CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074537

Trade Name : SELEGILINE HYDROCHLORIDE

Generic Name: Selegiline Hydrochloride Tablets 5mg

Sponsor : Granutec Inc./ Novopharm Ltd.

Approval Date: August 2, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074537

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Clinical Pharmacology Biopharmaceutics Review(s)				X
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074537

APPROVAL LETTER

ANDA 74-537

AUG 2 1996

Granutec, Inc.
U.S. Agent for: Novopharm, Ltd.
Attention: Therese M. Ast, Ph.D.
4409 Airport Drive N.W.
Wilson, NC 27896

Dear Madam:

This is in reference to your abbreviated new drug application dated August 23, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Selegiline Hydrochloride Tablets USP, 5 mg.

Reference is also made to your amendments dated April 23, June 25 and July 25, 1996.

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 Selegiline Hydrochloride Tablets USP, 5 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Eldepryl Tablets, 5 mg of Somerset Pharmaceuticals, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. 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 proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-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-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 8/2/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074537

FINAL PRINTED LABELING

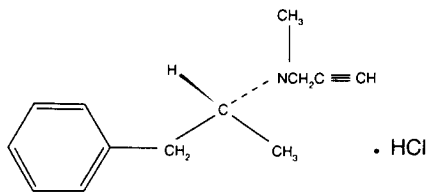
SELEGILINE HYDROCHLORIDE TABLETS USP

APPROVED AUG 2 1994

DESCRIPTION

Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as 1-deprenyl.

The chemical name is: (-)-(R)-*N*, α-dimethyl-*N* - 2-propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol, and has a molecular weight of 223.75. The structural formula is as follows:



Molecular Formula: $C_{13}H_{17}N{\cdot}HCl$

Each tablet, for oral administration, contains 5 mg of selegiline hydrochloride. Inactive ingredients are lactose monohydrate, starch (corn), povidone, magnesium stearate and talc.

CLINICAL PHARMACOLOGY

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

Selegiline is best known as an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. Selegiline inhibits MAO by acting as a 'suicide' substrate for the enzyme; that is, it is converted by MAO to an active moiety which combines irreversibly with the active site and/or the enzyme's essential FAD cofactor. Because selegiline has greater affinity for type B than for type A active sites, it can serve as a selective inhibitor of MAO type B if it is administered at the recommended dose.

MAOs are widely distributed throughout the body; their concentration is especially high in liver, kidney, stomach, intestinal wall, and brain. MAOs are currently subclassified into two types, A and B, which differ in their substrate specificity and tissue distribution. In humans, intestinal MAO is predominantly type A, while most of that in brain is type B.

In CNS neurons, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. MAO in the GI tract and liver (primarily type A), for example, is thought to provide vital protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed intact, to cause a 'hypertensive crisis', the so-called 'cheese reaction'. (If large amounts of certain exogenous amines gain access to the systemic circulation - e.g., from fermented cheese, red wine, herring, over-the-counter cough/cold medications, etc.- they are taken up by adrenergic neurons and displace norepinephrine from storage sites within membrane bound vesicles. Subsequent release of the displaced norepinephrine causes the rise in systemic blood pressure, etc.)

In theory, therefore, because MAO A of the gut is not inhibited, patients treated with selegiline at a dose of 10 mg a day can take medications containing pharmacologically active amines and consume tyramine-containing foods without risk of uncontrolled hypertension. However, one case of hypertensive crisis has been reported in a patient taking the recommended dose of selegiline and a sympathomimetic medication (ephedrine). The pathophysiology of the 'cheese reaction' is complicated and, in addition to its ability to inhibit MAO B selectively, selegiline's relative freedom from this reaction has been attributed to an ability to prevent tyramine and other indirect acting sympathomimetics from displacing norepinephrine from adrenergic neurons.

However, until the pathophysiology of the cheese reaction is more completely understood, it seems prudent to assume that selegiline can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO B (e.g., 10 mg/day). **In short, attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use although, as noted above, a case of hypertensive crisis has been reported at the recommended dose. (See WARNINGS and PRECAUTIONS.)**

It is important to be aware that selegiline may have pharmacological effects unrelated to MAO B inhibition. As noted above, there is some evidence that it may increase dopaminergic activity by other mechanisms, including interfering with dopamine re-uptake at the synapse. Effects resulting from selegiline administration may also be mediated through its metabolites. Two of its three principal metabolites, amphetamine and methamphetamine, have pharmacological actions of their own; they interfere with neuronal uptake and enhance release of several neurotransmitters (e.g., norepinephrine, dopamine, serotonin). However, the extent to which these metabolites contribute to the effects of selegiline are unknown.

Rationale for the Use of a Selective Monoamine Oxidase Type B Inhibitor in Parkinson's Disease:

Many of the prominent symptoms of Parkinson's disease are due to a deficiency of striatal dopamine that is the consequence of a progressive degeneration and loss of a population of dopaminergic neurons which originate in the substantia nigra of the midbrain and response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS

Selegiline hydrochloride tablets are contraindicated in patients with a known hypersensitivity to this drug.

Selegiline hydrochloride tablets are contraindicated for use with meperidine hydrochloride. This contraindication is often extended to other opioids. (See **Drug Interactions.**)

WARNINGS

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See **CLINICAL PHARMACOLOGY**).

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Severe CNS toxicity associated with hyperpyrexia and death have been reported with the combination of tricyclic antidepressants and non-selective MAOIs (Phenelzine, Tranylcypromine). A similar reaction has been reported for a patient on amitriptyline and selegiline. Another patient receiving protriptyline and selegiline developed tremors, agitation, and restlessness followed by unresponsiveness and death two weeks after selegiline was added. Related adverse events including hypertension, syncope, asystole, diaphoresis, seizures, changes in behavioral and mental status, and muscular rigidity have also been reported in some patients receiving selegiline and various tricyclic antidepressants.

Serious sometimes fatal, reactions with signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported with patients receiving a combination of fluoxetine hydrochloride and non-selective MAOIs. Similar signs have been reported in some patients on the combination of selegiline (10 mg a day) and selective serotonin re-uptake inhibitors including fluoxetine, sertraline and paroxetine.

Since the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid this combination of selegiline and tricyclic antidepressants as well as selegiline and selective serotonin re-uptake inhibitors. At least 14 days should elapse between discontinuation of selegiline and initiation of treatment with a tricyclic antidepressant or selective serotonin re-uptake inhibitors. Because of the long half lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of treatment with selegiline.

PRECAUTIONS

General:

Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reaction with super-sensitive postsynaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline.

Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients:

Patients should be advised of the possible need to reduce levodopa dosage after the initiation of selegiline hydrochloride therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. While hypertensive reactions with selegiline associated with dietary influences have not been reported, documented experience is limited.

Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests:

No specific laboratory tests are deemed essential for the management of patients on selegiline hydrochloride. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions:

ed in a patient taking the recommended dose of selegiline and a sympathomimetic medication (ephedrine). The pathophysiology of the 'cheese reaction' is complicated and, in addition to its ability to inhibit MAO B selectively, selegiline's relative freedom from this reaction has been attributed to an ability to prevent tyramine and other indirect acting sympathomimetics from displacing norepinephrine from adrenergic neurons.

However, until the pathophysiology of the cheese reaction is more completely understood, it seems prudent to assume that selegiline can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO B (e.g., 10 mg/day). **In short, attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use although, as noted above, a case of hypertensive crisis has been reported at the recommended dose. (See WARNINGS and PRECAUTIONS.)**

It is important to be aware that selegiline may have pharmacological effects unrelated to MAO B inhibition. As noted above, there is some evidence that it may increase dopaminergic activity by other mechanisms, including interfering with dopamine re-uptake at the synapse. Effects resulting from selegiline administration may also be mediated through its metabolites. Two of its three principal metabolites, amphetamine and methamphetamine, have pharmacological actions of their own; they interfere with neuronal uptake and enhance release of several neurotransmitters (e.g., norepinephrine, dopamine, serotonin). However, the extent to which these metabolites contribute to the effects of selegiline are unknown.

Rationale for the Use of a Selective Monoamine Oxidase Type B Inhibitor in Parkinson's Disease:

Many of the prominent symptoms of Parkinson's disease are due to a deficiency of striatal dopamine that is the consequence of a progressive degeneration and loss of a population of dopaminergic neurons which originate in the substantia nigra of the midbrain and project to the basal ganglia or striatum. Early in the course of Parkinson's disease, the deficit in the capacity of these neurons to synthesize dopamine can be overcome by administration of exogenous levodopa, usually given in combination with a peripheral decarboxylase inhibitor (carbidopa).

With the passage of time, due to the progression of the disease and/or the effect of sustained treatment, the efficacy and quality of the therapeutic response to levodopa diminishes. Thus, after several years of levodopa treatment, the response, for a given dose of levodopa, is shorter, has less predictable onset and offset (i.e., there is 'wearing off'), and is often accompanied by side effects (e.g., dyskinesia, akinesias, on-off phenomena, freezing, etc.).

This deteriorating response is currently interpreted as a manifestation of the inability of the ever decreasing population of intact nigrostriatal neurons to synthesize and release adequate amounts of dopamine.

MAO B inhibition may be useful in this setting because, by blocking the catabolism of dopamine, it would increase the net amount of dopamine available (i.e., it would increase the pool of dopamine). Whether or not this mechanism or an alternative one actually accounts for the observed beneficial effects of adjunctive selegiline is unknown.

