call Received on August 25, 2003)

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application, which is currently under review and to a telephone call received on August 25, 2003 from Mr. Craig Kiester, of your Office, regarding our drug product specifications for Midodrine Hydrochloride Tablets. In response to the Agency's comments of August 25, Mylan wishes to amend the application as follows:

FDA COMMENT:

Concerning the drug product specifications, revise the release and stability specifications for Assay to [redacted]

MYLAN RESPONSE:

The Assay specification for Midodrine Tablets, 2.5mg, 5mg and 10mg has been tightened to [redacted] from [redacted]% as requested by the Agency. Revised finished product specifications, and pre- and post-approval stability protocols are provided in Attachments A and B, respectively.

FDA COMMENT:
Concerning the drug product specifications, revise the specification for Any Unknown Impurity from Not More Than [redacted]% to Not More Than [redacted] % for product release.

MYLAN RESPONSE:

As requested by the Agency, the Related Compounds specification for Any Unknown Impurity for Midodrine Tablets, 2.5mg, 5mg and 10mg has been tightened to Not More Than [redacted]. Revised finished product specifications are provided in Attachment A.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 11, 2003

MINOR AMENDMENT
(CMC AND LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

DRUG AMENDMENT
N/AM

RE: MIDODRINE HYDROCHLORIDE TABLETS, 2.5MG, 5MG AND 10MG
ANDA 76-577
RESPONSE TO AGENCY CORRESPONDENCE DATED MAY 22, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the CMC and Labeling comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated May 22, 2003 (provided in Attachment L). In response to the Agency's comments of May 22nd, Mylan wishes to amend this application as follows.

A. Deficiencies

FDA COMMENT 1: DMF [redacted] has been found deficient. Please do not respond to any of these deficiencies until the DMF holder has informed you that they have responded to the DMF deficiencies.

MYLAN RESPONSE: Mylan has been notified by [redacted] that an amendment that addresses all deficiencies noted by the Agency has been submitted to DMF [redacted] A copy of Industriale [redacted] letter to the Agency dated May 15, 2003 is provided in Attachment A for the convenience of the reviewer.

FDA COMMENT 2: We recommend that you reduce the [redacted] acceptance criterion in your drug substance specification to "NMT [redacted]

MYLAN RESPONSE: As requested by the agency, Mylan has reduced the [redacted] acceptance criterion in the drug substance specification to "NMT [redacted] Revised drug substance specifications are provided in Attachment B.

In addition Mylan has revised the drug substance specifications for residual solvents and related compounds to harmonize the specifications with those of the supplier. The supplier's specifications were tightened as requested by the Agency. The residual solvents specifications for [redacted] were tightened to not more than (NMT) [redacted] from NMT [redacted] and for [redacted] to NMT [redacted] from NMT [redacted]. The related compounds specification for Total Impurities was tightened to NMT [redacted] from NMT [redacted]

Also, based upon recent drug substance batch data Mylan has shifted the tapped density specifications to [redacted] from [redacted]

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JUN 12 2003

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0468	Quality Assurance	(304) 598-5407
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

following table summarizes the tapped density and particle size data results for all drug substance batches received to date.

Batch No.	D (NMT	D (NMT	Tapped Density
S-2616/7 (exhibit batch)			
20118 (exhibit batch)			
20458			
20502			

Revised drug substance specifications and certificates of analysis for both lots of material used in the exhibit batches are provided in Attachments B and C, respectively.

FDA COMMENT 3: Please provide drug substance method validation for the assay and related compounds methods.

MYLAN RESPONSE: Mylan's methods and methods validation for the drug product is inclusive of the API and satisfies all USP and ICH requirements for method validation. The drug substance method validation requested is a subset of the submitted method validation for the drug product. Method validation for the assay method is found on pages 5515 – 5607 of the original ANDA application while method validation for the related compounds method is found on pages 5608 - 5723. For the reviewer's convenience, a copy of these pages is provided in Attachment D.

FDA COMMENT 4: We note that you stated on page 4655 that each test described in the inactive ingredient specification is performed on each and every lot of inactive ingredient either by supplier or Mylan prior to its release for use. Mylan states that they do not use the vendor's COA as the sole basis for release. Please indicate whether this practice relates to your company's vendor validation protocol. Do not send any SOP's regarding your vendor validation procedures.