Selegiline's benefit in Parkinson's disease has only been documented as an adjunct to levodopa/carbidopa. Whether or not it might be effective as a sole treatment is unknown, but past attempts to treat Parkinson's disease with non-selective MAOI monotherapy are reported to have been unsuccessful. It is important to note that attempts to treat Parkinsonian patients with combinations of levodopa and currently marketed non-selective MAO inhibitors were abandoned because of multiple side effects including hypertension, increase in involuntary movement, and toxic delirium.

Pharmacokinetic Information (Absorption, Distribution, Metabolism and Elimination—ADME):

Only preliminary information about the details of the pharmacokinetics of selegiline and its metabolites is available.

Data obtained in a study of 12 healthy subjects that was intended to examine the effects of selegiline on the ADME of an oral hypoglycemic agent, however, provides some information. Following the oral administration of a single dose of 10 mg of selegiline hydrochloride to these subjects, serum levels of intact selegiline were below the limit of detection (less than 10 ng/mL). Three metabolites, N-desmethyldeprenyl, the major metabolite (mean half-life 2.0 hours), amphetamine (mean half-life 17.7 hours), and methamphetamine (mean half-life 20.5 hours), were found in serum and urine. Over a period of 48 hours, 45% of the dose administered appeared in the urine as these 3 metabolites.

In an extension of this study intended to examine the effects of steady state conditions, the same subjects were given a 10 mg dose of selegiline hydrochloride for seven consecutive days. Under these conditions, the mean trough serum levels for amphetamine were 3.5 ng/mL and 8.0 ng/mL for methamphetamine; trough levels of N-desmethyldeprenyl were below the levels of detection.

The rate of MAO B regeneration following discontinuation of treatment has not been quantitated. It is this rate, dependent upon de novo protein synthesis, which seems likely to determine how fast normal MAO B activity can be restored.

INDICATIONS AND USAGE

Selegiline hydrochloride tablets are indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their

ing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline.

Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients:

Patients should be advised of the possible need to reduce levodopa dosage after the initiation of selegiline hydrochloride therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. While hypertensive reactions with selegiline associated with dietary influences have not been reported, documented experience is limited.

Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests:

No specific laboratory tests are deemed essential for the management of patients on selegiline hydrochloride. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions:

The occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in some patients receiving the combination of selegiline and meperidine. Symptoms usually resolve over days when the combination is discontinued. This is typical of the interaction of meperidine and MAOIs. Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients (See **CONTRAINDICATIONS**). Severe toxicity has also been reported in patients receiving the combination of tricyclic antidepressants and selegiline and selective serotonin re-uptake inhibitors and selegiline. (See **WARNINGS** for details.) One case of hypertensive crisis has been reported in a patient taking the recommended doses of selegiline and a sympathomimetic medication (ephedrine).

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Assessment of the carcinogenic potential of selegiline in mice and rats is ongoing.

Selegiline did not induce mutations or chromosomal damage when tested in the bacterial mutation assay in *Salmonella typhimurium* and an *in vivo* chromosomal aberration assay. While these studies provide some reassurance that selegiline is not mutagenic or clastogenic, they are not definitive because of methodological limitations. No definitive *in vitro* chromosomal aberration or *in vitro* mammalian gene mutation assays have been performed.

The effect of selegiline on fertility has not been adequately assessed.

Pregnancy: *Teratogenic Effects, Pregnancy Category C*

No teratogenic effects were observed in a study of embryo-fetal development in Sprague-Dawley rats at oral doses of 4, 12 and 36 mg/kg or 4, 12 and 35 times the human therapeutic dose on a mg/m^2 basis. No teratogenic effects were observed in a study of embryo-fetal development in New Zealand White rabbits at oral doses of 5, 25 and 50 mg/kg or 10, 48 and 95 times the human therapeutic dose on a mg/m^2 basis; however, in this study, the number of litters produced at the two higher doses was less than recommended for assessing teratogenic potential. In the rat study, there was a decrease in fetal body weight at the highest dose tested. In the rabbit study, increase in total resorptions and % post-implantation loss, and a decrease in the number of live fetuses per dam occurred at the highest dose tested. In a peri- and postnatal development study in Sprague-Dawley rats (oral doses of 4, 16 and 64 mg/kg or 4, 15 and 62 times the human therapeutic dose on a mg/m^2 basis), an increase in the number of stillbirths and decreases in the number of pups per dam, pup survival, and pup body weight (at birth and throughout the lactation period) were observed at the two highest doses. At the highest dose tested, no pups born alive survived to Day 4 postpartum. Postnatal development at the highest dose tested in dams could not be evaluated because of the lack of surviving pups. The reproductive performance of the untreated offspring was not assessed.

There are no adequate and well-controlled studies in pregnant women. Selegiline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

It is not known whether selegiline is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use:

The effects of selegiline hydrochloride in pediatric patients have not been evaluated.

ADVERSE REACTIONS

Introduction:

The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have also been reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris, and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness, and weight loss.

Experience with selegiline hydrochloride obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

INCIDENCE OF TREATMENT-EMERGENT ADVERSE EXPERIENCES IN THE PLACEBO-CONTROLLED CLINICAL TRIAL

Adverse Event	Number of Patients Reporting Events	
	Selegiline Hydrochloride	Placebo
	N=49	N=50
Nausea	10	3
Dizziness/Lightheaded/ Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

Central Nervous System:

Motor/Coordination/Extrapyramidal: increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric: hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation: headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

Autonomic Nervous System: dry mouth, blurred vision, sexual dysfunction.

Cardiovascular: orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

Gastrointestinal: nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of pre-existing ulcer disease).

Genitourinary/Gynecologic/Endocrine: slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

Skin and Appendages: increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

Treatment Suggestions For Overdose:

NOTE: Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physician's Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required.

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION

Selegiline Hydrochloride Tablets are intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of Selegiline Hydrochloride Tablets are 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/cabidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo controlled trails who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

HOW SUPPLIED

Selegiline Hydrochloride Tablets USP are available containing 5 mg of selegiline hydrochloride. Each white to off white, round, unscored, flat face beveled edge, compressed tablet is engraved with **N** over **179** on one side and 5 on the reverse.

They are available as:

NDC	55953-179-35	bottles of 60
NDC	55953-179-70	bottles of 500
NDC	55953-179-80	bottles of 1000
NDC	55953-179-41	unit dose of 100

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Manufactured by: Novopharm Limited
Toronto, Canada
M1B 2K9

Manufactured for: Novopharm USA Inc.
Schaumburg, IL 60173

83515

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Sub. 03

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Mental Status/Behavioral/Psychiatric: hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation: headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

Autonomic Nervous System: dry mouth, blurred vision, sexual dysfunction.

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Gastrointestinal: nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of pre-existing ulcer disease).

Genitourinary/Gynecologic/Endocrine: slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

Skin and Appendages: increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

Miscellaneous: asthma, diplopia, shortness of breath, speech affected.

Postmarketing Reports:

The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of selegiline hydrochloride.

CNS:

Seizure in dialyzed chronic renal failure patient on concomitant medications.

*indicates events reported only at doses greater than 10 mg/day.

OVERDOSAGE

Selegiline:

No specific information is available about clinically significant overdoses with selegiline hydrochloride. However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,1-selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g., tranylcypromine sulfate, isocarboxazid, and phenelzine sulfate].

Overdose with Non-Selective MAO Inhibition:

NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose, is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

NDC 55953-179-35

60 TABLETS

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

Each tablet contains:
Selegiline Hydrochloride . . . . . 5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
Dispense in tight, light-resistant container.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

000001A-0000 Printed in Canada Rev. 00

12899 17935 4

NDC 55953-179-35

60 TABLETS

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

Each tablet contains:
Selegiline Hydrochloride . . . . . 5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
Dispense in tight, light-resistant container.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

000001A-0000 Printed in Canada Rev. 00

12899 17935 4

NDC 55953-179-35

60 TABLETS

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

Each tablet contains:
Selegiline Hydrochloride . . . . . 5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
Dispense in tight, light-resistant container.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

000001A-0000 Printed in Canada Rev. 00

12899 17935 4

032

NDC 55953-179-70 500 TABLETS

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

00000LA-0000 Printed in Canada Rev. 00

0 12899 17970 5

AUG 2 1996

Each tablet contains:
Selegiline Hydrochloride . . . . . .5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
Dispense in tight, light-resistant container.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

NDC 55953-179-70 500 TABLETS

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

00000LA-0000 Printed in Canada Rev. 00

0 12899 17970 5

Each tablet contains:
Selegiline Hydrochloride . . . . . .5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
Dispense in tight, light-resistant container.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

NDC 55953-179-70 500 TABLETS

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

00000LA-0000 Printed in Canada Rev. 00

0 12899 17970 5

AUG 2 1996

Each tablet contains:
Selegiline Hydrochloride . . . . . .5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
Dispense in tight, light-resistant container.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

033

NDC 55953-179-80

1000 TABLETS

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

00000LA-0000 Printed in Canada Rev. 00

0 12899 17980 4

Each tablet contains:
Selegiline Hydrochloride . . . . . 5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
Dispense in tight, light-resistant container.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

NDC 55953-179-80

1000 TABLETS

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

00000LA-0000 Printed in Canada Rev. 00

0 12899 17980 4

Each tablet contains:
Selegiline Hydrochloride . . . . . 5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
Dispense in tight, light-resistant container.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

NDC 55953-179-80

1000 TABLETS

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

00000LA-0000 Printed in Canada Rev. 00

0 12899 17980 4

Each tablet contains:
Selegiline Hydrochloride . . . . . 5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
Dispense in tight, light-resistant container.
Keep container tightly closed.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

NDC 55953-179-41

100 Tablets
Unit Dose

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

00000LA-0000 Printed in Canada Rev. 00

0 12899 17941 5

Each tablet contains:
Selegiline Hydrochloride . . . . . 5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

NDC 55953-179-41

100 Tablets
Unit Dose

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

00000LA-0000 Printed in Canada Rev. 00

0 12899 17941 5

Each tablet contains:
Selegiline Hydrochloride . . . . . 5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

NDC 55953-179-41

100 Tablets
Unit Dose

Selegiline Hydrochloride

Tablets

5 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm

USUAL ADULT DOSAGE:
Two tablets daily. See package insert.

00000LA-0000 Printed in Canada Rev. 00

0 12899 17941 5

Each tablet contains:
Selegiline Hydrochloride . . . . . 5 mg
Store at a controlled room temperature,
15° to 30°C (59° to 86°F)
This unit dose package is not child-resistant.

Manufactured by: Novopharm Limited, Toronto, Canada M1B 2K9
Manufactured for: Novopharm USA Inc., Schaumburg, IL 60173

Selegiline Hydrochloride Tablet, 5 mg
(L)00000 Exp. 00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173

PULL HERE

Selegiline Hydrochloride Tablet, 5 mg
(L)00000 Exp. 00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173

PULL HERE

Selegiline Hydrochloride Tablet, 5 mg
(L)00000 Exp. 00 00
Mfg. for: Novopharm USA Inc.
Schaumburg, IL 60173

PULL HERE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074537

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-537

3. NAME AND ADDRESS OF APPLICANT
Novopharm Limited
5691 Main Street West
Stouffville, Ontario, Canada L4A 1H5

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Selegiline Hydrochloride

9. AMENDMENTS AND OTHER DATES:

Original Submission	8/23/94
Refuse to File	9/21/94
Amendment (Pat. cert)	9/30/94
Receipt Ack. Letter	10/25/94
Amendment	7/27/95
Amendment	4/23/96
Amendment	6/25/96
Amendment	7/25/96

10. PHARMACOLOGICAL CATEGORY
Antiparkinson

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet

14. POTENCY
5 mg

15. CHEMICAL NAME AND STRUCTURE
(-)-(R)-N, -alpha-dimethyl-N-2-propynlphenethylamine hydrochloride
(Non-USP drug substance; non-USP drug product; first generic)

17. COMMENTS
First generic

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
5/20/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074537

BIOEQUIVALENCE REVIEW(S)

JUL 18 1996

Selegiline HCL
Tablet, 5 mg
ANDA #74-537
Reviewer: L.A. Ouderkirk
WP #74537s.095

Novopharm Limited
Stouffville, Ontario
Canada
Submission Date:
October 15, 1995
April 22, 1996

Review of Amendments to In-Vivo Bioequivalence Studies

BACKGROUND:

The firm previously submitted fasted and non-fasted in-vivo bioequivalence studies, #930491 and #940027, respectively, to its ANDA 74-537 (submission dated 8/23/94, reviewed by L.A. Ouderkirk, Division of Bioequivalence). The studies were found deficient as follows:

1. The analytical methods (SOP #2320) submitted to both in vivo studies had been expurgated. The firm was requested to submit a complete description of the analytical methods as a condition of approval.

2. The firm failed to adequately validate the stability of the samples under frozen storage conditions for the period of time between sample collection and assay (66 days for study #930491 and 108 days for study #940027).

In addition, pursuant to a revised Division policy regarding the evaluation of measured selegiline concentrations in subject plasma samples, the results presented for selegiline in the review of the firm's fasted bioequivalence study #930491 submission to ANDA 74-537 dated 8/23/94 are revised and supplemented below.

AMENDED STUDIES:

I. Response to Deficiency #1:

as submitted. The firm's response to Deficiency #1 is therefore found to be satisfactory (see also paragraph III, below).

II. Response to Deficiency #2:

The firm has responded by providing revised assay validation reports for the bioequivalence studies #930491 and #940027.

These revised validation studies provide stability data (**Table 1**) for the measured compounds in frozen plasma

III. Amendments to Concentrations Reported In Vivo Food Effects Study #940027 and in Vivo Fasting Study #930491

IV. Amended Statistical Analysis for Selegiline in Fasted Bioequivalence Study #930491 (20 Subject Data)

The results for selegiline plasma concentrations in 29 subjects for fasted bioequivalence study #930491 were previously presented in a review of the firm's 8/23/94 submission to ANDA 74-537 (reviewed by L.A. Ouderkirk, Division of Bioequivalence). Because of a change in policy regarding the evaluation of selegiline data for fasted in vivo studies, the data have been statistically re-analyzed for 20 subjects. Ten subjects (Nos. 2, 5, 6, 14, and 18) of the original thirty who began the study were eliminated from the statistical re-analysis because they either had fewer than four measurable plasma selegiline concentrations or had Cmax as the first measurable concentration.

The results of the statistical analysis for 20 subjects are summarized below in Table 8. The results indicate that the geometric mean ratios for lnAUCT, lnAUCI, and lnCmax met the

Division's point estimate criterion of 0.8-1.25 indicating bioequivalence of the test and reference products.

COMMENTS:

1. An inspection request for routine audit of the biostudies #930491 and #940027 was previously issued to the FDA Division of Scientific Investigations from the Division of Bioequivalence. The final determination of the acceptability of the in vivo studies will depend in part upon the outcome of this data audit.

2. The firm has previously met the in vitro dissolution requirements for the test product (see submission to ANDA 74-537 dated 7/6/95, reviewed by L.A. Ouderkirk, Division of Bioequivalence).

RECOMMENDATIONS:

1. The in vivo fasting bioequivalence study #930491 and the in vivo food effect study #940027 conducted by Novopharm, Ltd., on its selegiline HCL tablet, 5 mg, lot #PD2607, versus the reference listed product, Eldepryl® tablet, 5 mg, lot #3Z011N, manufactured by Somerset have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Novopharm's selegiline HCL tablet, 5 mg, is bioequivalent to Eldepryl® tablet, 5 mg, manufactured by Somerset.

3. From the Bioequivalence viewpoint, the firm has met the in-vitro dissolution requirements and the in vivo bioequivalence study requirements and the ANDA #74-537 is acceptable.

Larry A. Ouderkirk 7-18-96

Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

RD INITIALED YCHuang
FT INITIALED YCHuang 7/18/96

Concur: _____ Date: 7/18/96
Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-537 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Ouderkirk), Drug File, Division File

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TABLE 8

FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
RESULTS FOR SELEGILINE IN 20 SUBJECTS

I. ARITHMETIC MEANS OF SELECTED PK PARAMETERS

PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	(A/B)
AUC(T) [pg•hr/mL]	731.10	877.50	0.83
lnAUC(T) [pg•hr/mL]	6.1514	6.3809	-----
AUC(I) [pg•hr/mL]	1017.23	1081.56	0.94
lnAUC(I) [pg•hr/mL]	6.6167	6.5837	-----
Cmax [pg/mL]	1173.64	1291.26	0.91
lnCmax [pg/mL]	6.5635	6.8112	-----
Tmax [hr]	0.7295	0.7185	1.02
Kel [1/hr]	1.7108	1.5994	1.07
$T_{1/2}$ [hr]	0.4546	0.7731	0.59

II. LEAST-SQUARES MEANS OF SELECTED PK PARAMETERS

PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	(A/B)
lnAUC(T) [pg•hr/mL]	6.2233	6.3529	-----
(Geometric mean)	504.38	574.20	0.88
lnAUC(I) [pg•hr/mL]	6.4982	6.6468	-----
(Geometric mean)	663.93	770.32	0.86
lnCmax [pg/mL]	6.6386	6.7791	-----
(Geometric mean)	764.05	879.32	0.87

OCT 26 1995

Selegiline HCL
Tablet, 5 mg
ANDA #74-537
Reviewer: L.A. Ouderkirk
WP #74537d.795

Novopharm Limited
Stouffville, Ontario
Canada
Submission Date:
July 6, 1995

Review of In-Vitro Dissolution Data

BACKGROUND:

In its previous submission dated 8/23/94, the firm conducted dissolution testing comparing its selegiline HCL tablets, 5 mg, versus the listed reference product, Eldepryl® tablets, 5 mg, manufactured by Somerset. The dissolution testing was found incomplete because the firm used a dissolution method which differed from that recommended by the Division of Bioequivalence (see review of firm's submission to ANDA 74-537, dated 8/23/94, by L.A. Ouderkirk, Division of Bioequivalence). A dissolution requirement for this product does not appear in the USP 23. The firm was advised to repeat the comparative dissolution testing using the following recommended method:

Apparatus:	Basket
RPM:	50
Medium:	Deaerated Water
Volume:	500 mL
Sampling Times:	10, 20, 30 minutes
Tolerance (Proposed):	NLT 'Q) in 20 minutes

FIRM'S RESPONSE:

The firm has responded to the Division's request and has submitted dissolution data comparing lot #PD 2607 of the Novopharm test selegiline tablets versus lot #3Z011N of the Somerset reference selegiline tablets using the method recommended by the Division of Bioequivalence. The firm has referenced this dissolution method as House Method S-060-02-V-2.00S. The firm has referenced the analytical portion of the dissolution method as House Method S-049-02-V-2.00S and has submitted a validation study for the method. The assay uses an

The comparative dissolution testing data are presented in **Table 1**.