MYLAN RESPONSE: The statement to which the reviewer refers was not meant to imply that Mylan has a global vendor validation protocol and/or program. As part of our evaluation of all incoming raw materials, Mylan does review the suppliers' test results reported on their COAs. Mylan maintains a practice of using the suppliers' test results for release in two very limited cases. First, if applicable, we may not routinely test for solvents specified in the USP test for Organic Volatile Impurities <467> if we have an acceptable certification statement from the vendor stating that there is no potential for the specified solvents to be present. Second, for microcrystalline cellulose products Mylan maintains a reduced testing program. In this case, Mylan will use test results for

All other required testing for is conducted by Mylan on each and every lot.

FDA COMMENT 5: Please add the identity of "Impurity A" to the drug product tentative COAs, to the Pre-Approval Stability Protocols, and to the Post-Approval Stability Protocols shown on pages 5023-5025, pages 5726-5768 and pages 5766-5768, respectively. Please add the identity of "Impurity A" to the blank tentative stability forms for the three strengths of the drug product (not provided). Please provide revised copies.

MYLAN RESPONSE: As requested by the agency, Mylan has added the identity of Impurity A to the drug product tentative Certificates of Analysis, the Pre-Approval Stability Protocols and the Post-Approval Stability Protocols for all three strengths of drug product. Please find in Attachments E and F the revised drug product Certificates of Analysis and Pre- and Post- Approval Stability Protocols for the three dosages of the drug product, respectively.

Although not requested, Mylan would like to take this opportunity to submit all updated methods that include reference to Impurity A. Drug substance Assay and Related Compounds procedures, House standard Chromatographic Purity procedure, and Finished Product Assay, Uniformity of Dosage Units, and Related Compounds procedures are provided in Attachment G.

FDA COMMENT 6: We recommend that you tighten the release and stability assay acceptance criterion to agree more closely with the reported data. Please advise.

MYLAN RESPONSE: Mylan recognizes the Agency's request to tighten the release and stability assay acceptance criterion to agree more closely with the reported data. After further review of the data, Mylan has tightened the release and stability assay specification to not less than [redacted] and not more than [redacted] of the labeled claim of Midodrine Hydrochloride is present in the drug product. Revised Certificates of Analysis, Pre- and Post-Approval Stability Protocols, and drug product specifications are provided in Attachments E, F, and H, respectively.

FDA COMMENT 7: We recommend that you add a [redacted] test to the release and stability specifications for all the strengths of the drug product.

MYLAN RESPONSE: As requested by the Agency, Mylan has added a [redacted] specification to the release and stability specifications for all three strengths of the drug product. After review of the available data Mylan has established a [redacted] specification for Midodrine Hydrochloride Tablets to be not more than [redacted] as determined by method FP-MIDOD-KF-M. Revised drug product specifications and the method for [redacted] determination are provided in Attachments H and I, respectively.

FDA COMMENT 8: Please provide the lot number and data obtained from the characterization of the in-house drug substance reference standard.

MYLAN RESPONSE: The lot number for the in-house reference standard is RD-S-2616/7. The data for the characterization of the house reference standard is included in the raw materials section (Section VIII) located on pages 4624 - 4649 of the ANDA. For the reviewer's convenience, a copy of these pages is provided in Attachment J.

Please note that the [redacted] procedure (RA-MIDOD-CP1-M) on pages 4639-4640 of the original submission has been revised and is provided in Attachment G (see Comment 5) and the Verification of Chromatographic Purity procedure on pages 4647-4648 of the original submission has been revised and is provided in Attachment K (see Comment 9).

FDA COMMENT 9: We note that you show a [redacted] showing a spot for "[redacted]" - In-house standard which you report as lot S-2616/7 and a [redacted] for the same lot number (pages 5308-5309). Please clarify.

MYLAN RESPONSE: The resolution solution in the Verification of [redacted] method is prepared by the addition of Impurity A into a suitable Midodrine Hydrochloride test preparation. The test material was used for this analysis as it was the lot of material being controlled as the house reference standard. The preparation of the resolution solution has been clarified in the revised procedure (RA-MIDOD-CP2-M), which is provided in Attachment K.

FDA COMMENT 10: Please provide a list of reference standards, including lot numbers, used in the method validation studies for the drug substance and drug product.

MYLAN RESPONSE: Two qualified reference standards were used in the method validation studies of Midodrine Hydrochloride drug substance and drug product. The Midodrine Hydrochloride House Reference Standard was qualified by Mylan and the lot number is Lot # RD-S-2616/7: The Impurity A used for methods validation was an authentic reference material provided by the drug substance supplier and the Lot # is A-2323.