COMMENTS:

1. The firm has used only 6 tablets per sample to generate the dissolution profiles in **Table 1**. Additional testing using 12 tablets was performed at the 20 minute time point for both the test and reference products. In the future, the firm should

report the results for 12 units of the test and reference products when performing comparative dissolution profile testing.

2. The dissolution profiles for the test and reference products indicate that the reference product dissolves faster than does the test product, but that both products easily meet a tolerance of NLT dissolved in 20 minutes. A similar but smaller difference in dissolution rate was also observed in the dissolution data submitted 8/23/95 (**Table 2**) which are included for comparison.

DEFICIENCIES:

1. The following deficiencies in the firm's 8/23/94 submission to ANDA 74-537 have been communicated to the firm, but no response has been received to date. The in-vivo bioequivalence portion of the firm's submission remains incomplete as follows:

a). The analytical method SOP #2320 submitted to both in vivo studies #930491 and #940027, is incomplete. A complete description of the analytical method, including the complete text of all analytical SOP Sections, must be submitted to the application as a condition of product approval.

b). In the analytical sections of the bioequivalence studies #930491 and #940027, the firm has not provided data to support the stability of the samples under the frozen storage conditions used in the studies for the period of time between sample collection and assay for study #930491 and for study #940027).

RECOMMENDATIONS:

1. The dissolution testing conducted by the firm on its selegiline HCL tablet, 5 mg, lot #PD2607, versus the listed reference product, Eldepryl®, lot #3Z011N, manufactured by Somerset, has been found acceptable by the Division of Bioequivalence. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml deaerated water at 37C using USP 23 apparatus 1 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 20 minutes.

2. From the Bioequivalence viewpoint, the firm has met the in-vitro dissolution requirements but has not met the in-vivo bioequivalence requirements for the reasons given in the above Deficiencies and the ANDA #74-537 is incomplete.

The firm should be advised of the Comments, Deficiencies, and Recommendations, above.

Larry A. Ouderkirk
10-26-95

Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

RD INITIALED YCHuang
FT INITIALED YCHuang 10/26/95

cc: ANDA 74-537 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Ouderkirk), Drug File, Division File

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Table 1 - In Vitro Dissolution Testing

Drug (Generic Name): Selegiline HCL Tablets
Dose Strength: 5 mg
ANDA No.: 74-537
Firm: Novopharm, Ltd.
Submission Date: 7/6/95
File Name: WP #74537.795

I. Conditions for Dissolution Testing: (No dissolution method in USP 23)

Apparatus: USP 23 basket, 50 RPM
No. Units Tested: 6 or as indicated
Medium: deaerated water
Volume: 500 mL
Reference Drug: Eldepryl® Tablets, 5 mg
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # PD2607 Strength: 5 mg			Reference Product Lot # 3Z011N Strength: 5 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	31.4		10.5	82.7		9.4
10	58.3		7.2	95.3		3.6
20	98.3		3.3	98.3		1.1
30	102.0		2.1	98.2		1.5
20*	98.3		1.8	90.7		9.0

*(N=12 Tablets)

Table 2 - In Vitro Dissolution Testing

Drug (Generic Name): Selegiline HCL Tablets
Dose Strength: 5 mg
ANDA No.: 74-537
Firm: Novopharm, Ltd.
Submission Date: 8/23/94
File Name: WP #74537.795

I. Conditions for Dissolution Testing: (No dissolution method in USP 23)

Apparatus: USP 23 paddle, 50 RPM
No. Units Tested: 12
Medium: 0.1N HCL
Volume: 900 mL
Reference Drug: Eldepryl® Tablets, 5 mg
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # PD2607 Strength: 5 mg			Reference Product Lot # 3Z011N Strength: 5 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	46.7		15.2	97.2		3.3
20	85.5		5.6	98.0		2.7
30	99.0		2.5	98.5		2.4
40	100.5		1.6	98.8		2.1

JUL 26 1995

Selegiline HCL
Tablet, 5 mg
ANDA #74-537
Reviewer: L.A. Ouderkirk
WP #74537sd.894

Novopharm Limited
Stouffville, Ontario
Canada
Submission Date:
August 23, 1994

Review of Fasting and Non-Fasting In-Vivo Bioequivalence Studies and In-Vitro Dissolution Data

BACKGROUND:

Selegiline [(R)(-)N, 2-dimethyl-N-2-propynyl-phenethylamine hydrochloride] an irreversible inhibitor of monoamine oxidase (MAO), is used to potentiate and prolong the effects of levodopa therapy in the treatment of Parkinson's Disease, although the exact mechanism by which this is accomplished is unknown. It is thought likely, however, that selegiline may increase brain dopamine levels by blocking dopamine catabolism.

Selegiline is rapidly and readily absorbed from the GI tract. Following oral administration, maximum blood concentrations are reached in 0.5-2 hours. There is a considerable first-pass effect following oral dosing. Three metabolites have been identified: desmethylselegiline (D), methamphetamine (M), and amphetamine (A). The major metabolite, (D), has an elimination half-life of about 2-4 hours; the other metabolites, (M), and (A), have half-lives of from 10 to 20 hours.

The (M) and (A) metabolites are essentially inactive as MAO-B inhibitors, but have other pharmacological actions of their own. They are known to interfere with neuronal uptake and enhance release of several neurotransmitters; however, the extent to which these metabolites contribute to the effects of selegiline is unknown. The (D) metabolite is also far less potent than selegiline in inhibiting MAO and probably has only a small therapeutic effect.

Due to a large volume of distribution (about 300 L) and extensive first-pass hepatic metabolism, selegiline concentrations following a 10 mg oral dose are very low and historically difficult to detect; however, with advances in chromatographic techniques, selegiline can now be detected at very low levels (pg/mL) after usual doses.

The recommended dose is 10 mg/day administered as divided doses of 5 mg each at breakfast and lunch. The listed reference product is Eldepryl® tablets, 5 mg, sponsored by Somerset Pharmaceuticals.

I. IN-VIVO BIOEQUIVALENCE STUDY UNDER FASTED CONDITIONS (PROTOCOL #930491):

A. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

The bioequivalence study was conducted at

The study medical director was

B. INFORMED CONSENT AND IRB APPROVAL:

Subjects gave written, informed consent before their acceptance into the study. The study protocol was reviewed and approved by an IRB prior to its initiation.

C. STUDY OBJECTIVE:

The objective of the study was to compare the rate and extent of absorption of the test versus the reference formulation to determine if the test and reference products were bioequivalent.

D. STUDY DESIGN:

The study was designed as a random, two-period, two-treatment, two-sequence crossover using 30 healthy male subjects.

E. SUBJECT SELECTION CRITERIA:

Subjects selected for the study met the following acceptance criteria:

1. Aged 18-45 years.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
3. No concurrent illness, acute or chronic diseases or history of serious cardiovascular, pulmonary, renal, G.I., hepatic, endocrine, immunologic, dermatologic, neurologic, or psychiatric diseases.
4. No history of alcohol or drug abuse or allergy to the drug under test.
5. Allergy or hypersensitivity to amphetamine, selegiline, or other MAO inhibitors.
6. Weight within 10% of ideal for height (Metropolitan Life Insurance Company Bulletin, 1983).
7. Nonusers of tobacco products.

F. SUBJECT RESTRICTIONS:

1. No alcohol or xanthine consumption beginning 48 hours before dosing and throughout the period of sample collection.
2. No concurrent medication of any type.
3. No Rx or OTC drugs beginning two weeks before the study.
4. Controlled diet - no consumption of foods rich in tyramine such as cheese, fish, fermented sausages,

yeast extracts, or red wine for at least three days before dosing, during the washout period, and for five days following study completion.

G. **STUDY SCHEDULES:**

Subjects were confined to the clinical facility beginning 18 hours before dosing until after the 24-hour blood sample. Subjects fasted for ten hours overnight before dosing. The volunteers were randomly numbered and divided into two dosing groups of equal number. A 2 X 5 mg oral dose of the test or reference product was administered with 240 ml of water in order of subject number. Subjects continued to fast for two hours post-dose, when a standard lunch was served. A standard dinner was served at nine hours post-dose and other standardized meals were served at scheduled intervals thereafter. Water was prohibited from two hours pre-dose until four hours post-dose.

Venous blood samples (10 ml) were drawn pre-dose (0 hours) and at 0.167, 0.33, 0.5, 0.67, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, and 144 hours post-dose. The plasma was separated by refrigerated centrifugation and divided into multiple aliquots that were stored frozen at -12^0 C. or lower pending assay. A three-week washout period was observed between Phase 1 and 2 dosing.

To monitor safety, blood pressure and sitting heart rate were measured before dosing and at 0.5, 1, 1.5, 2, 4, 8, and 12 hours post-dose. No safety problems were encountered.

H. **DRUG TREATMENTS:**

1. **Test Product A**: Selegiline tablets, 2 x 5 mg, (Novopharm, Ltd.), Lot #PD2607, Assayed Potency = 98.6%, Batch Size = , Manuf. Date = 3/94, Expiration Date = 3/96 (Proposed).