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

FDA COMMENT 1: Please provide current room temperature stability data.

MYLAN RESPONSE: In response to the Agency's request, updated room temperature stability data through 9 months is provided in Attachment M for Midodrine Hydrochloride Tablets, 2.5mg - Lot R1K2292, 5mg - Lot R1K2293 and 10mg - Lot R1K2294. Please note that the stability sheets have been revised to reflect the identity of Impurity A as requested in Comment 5, the assay specification proposed in Comment 6, and the limit for [redacted] proposed in Comment 7 above.

FDA COMMENT 2: The bioequivalence section of your ANDA is under review by the Division of Bioequivalence. Once we have completed the review, deficiencies, if any, will be communicated to you under a separate cover.

MYLAN RESPONSE: Mylan acknowledges that our bio-equivalency information is pending review and deficiencies will be communicated separately. Mylan will resolve any issues identified by the Division of Bioequivalence at that time.

FDA COMMENT 3: The firms referenced in your ANDA application relative to the manufacturing and testing of the drug product must be in compliance with the cGMPs at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

MYLAN RESPONSE: Mylan acknowledges that the firms referenced in the application must be in compliance with cGMPs at the time of approval and that an evaluation has been requested.

FDA COMMENT 4: The drug substance and drug product do not have USP monographs. Method Validation of the analytical methods used for both the drug substance and the drug product are required. Once the drug substance method validation deficiencies have been addressed, the revised method validation package will be requested and this package will be sent to the method validation coordinator.

MYLAN RESPONSE: Mylan acknowledges that since the drug substance and the drug product are not covered by any USP official monograph, the analytical methods have to be validated by an FDA field laboratory and that samples will be requested by the FDA at the appropriate time.

C. REGARDING LABELING DEFICIENCIES

MYLAN RESPONSE: Regarding the labeling deficiencies, Attachment P contains twelve (12) copies of the following final printed bottle labels and outsert for Midodrine Hydrochloride Tablets, 2.5mg, 5mg and 10mg.

BOTTLE LABELS

2.5mg
Code RM1901A - Bottles of 100 Tablets
Code RM1901B - Bottles of 500 Tablets

5mg
Code RM1902A - Bottles of 100 Tablets
Code RM1902B - Bottles of 500 Tablets

10mg
Code RM1903A - Bottles of 100 Tablets
Code RM1903B - Bottles of 500 Tablets

OUTSERT
Code MIDO:R1, Revised May 2003

The enclosed labeling incorporates the revisions requested in the Agency's letter of May 22, 2003. A copy of this correspondence is provided in Attachment L for the convenience of the reviewer.

In order to facilitate the review of this labeling, Attachment N contains a side-by-side comparison of the revised final printed bottle labels to those previously submitted draft bottle labels and Attachment O contains a side-by-side comparison of the revised final printed outsert (MIDO:R1) to the draft outsert that was previously submitted (MIDO:RX). Mylan acknowledges that prior to approval of this application, the Agency may request further changes to the labeling. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn
Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 10, 2003

TELEPHONE AMENDMENT
(BIOEQUIVALENCE INFORMATION ENCLOSED)

ORIG AMENDMENT

N/AB

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MIDODRINE HYDROCHLORIDE TABLETS, 2.5MG, 5MG AND 10MG
ANDA 76-577
(Response to FDA Telephone Call Received on June 3, 2003)

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application, which is currently under review. Reference is also made to a telephone call received on June 3, 2003 from Mr. Steven Mazzella, of your Office, regarding our bioanalytical report included in our original ANDA for Midodrine Hydrochloride Tablets. In response to the request received on June 3rd, Mylan wishes to amend the application as follows:

FDA COMMENT:

Regarding the analytical section of your bioequivalence study report, please provide recovery data for Midodrine and for the internal standard.

MYLAN RESPONSE:

The assay method used to analyze plasma samples from the Midodrine bioequivalence study utilizes a [redacted]. For the reviewer's reference, a detailed description of the Midodrine assay method is summarized below (see Summary of Midodrine Assay).