2. **Reference Product B:** Eldepryl® tablets, 2 x 5 mg, (Somerset), Lot #3Z011N, Assayed Potency = 97.7%, Expiration Date = 7/95

I. **ANALYTICAL:**

TABLE 1 - PRE-STUDY ASSAY VALIDATION

**

TABLE 2 - ASSAY PERFORMANCE FOR STUDY #930491

K. STATISTICAL ANALYSIS:

The study data were analyzed by ANOVA and the F-test to determine statistically significant (p=0.05) differences between treatments, dosing sequence, subjects within sequence, and days of administration for areas under the curve (AUC), maximum plasma drug levels (Cmax), time to maximum drug levels (Tmax), elimination constants (Kel) and half-life values ($T_{1/2}$). Mean pharmacokinetic (PK) parameters were also calculated using ln-transfomed data. The ln-transformed data were used to calculate 90% confidence intervals (two one-sided tests procedure) for these PK parameters. ANOVA was performed for subject plasma drug concentrations at each sampling time and included all sums of squares (Types I-IV). The ESTIMATE option of SAS GLM was used to generate linear estimates of adjusted treatment mean differences.

L. CLINICAL NOTES:

For Subjects #1-15 and #17-31, Study Phase 1 and 2 dosing was conducted on March 28 and April 18, 1994, respectively. For Subjects #16 and #32, Study Phase 1 and 2 dosing was conducted on April 17 and May 8, 1994, respectively. Of the 32 subjects who entered this study, 30 finished both phases. Subject #2 withdrew from the study for personal reasons after the 72-hour blood draw in Period 1. Subject #23 withdrew for personal reasons before Period 2. Several minor deviations from the study protocol were recorded in the study report, but none was judged likely to affect the validity of the study. All adverse episodes were judged minor or moderate in intensity, and in each case the study participants continued in the study.

M. **RESULTS OF FASTING BIOEQUIVALENCE STUDY:**

The mean plasma versus time data for the test and reference products are summarized in Tables 3-6 and represented graphically in Figures 1-4. A pharmacokinetic summary of the mean study results is given in Table 7.

a.) Selegiline: Because selegiline undergoes extensive first-pass metabolism and has a large volume of distribution, it is present in the blood only at very low levels following a 10 mg oral dose. Therefore, the results obtained for the parent compound may not reliably measure product bioequivalence and data collected for the three principle metabolites are considered determinative. The selegiline results calculated by the firm are presented here for informational purposes, but are not considered as pivotal to the determination of product bioequivalence.

No quantifiable drug concentrations were detected for Subject #20 after administration of Test Treatment "A" and only two concentration values were reported for this subject after administration of Reference Treatment "B". Therefore, additional statistical analyses were performed by the firm with this subject excluded (29 subjects total). Due to the very low levels of selegiline observed in many subjects, it was very difficult to fully characterize all pharmacokinetic parameters for all subjects. Because some subjects had only a very few measurable drug concentrations, the firm noted that the results for AUC(T) should be "interpreted with caution" for some subjects.

Results presented by the firm for AUC(I) yielded test/reference ratios of the least-squares and arithmetic means equal to 0.93 and 1.16, respectively. Cmax test/reference ratios of the least-squares and arithmetic means were 1.06 and 1.08, respectively. The 90% confidence intervals for ln-transformed AUC(I) and Cmax were 84.2-135.7%, and 72.2-112.3%, respectively.

b.) Desmethylselegiline: Results for 30 subjects yielded test/reference ratios of the least-squares and arithmetic means for AUC(T), AUC(I), and Cmax equal to 1.02 for all parameters. The 90% confidence intervals for ln-transformed AUC(T), AUC(I) and Cmax were 96.0-105.3%, 96.2-105.0%, and 91.0-108.2%, respectively, which were inside the 80-125% range indicating bioequivalence. No statistically significant sequence effects were found.

c.) Amphetamine: Results for 30 subjects yielded test/reference ratios of the least-squares and arithmetic means for AUC(T), AUC(I), and Cmax equal to 1.06, 1.07, and 1.03, respectively. The 90% confidence intervals for ln-transformed AUC(T), AUC(I) and Cmax were 99.8-113.5%, 99.0-114.4%, and 98.0-108.3%, respectively, which were inside the 80-125% range indicating bioequivalence. No statistically

significant sequence effects were found.

d.) **Methamphetamine**: Results for 30 subjects yielded test/reference ratios of the least-squares and arithmetic means for AUC(T), AUC(I), and Cmax equal to 1.05, 1.05, and 1.01, respectively. The 90% confidence intervals for ln-transformed AUC(T), AUC(I) and Cmax were 100.2-111.2%, 100.7-111.4%, and 96.4-107.7%, respectively, which were inside the 80-125% range indicating bioequivalence. A statistically significant sequence effect ($P < 0.1$) was found for ln Cmax, but since the mitigating criteria specified in the OGD statistical guidance were met, the sequence effect did not invalidate the bioequivalence assessment.

II. IN-VIVO FOOD EFFECTS STUDY CONDUCTED UNDER FASTING AND NON-FASTING CONDITIONS (PROTOCOL #940027):

The in vivo food effects study was conducted according to the protocol #930491, above, for the fasted in vivo study, with the following exceptions:

A. STUDY OBJECTIVE:

The objective of the study was to compare the rate and extent of absorption of the test and reference formulations when both were given immediately after a standard meal[1] (without cheese) and to compare the rate and extent of absorption of the test product under non-fasting versus fasting conditions.

B. STUDY DESIGN:

The study was designed as a random, three-period, three-treatment, six-sequence crossover using 18 healthy male subjects.

C. STUDY SCHEDULES:

Subjects were confined to the clinical facility beginning 18 hours before dosing until after the 24 hour blood sample. Subjects returned for blood drawing at 48, 72, and 96 hours. Subjects were fasted for ten hours overnight before dosing. The volunteers were randomly numbered and divided into three dosing groups of equal number. For the fasted Treatment "A", below, the subjects were administered a 2 X 5 mg oral dose of the test product with 240 ml of water only. For the non-fasted treatments

---

[1] Thirty minutes before drug administration, each subject consumed a standardized, high fat content meal consisting of:

two slices of toast with butter
two eggs fried in butter
two slices of bacon
one serving of hash brown potatoes (60 grams)
Eight fluid oz. (240 mL) of whole milk

"B" and "C", the subjects were given 30 minutes to consume a standard breakfast and were then administered a 2 X 5 mg oral dose of the test or reference product with 240 ml of water in order of subject number. Subjects fasted for four hours post-dose, when a standard lunch was served. A standard dinner was served at 9 hours post-dose and other standardized meals were served at scheduled intervals thereafter. Water was prohibited from two hours before until four hours after dosing.

Venous blood samples (10 ml) were drawn pre-dose (0 hours) and at 0.25, 0.5, 0.67, 0.833, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 hours post-dose. The plasma was separated by refrigerated centrifugation and divided into aliquots that were stored frozen at -12^0 C. or lower pending assay. A three-week washout period was observed between study Phases.

To monitor safety, blood pressure and sitting heart rate were measured before dosing and at 0.5, 1, 1.5, 2, 4, 8, and 12 hours post-dose. No safety problems were encountered.

D. DRUG TREATMENTS:

1. Test Treatment A (Fasting Conditions): Selegiline tablets, 2 x 5 mg, (Novopharm, Ltd.), Lot #PD2607

2. Test Treatment B (Fed Conditions): Selegiline tablets, 2 x 5 mg, (Novopharm, Ltd.), Lot #PD2607

3. Reference Treatment C (Fed Conditions): Eldepryl® tablets, 2 x 5 mg, (Somerset), Lot #3Z011N

E. ANALYTICAL:

G. STATISTICAL ANALYSIS:

The study data were analyzed by ANOVA and the F-test to determine statistically significant (p=0.05) differences between treatments, dosing sequence, subjects within sequence, and days of administration for areas under the curve (AUC), maximum plasma

drug levels (Cmax), time to maximum drug levels (Tmax), elimination constants (Kel) and half-life values ($T_{1/2}$). ANOVA was performed for subject plasma drug concentrations at each sampling time and included all sums of squares (Types I-IV). The ESTIMATE option of SAS GLM was used to generate linear estimates of adjusted treatment mean differences.

H. **CLINICAL NOTES:**

Study Phase 1, 2, and 3 dosing was conducted on March 27, April 17, and May 8, 1994, respectively. Each of the 20 subjects who entered the study completed all phases, but only the data from the first 18 subjects (subjects #1-#18) were analyzed, as was specified in the study protocol. Several minor deviations from the study protocol were recorded in the study report, but none was judged likely to affect the validity of the study. All adverse medical events during the study were judged to be minor or moderate in intensity, and in each case the study participants continued in the study.

I. **RESULTS OF FOOD EFFECTS STUDY:**

Because selegiline undergoes extensive first-pass metabolism and has a large volume of distribution, it is present in the blood only at very low levels following a 10 mg oral dose. Therefore, the results obtained for the parent compound may not reliably measure product bioequivalence and data collected for the three principle metabolites are considered determinative. The selegiline results calculated by the firm are presented here for informational purposes, but are not considered as pivotal to the determination of product bioequivalence.

Due to the low levels of the parent compound which were detected in this study, it was very difficult to fully characterize pharmacokinetic parameters such as AUC(T), though the firm attempted to do so, noting that these results should be "interpreted with caution". For these reasons, the selegiline results as calculated by the firm are presented for informational purposes, but are not considered pivotal to the determination of equivalent food effects.

1. **Test Product Non-fasting Treatment B Versus Reference Product Non-fasting Treatment C In 18 Subjects**

Selegiline The data are summarized in Tables 9 and 13, below. For the entire period of sample collection, Subject #5 had only three measurable selegiline concentrations for Treatment B and none for Treatment C. Therefore, additional statistical analyses were performed excluding this subject (N=17). Ratios of least-squares means for the non-fasting treatments (Test Treatment B/Reference Treatment C) for untransformed AUC(T), AUC(I), and Cmax were 1.05, 1.00, and 0.72, respectively; ratios of arithmetic means for these parameters were 0.96, 1.11, and 0.71, respectively.

Desmethylselegiline The data are summarized in Tables 10 and 13, below. Ratios of least-squares means for the non-fasting treatments (Test Treatment B/Reference Treatment C) for untransformed AUC(T), AUC(I), and Cmax were 1.03, 1.02, and 0.91, respectively; ratios of arithmetic means for these parameters were 1.03, 1.01, and 0.91, respectively, indicating a comparable effect of food on the rate and extent of absorption for the test and reference products. The ratio of mean Tmax values for the test versus the reference products was 1.54.

Amphetamine The data are summarized in Tables 11 and 13, below. Ratios of least-squares means for the non-fasting treatments (Test Treatment B/Reference Treatment C) for untransformed AUC(T), AUC(I), and Cmax were 1.01, 0.95, and 1.07, respectively; ratios of arithmetic means for these parameters were 1.03, 0.98, and 1.08, respectively, indicating a comparable effect of food on the rate and extent of absorption for the test and reference products. The ratio of mean Tmax values for the test versus the reference products was 1.25.

Methamphetamine The data are summarized in Tables 12 and 13, below. Ratios of least-squares means for the non-fasting treatments (Test Treatment B/Reference Treatment C) for untransformed AUC(T), AUC(I), and Cmax were 1.06, 1.01, and 1.07, respectively; ratios of arithmetic means for these parameters were 1.08, 1.01, and 1.05, respectively, indicating a comparable effect of food on the rate and extent of absorption for the test and reference products. The ratio of mean Tmax values for the test versus the reference products was 0.98.

2. Results -- Test Non-fasting Treatment B Versus Test Fasting Treatment A in 18 Subjects

Selegiline The data are summarized in Tables 9 and 13, below. For the entire period of sample collection, Subject #5 had only three measurable selegiline concentrations for Treatment B and two for Treatment A. Therefore, additional statistical analyses were performed excluding this subject (N=17). Ratios of least-squares means for the test product given under non-fasting conditions versus fasting conditions (Test Treatment B/Test Treatment A) for untransformed AUC(T), AUC(I), and Cmax were 2.44, 1.96, and 1.16, respectively; ratios of arithmetic means for these parameters were 2.20, 2.04, and 1.23, respectively.

Desmethylselegiline The data are summarized in Tables 10 and 13, below. The least-squares means for the test product given under non-fasting conditions versus fasting conditions (Test Treatment B/Test Treatment A) increased 16% for AUC(T), 15% for AUC(I) and decreased 31% for Cmax. This indicates that the presence of food in the GI tract did not greatly affect the extent of selegiline absorption, but slowed the rate of absorption somewhat, as

measured by this metabolite. The ratio of mean Tmax values for the non-fasting versus the fasting treatments was 1.69, indicating delayed absorption.

Amphetamine The data are summarized in Tables 11 and 13, below. The least-squares means for the test product given under non-fasting conditions versus fasting conditions (Test Treatment B/Test Treatment A) increased 1% for AUC(T), decreased 7% for AUC(I) and increased 13% for Cmax. This indicates that the presence of food in the GI tract had little effect on drug absorption, as measured by this metabolite. The ratio of mean Tmax values for the non-fasting versus the fasting treatments was 0.99.

Methamphetamine The data are summarized in Tables 12 and 13, below. The least-squares means for the test product given under non-fasting conditions versus fasting conditions (Test Treatment B/Test Treatment A) increased 3% for AUC(T), decreased 8% for AUC(I) and increased 4% for Cmax. This indicates that the presence of food in the GI tract had minimal effect on drug absorption, as measured by this metabolite. The ratio of mean Tmax values for the non-fasting versus the fasting treatments was 1.06.

III. IN-VITRO TESTING RESULTS:

The firm conducted dissolution testing on its selegiline HCL tablet, 5 mg, lot #PD2607, versus the reference product, Eldepryl® tablets, 5 mg, Lot #3Z011N, manufactured by Somerset. The results of the dissolution testing and the method used are given in Table 14.

Content uniformity testing was performed on the test and reference product lots. The results were 99.6% (1.1% CV) for the test product lot and 96.0% (2.0% CV) for the reference product lot.

IV. PRODUCT FORMULATION:

The formulation of the product, as supplied by the manufacturer, is given in Table 15.

COMMENT:

1. An inspection request for routine audit of the biostudies #930491 and #940027, has been issued to the FDA Division of Scientific Investigations from the Division of Bioequivalence. The final determination of the acceptability of the study will depend in part upon the outcome of this data audit.

DEFICIENCIES:

1. The analytical method SOP #2320 submitted to both in vivo studies #930491 and #940027, is incomplete. A complete description of the analytical method, including the complete text of all analytical SOP Sections, must be submitted to the application as a condition of product approval.

2. In the analytical sections of the bioequivalence studies #930491 and #940027, the firm has not provided data to support the stability of the samples under the frozen storage conditions used in the studies for the period of time between sample collection and assay (_ for study #930491 and _ for study #940027).

3. The firm has performed the dissolution testing on this product using a method which is not currently recommended. The Division of Bioequivalence recommends that additional dissolution testing be performed on the test and reference lots using the following method:

Apparatus:	Basket
RPM:	50
Medium:	Deaerated Water
Volume:	500 mL
Sampling Times:	10, 20, 30 minutes
Tolerance (Proposed):	NLT (Q) in 20 minutes

RECOMMENDATIONS:

1. The in vivo fasting bioequivalence study #930491 and the in vivo food effect study #940027 conducted by Novopharm, Ltd., on its selegiline HCL tablet, 5 mg, lot #PD2607, versus the reference listed product, Eldepryl®, lot #3Z011N, manufactured by Somerset have been found incomplete by the Division of Bioequivalence for the reasons stated in the Deficiencies #1 and #2, above, and the firm should comply with the recommendations therein.

2. The dissolution testing conducted by the firm on its selegiline HCL tablet, 5 mg, lot #PD2607, versus the listed reference product, Eldepryl®, lot #3Z011N, manufactured by Somerset, has been found unacceptable by the Division of Bioequivalence for the reasons stated in Deficiency #3, above, and the firm should comply with the recommendations therein.

3. From the Bioequivalence viewpoint, the firm has not met the in-vivo bioequivalence and in-vitro dissolution requirements for the ANDA #74-537.

The firm should be advised of the Comment, Deficiencies, and Recommendations, above.

Larry A. Ouderkirk 6-30-95

Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

RD INITIALED YCHuang
FT INITIALED YCHuang 7/5/95

Concur: Date: 7/26/95
Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-537 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CVishwanathan), HFD-652 (Huang, Ouderkirk), Drug File, Division File

LAO/dbm/062995/WP74537sd.894

TABLE 3

I. FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
MEAN SELEGILINE PLASMA LEVELS [PG/ML] VERSUS TIME (CV%)
IN 29 SUBJECTS

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT A	RATIO (A/B)
0	0.00	0.00	-----
0.17	3.98 (539)	0.00	-----
0.33	103.10 (123)	448.63 (235)	0.23
0.5	894.87 (160)	846.00 (147)	1.06
0.67	945.63 (110)	878.81 (98)	1.08
0.83	812.03 (104)	631.76 (94)	1.29
1.0	572.78 (103)	464.82 (98)	1.23
1.25	282.87 (95)	264.38 (98)	1.07
1.5	159.18 (95)	160.51 (101)	0.99
1.75	108.69 (103)	110.48 (120)	0.98
2.0	82.40 (115)	75.52 (132)	1.09
2.5	34.90 (172)	39.80 (188)	0.88
3.0	20.25 (245)	20.13 (214)	1.01
4.0	6.49 (404)	10.04 (382)	0.65
5.0	5.05 (387)	7.62 (401)	0.66
6.0	4.29 (539)	6.57 (414)	0.65
8.0	2.23 (539)	0.00	----
12.0	0.00	0.00	----
16.0	0.00	0.00	----
24.0	0.00	0.00	----

TABLE 3 [Con't.]

II. FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS
FOR SELEGILINE IN 29 SUBJECTS

PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	(A/B)
AUC(T) [pg•hr/mL]	776.4 (116)	768.1 (126)	1.01
ln AUC(T) [pg•hr/mL]	6.05	6.11	-----
(Geometric mean)	424.1	450.3	0.94
AUC(I)[a] [pg•hr/mL]	1122.6 (91)	966.7 (130)	1.16
ln AUC(I)[a] [pg•hr/mL]	6.68	6.41	-----
(Geometric mean)	796.3	607.9	1.30
Cmax [pg/mL]	1232.6 (116)	1136.4 (110)	1.08
ln Cmax [pg/mL]	6.539	6.622	-----
(Geometric mean)	691.6	751.4	0.92
Tmax [hr]	0.72 (29)	0.66 (34)	1.09
Kel[a] [1/hr]	1.649 (48)	1.699 (53)	0.97
$T_{1/2}$[a] [hr]	0.570 (78)	0.744 (154)	0.77

[a] (N=19 for test, N=23 for reference)

TABLE 4

I. FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
MEAN DESMETHYLSELEGILINE PLASMA LEVELS [PG/ML]
VERSUS TIME (CV%) IN 30 SUBJECTS

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO A/B
0	0.00	0.00	-----
0.17	12.93 (548)	58.20 (333)	0.22
0.33	1253.85 (129)	2483.86 (141)	0.50
0.5	6552.47 (84)	8071.42 (65)	0.82
0.67	10131.98 (61)	11809.16 (42)	0.86
0.83	11808.53 (43)	12105.23 (34)	1.03
1.0	11607.52 (33)	11646.43 (29)	1.00
1.25	11069.05 (32)	9894.32 (28)	1.12
1.5	8712.23 (26)	8381.41 (29)	1.04
1.75	7404.61 (31)	6946.45 (35)	1.07
2.0	6225.52 (29)	5795.84 (39)	1.07
2.5	4848.92 (31)	4623.04 (41)	1.05
3.0	3822.00 (36)	3439.42 (32)	1.11
4.0	2442.63 (35)	2425.19 (38)	1.01
5.0	1646.71 (38)	1567.55 (42)	1.05
6.0	1227.74 (44)	1189.58 (43)	1.03
8.0	696.14 (46)	683.20 (45)	1.02
12.0	295.19 (83)	297.84 (72)	----
16.0	153.11 (129)	128.20 (150)	----
24.0	32.13 (305)	32.08 (313)	----

TABLE 4 [Con't.]

II. FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491 ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR DESMETHYLSELEGILINE IN 30 SUBJECTS

PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	(A/B)
AUC(T) [pg•hr/mL]	31255 (34)	30728 (33)	1.02
ln AUC(T) [pg•hr/mL]	10.29	10.28	------
(Geometric mean)	29437	29144	1.01
AUC(I)[a] [pg•hr/mL]	32879 (35)	32081 (34)	1.02
ln AUC(I)[a] [pg•hr/mL]	10.33	10.32	-------
(Geometric mean)	30638	30333	1.01
Cmax [pg/mL]	14286 (30)	14079 (26)	1.02
ln Cmax [pg/mL]	9.510	9.518	-------
(Geometric mean)	13494	13602	0.99
Tmax [hr]	0.96 (25)	0.84 (28)	1.14
Kel[a] [1/hr]	0.2323 (45)	0.2300 (41)	-------
$T_{1/2}$[a] [hr]	3.888 (64)	3.598 (47)	-------

[a] (N = 29 for test and reference)

TABLE 5

I. FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
MEAN AMPHETAMINE PLASMA LEVELS [PG/ML] VERSUS TIME (CV%) IN 30 SUBJECTS

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)
0	0.00	0.00	----
0.17	0.00	0.00	----
0.33	3.7 (548)	19.7 (337)	0.19
0.5	126.8 (124)	191.7 (102)	0.66
0.67	389.8 (82)	596.2 (95)	0.65
0.83	801.4 (62)	981.1 (78)	0.82
1.0	983.2 (50)	1205.7 (64)	0.82
1.25	1227.4 (50)	1514.1 (67)	0.81
1.5	1366.0 (41)	1602.0 (63)	0.85
1.75	1507.5 (37)	1616.0 (55)	0.93
2.0	1745.8 (62)	1590.2 (52)	1.10
2.5	1731.4 (64)	1569.5 (42)	1.10
3.0	1636.0 (32)	1580.3 (39)	1.04
4.0	1676.4 (30)	1729.5 (39)	0.97
5.0	1888.7 (41)	1858.2 (50)	1.02
6.0	1826.3 (30)	1771.4 (29)	1.03
8.0	1794.2 (28)	1795.4 (31)	1.00
12.0	1609.5 (30)	1495.4 (25)	1.08
16.0	1446.2 (31)	1340.7 (24)	1.08
24.0	998.6 (29)	900.3 (27)	1.11
48.0	308.2 (43)	316.1 (37)	0.98
72.0	85.1 (96)	61.4 (131)	1.39
96.0	8.6 (381)	0.00	----
144.0	0.00	0.00	----

TABLE 5 [Con't.]

II. FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS
FOR AMPHETAMINE IN 30 SUBJECTS

PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	(A/B)
AUC(T) [ng•hr/mL]	53.96 (28)	50.76 (27)	1.06
ln AUC(T) [ng•hr/mL]	3.953	3.891	-----
(Geometric mean)	52.09	48.96	1.06
AUC(I) [ng•hr/mL]	60.15 (28)	56.36 (26)	1.07
ln AUC(I) [ng•hr/mL]	4.061	4.000	-----
(Geometric mean)	58.03	54.60	1.06
Cmax [ng/mL]	2.31 (54)	2.24 (52)	1.03
ln Cmax [ng/mL]	0.745	0.715	-----
(Geometric mean)	2.11	2.04	1.03
Tmax [hr]	4.71 (55)	4.28 (62)	1.10
Kel [1/hr]	0.04515 (24)	0.04446 (25)	1.02
$T_{1/2}$ [hr]	16.37 (29)	16.53 (25)	0.99

TABLE 6

I. FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
MEAN METHAMPHETAMINE PLASMA LEVELS [PG/ML] VERSUS TIME (CV%) FOR 30 SUBJECTS

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)
0	0.00	0.00	----
0.17	0.00	0.00	----
0.33	20.3 (548)	303.4 (225)	0.07
0.5	1371.0 (108)	2126.9 (96)	0.64
0.67	3599.7 (78)	5362.4 (73)	0.67
0.83	6513.0 (57)	7765.2 (63)	0.84
1.0	7927.1 (47)	8920.6 (46)	0.89
1.25	9267.6 (40)	10431.4 (40)	0.89
1.5	10018.7 (33)	10617.9 (35)	0.94
1.75	10632.3 (24)	10570.5 (30)	1.01
2.0	10732.5 (26)	10433.5 (31)	1.03
2.5	10567.0 (24)	10412.9 (26)	1.01
3.0	10723.9 (22)	10284.8 (27)	1.04
4.0	10457.3 (23)	10406.5 (23)	1.00
5.0	10870.9 (21)	10441.0 (22)	1.04
6.0	10407.5 (21)	10200.2 (24)	1.02
8.0	9733.4 (19)	9728.7 (21)	1.00
12.0	8104.3 (22)	7674.7 (22)	1.06
16.0	6904.3 (24)	6483.9 (26)	1.06
24.0	4465.9 (25)	4018.0 (29)	1.11
48.0	1268.6 (50)	1226.0 (45)	1.03
72.0	312.6 (127)	289.6 (133)	1.08
96.0	43.5 (393)	31.5 (381)	1.38
144.0	0.00	0.00	----

TABLE 6 [Con't.]

II. FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS
FOR METHAMPHETAMINE IN 30 SUBJECTS

PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	(A/B)
AUC(T) [ng•hr/mL]	268.6 (22)	256.9 (26)	1.05
ln AUC(T) [ng•hr/mL]	5.57	5.51	-----
(Geometric mean)	262.43	247.15	1.06
AUC(I) [ng•hr/mL]	286.3 (22)	272.0 (24)	1.05
ln AUC(I) [ng•hr/mL]	5.63	5.58	-----
(Geometric mean)	278.66	265.07	1.05
Cmax [ng/mL]	13.02 (22)	12.95 (28)	1.01
ln Cmax [ng/mL]	2.533	2.514	-----
(Geometric mean)	12.59	12.35	1.02
Tmax [hr]	3.24 (64)	3.22 (66)	1.00
Kel [1/hr]	0.05261 (25)	0.05203 (27)	1.01
$T_{1/2}$ [hr]	14.03 (26)	14.32 (27)	0.98

TABLE 7

FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
LEAST-SQUARES MEANS AND 90% CONFIDENCE INTERVALS
FOR PHARMACOKINETIC PARAMETERS

I. SELEGILINE (N=29 or as noted)

PARAMETER	TEST (A)	REF. (B)	(A/B)	90% C.I.
AUC(T) [pg•hr/mL]	771.2	778.7	0.99	----------
ln AUC(T) [pg•hr/mL]	6.037	6.126	-----	----------
(Geometric mean)	418.6	457.6	0.91	74.5-112.4
AUC(I)[a] [pg•hr/mL]	890.5	958.8	0.93	----------
ln AUC(I)[a] [pg•hr/mL]	6.492	6.425	------	----------
(Geometric mean)	659.8	617.1	1.07	84.2-135.7
Cmax [pg/mL]	1224.3	1151.7	1.06	----------
ln Cmax [pg/mL]	6.528	6.633	-----	----------
(Geometric mean)	684.0	759.8	0.90	72.2-112.3
Tmax [hr]	0.72	0.66	1.09	----------
Kel[a] [1/hr]	1.9152	1.6706	1.15	----------
$T_{1/2}$[a] [hr]	0.38	0.72	0.53	----------

II. DESMETHYLSELEGILINE (N=30 or as noted)

PARAMETER	TEST (A)	REF. (B)	(A/B)	90% C.I.
AUC(T) [pg•hr/mL]	31255	30728	1.02	----------
ln AUC(T) [pg•hr/mL]	10.29	10.28	------	----------
(Geometric mean)	29437	29143	1.01	96.0-105.3
AUC(I)[b] [pg•hr/mL]	32751	32142	1.02	----------
ln AUC(I)[b] [pg•hr/mL]	10.33	10.33	------	----------
(Geometric mean)	30638	30638	1.00	96.2-105.0
Cmax [pg/mL]	14286	14079	1.02	----------
ln Cmax [pg/mL]	9.510	9.518	------	----------
(Geometric mean)	13494	13602	0.99	91.0-108.2
Tmax [hr]	0.96	0.84	1.14	----------
Kel[b] [1/hr]	0.2311	0.2292	1.01	----------
$T_{1/2}$[b] [hr]	3.87	3.59	1.08	----------

[a] (N=19 for test, N=23 for reference) [b] (N=29 for test and reference)

TABLE 7 [CON'T.]