In an effort to determine [redacted], for the Midodrine assay, it was determined that there was no scientifically viable approach to obtain traditional recovery data, specifically data representing the 100% recovery standard (standard for comparison to extracted samples) with the [redacted] employed. As a result, the validation of the [redacted] method for the determination of Midodrine and Desglymidodrine in human plasma did not include analytical recovery data (ANDA Volume 1.2, Page 572 which is Section 16, Page 11 of the Validation Report). The absence of the recovery data does not indicate a weakness in the method, as the other validation experiments have shown that the Midodrine assay is selective, sensitive and is capable of generating results that are consistent, precise, accurate and reproducible. The inter-day accuracy and precision experiments indicated that analytical CVs are [redacted] for Midodrine, and [redacted] for Desglymidodrine at low, medium, and high concentrations (ANDA Volume 1.2, Pages 577-580 which is Table 3 in the Validation Report), and [redacted] for internal standard (ANDA Volume 1.2. Page 666 which is Attachment 3 of the Validation Report). In addition, [redacted], is a measure of recovery with respect to different plasma sources (ANDA Volume 1.2, Page 572 which is Section 13, page 11 of the Validation Report).

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Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
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The Agency's Guidance document entitled *Bioanalytical Method Validation* states that the "guidance provides general recommendations for bioanalytical method validation. The recommendations can be adjusted or modified depending on the specific type of analytical method used." Using a [redacted], collection of traditional recovery data is not feasible.

Summary of Midodrine Assay

[redacted]

If there are remaining issues following the review of this Telephone Amendment, we would appreciate the opportunity to discuss our bioanalytical method validation in a telephone conference with the Division of Bioequivalence prior to any further action being taken by the Agency.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 22, 2003

TELEPHONE AMENDMENT
(PATENT AMENDMENT ENCLOSED)

NEW CORRESP

NC

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MIDODRINE HYDROCHLORIDE TABLETS, 2.5MG, 5MG AND 10MG
ANDA 76-577
(Response to FDA Telephone Call Received on January 17, 2003)

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application, which is currently under review, and to a telephone call received on January 17, 2003 from Ms. Christine Bina, of your office, regarding our Patent/Exclusivity Certification included in our original ANDA for the 10mg tablet strength. Ms. Bina informed us that FDA's document entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", the Orange Book, contains an error and the Orphan Drug Exclusivity ("ODE") actually covers all three strengths of the product. The information contained in the current version of the Electronic Orange Book excludes the 10mg from the ODE.

As requested by Ms. Bina, we wish to submit a Patent Amendment to certify that the 10mg strength of Midodrine Hydrochloride Tablets is covered by Orphan Drug Exclusivity which expires September 6, 2003. A Patent Amendment letter is provided in Attachment A

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Tse for

Frank R. Sisto
Executive Vice President
Regulatory Affairs and Generic Drug Development

FRS/dn

Enclosure

RECEIVED
JAN 23 2003
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ANDA 76-577

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

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 January 17, 2003 and your correspondence dated January 22, 2003.

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

DATE OF APPLICATION: December 17, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 18, 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/ for

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

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

505(b)(2)(A)OK
28-JAN-2003
IS

December 17, 2002

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MIDODRINE HYDROCHLORIDE TABLETS, 2.5MG, 5MG AND 10MG

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Midodrine Hydrochloride Tablets, 2.5mg, 5mg and 10mg
This application consists of a total of 27 volumes.
Archival Copy - 12 volumes.
Review Copy - 13 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 10 volumes.
Analytical Methods - 2 extra copies; 1 volume each.
NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application.

This application provides for the manufacture of Midodrine Hydrochloride Tablets, 2.5mg, 5mg and 10mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Sales & Marketing	(304) 598-3232

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

for

Frank R. Sisto
Executive Vice President
Regulatory Affairs and Generic Drug Development

FRS/dn

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

December 17, 2002

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MIDODRINE HYDROCHLORIDE TABLETS, 2.5MG, 5MG AND 10MG

Dear Mr. Buehler:

Mylan certifies the following:

1) The conditions of use prescribed, recommended or suggested in the labeling proposed by Mylan for this product, Midodrine Hydrochloride Tablets, have been previously approved for the listed drug, ProAmatine® (Midodrine Hydrochloride) Tablets. This certification is based upon a comparison of Mylan's proposed labeling to that currently approved for the reference listed drug;

2) The active ingredient, Midodrine Hydrochloride, contained in the proposed drug product is the same as that of the reference listed drug;

3) The route of administration, dosage forms and strengths of the proposed drug product are the same as those for the reference listed drug.

Please see the attached Table of Comparison and Annotated Labeling illustrating the foregoing.

Sincerely,

Frank R. Sisto
Executive Vice President
Regulatory Affairs and Generic Drug Development

FRS/dn

Enclosures

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