FASTING IN VIVO BIOEQUIVALENCE STUDY NO. 930491
LEAST-SQUARES MEANS AND 90% CONFIDENCE INTERVALS FOR
PHARMACOKINETIC PARAMETERS

III. AMPHETAMINE (N=30)

PARAMETER	TEST (A)	REF. (B)	(A/B)	90% C.I.
AUC(T) [ng•hr/mL]	53.965	50.757	1.06	----------
ln AUC(T) [ng•hr/mL]	3.953	3.891	------	----------
(Geometric mean)	52.09	48.96	1.06	99.8-113.5
AUC(I) [ng•hr/mL]	60.146	56.364	1.07	----------
ln AUC(I) [ng•hr/mL]	4.061	4.000	------	----------
(Geometric mean)	58.03	54.60	1.06	99.0-114.4
Cmax [ng/mL]	2.313	2.241	1.03	----------
ln Cmax [ng/mL]	0.745	0.715	1.03	----------
(Geometric mean)	2.106	2.044	1.03	98.0-108.3
Tmax [hr]	4.71	4.28	1.10	----------
Kel [1/hr]	0.04515	0.04446	1.02	----------
$T_{1/2}$ [hr]	16.37	16.53	0.99	----------

IV. METHAMPHETAMINE (N=30)

PARAMETER	TEST (A)	REF. (B)	(A/B)	90% C.I.
AUC(T) [ng•hr/mL]	268.551	256.888	1.05	----------
ln AUC(T) [ng•hr/mL]	5.57	5.51	------	----------
(Geometric mean)	262	247	1.06	100.2-111.2
AUC(I) [ng•hr/mL]	286.263	272.030	1.05	----------
ln AUC(I) [ng•hr/mL]	5.63	5.58	------	----------
(Geometric mean)	279	265	1.05	100.7-111.4
Cmax [ng/mL]	13.017	12.948	1.01	----------
ln Cmax [ng/mL]	2.533	2.514	------	----------
(Geometric mean)	12.59	12.35	1.02	96.4-107.7
Tmax [hr]	3.24	3.22	1.01	----------
Kel [1/hr]	0.0526	0.0520	1.01	----------
$T_{1/2}$ [hr]	14.03	14.32	0.97	----------

TABLE 8

ASSAY PERFORMANCE FOR FOOD STUDY #940027

Parameter	(S)	(D)	(A)	(M)
Sensitivity/LOQ (pg/mL)	50	200	100	399
Quality Control Conc. (pg/mL)				
Linear Range (pg/mL)				
Interbatch Precision (%CV)				
Interbatch Accuracy (%CV)	96-98	93-97	97-100	93-100

TABLE 9

IN VIVO FOOD EFFECT STUDY NO. 940027; 17 SUBJECTS

I. SELEGILINE - ARITHMETIC MEAN PLASMA LEVELS [PG/ML] VERSUS TIME (CV%)

TIME (HR)	FASTED TEST (TREATMENT A)	FED TEST (TREATMENT B)	FED REFERENCE (TREATMENT C)	RATIO (B/C)	RATIO (B/A)
0	0.00	0.00	0.00	----	----
0.25	6.72 (400)	51.52 (176)	362.80 (251)	0.14	7.67
0.5	273.59 (93)	302.03 (147)	1151.27 (99)	0.26	1.10
0.67	736.25 (98)	548.69 (127)	1140.60 (106)	0.48	0.75
0.83	768.56 (97)	690.35 (130)	912.39 (74)	0.76	0.90
1	611.56 (106)	715.92 (106)	835.33 (73)	0.86	1.17
1.5	218.44 (102)	666.51 (107)	521.82 (68)	1.28	3.06
2	129.16 (133)	525.86 (127)	445.43 (86)	1.18	4.08
2.5	63.82 (115)	320.77 (85)	192.17 (102)	1.67	5.01
3	38.83 (141)	289.74 (127)	135.72 (108)	2.13	7.44
4	13.49 (230)	100.42 (127)	67.62 (136)	1.47	7.41
5	9.63 (283)	67.62 (252)	39.99 (164)	1.68	7.02
6	3.97 (412)	22.06 (216)	15.90 (230)	1.38	5.56
8	---------	7.06 (412)	4.59 (412)	1.54	----
12	---------	---------	---------	----	----
16	---------	---------	---------	----	----
24	---------	---------	---------	----	----

II. ARITHMETIC MEANS FOR PK PARAMETERS (CV%)

PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REFERENCE TREATMENT C	B/C	B/A
AUC(T) [pg•hr/mL]	753.1 (100)	1660.4 (86)	1735.6 (80)	0.96	2.20
AUC(I)[a] [pg•hr/mL]	1103.5 (85)	2251.4 (65)	2030.3 (73)	1.11	2.04
Cmax [pg/mL]	916.1 (86)	1131.1 (96)	1597.5 (74)	0.71	1.23
Tmax [hr]	0.82 (17)	1.47 (46)	0.78 (50)	1.89	1.79
Kel[a] [1/hr]	1.4431 (60)	0.8180 (54)	0.9968 (56)	0.82	0.57
$T_{1/2}$[a] [hr]	0.78 (94)	1.03 (43)	0.97 (61)	1.07	1.32

[a] (N=9-13 Subjects)

TABLE 10

IN VIVO FOOD EFFECT STUDY NO. 940027; 18 SUBJECTS

I. DESMETHYLSELEGILINE - ARITHMETIC MEAN PLASMA LEVELS [PG/ML] VS. TIME (CV%)

TIME (HR)	FASTED TEST (TREATMENT A)	FED TEST (TREATMENT B)	FED REFERENCE (TREATMENT C)	RATIO (B/C)	RATIO (B/A)
0	0.00	0.00	0.00	----	----
0.25	39.86 (304)	182.08 (193)	727.10 (166)	0.25	4.55
0.5	3992.51 (71)	2114.09 (132)	7055.26 (78)	0.30	0.53
0.67	9237.00 (48)	4277.04 (100)	7833.78 (63)	0.55	0.46
0.83	12163.7 (28)	5350.91 (83)	8199.66 (47)	0.65	0.44
1	13344.4 (26)	6382.68 (68)	8518.16 (35)	0.75	0.48
1.5	9579.23 (26)	7772.04 (68)	8026.71 (24)	0.97	0.81
2	7042.74 (31)	7481.86 (42)	7343.00 (31)	1.02	1.06
2.5	5311.30 (39)	6866.71 (32)	6032.31 (29)	1.14	1.29
3	4135.76 (40)	6218.58 (29)	4726.44 (33)	1.32	1.50
4	2579.62 (40)	4348.64 (29)	3491.24 (40)	1.25	1.69
5	1793.64 (49)	2889.02 (48)	2275.74 (44)	1.27	1.61
6	1402.43 (49)	2016.97 (45)	1542.67 (47)	1.31	1.44
8	892.49 (65)	1122.73 (51)	944.05 (48)	1.19	1.26
12	367.39 (71)	492.96 (72)	538.22 (87)	0.92	1.34
16	43.27 (236)	99.49 (150)	90.36 (149)	1.10	2.30
24	--------	---------	---------	----	----

II. ARITHMETIC MEANS FOR PK PARAMETERS (CV%)

PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REF. TREATMENT C	B/C	B/A
AUC(T) [pg•hr/mL]	33635 (35)	36826 (41)	35888 (35)	1.03	1.09
AUC(I) [pg•hr/mL]	34777 (35)	38740 (41)	38185 (34)	1.01	1.11
Cmax [pg/mL]	14153 (20)	9853.8 (46)	10848 (38)	0.91	0.70
Tmax [hr]	1.02 (29)	1.73 (37)	1.12 (48)	1.54	1.69
Kel [1/hr]	0.2424 (45)	0.2346 (48)	0.2144 (57)	1.09	0.97
$T_{1/2}$ [hr]	3.57 (52)	3.84 (55)	4.43 (59)	0.87	1.07

TABLE 11

IN VIVO FOOD EFFECT STUDY NO. 940027; 18 SUBJECTS

I. AMPHETAMINE - ARITHMETIC MEAN PLASMA LEVELS [PG/ML] VS. TIME (CV%)

TIME (HR)	FASTED TEST (TREATMENT A)	FED TEST (TREATMENT B)	FED REFERENCE (TREATMENT C)	RATIO (B/C)	RATIO (B/A)
0	0.0	0.0	0.0	-----	-----
0.25	6.3 (412)	0.0	0.0	-----	-----
0.5	15.9 (283)	54.4 (221)	284.2 (110)	0.19	3.42
0.67	245.2 (96)	176.8 (130)	465.3 (112)	0.38	0.72
0.83	444.7 (55)	263.0 (97)	603.9 (89)	0.44	0.59
1	708.6 (36)	384.8 (80)	732.5 (70)	0.53	0.54
1.5	1088.7 (26)	718.4 (53)	1046.3 (51)	0.69	0.66
2	1292.9 (28)	1006.8 (49)	1265.2 (43)	0.80	0.78
2.5	1416.5 (20)	1209.7 (54)	1395.9 (36)	0.87	0.85
3	1487.0 (23)	1406.9 (52)	1387.1 (25)	1.01	0.95
4	1479.2 (18)	1628.9 (37)	1640.3 (31)	0.99	1.10
5	1753.5 (19)	1767.4 (40)	1737.7 (33)	1.02	1.01
6	1693.6 (35)	1882.6 (44)	1628.2 (18)	1.16	1.11
8	1669.3 (22)	1709.7 (28)	1639.6 (25)	1.04	1.02
12	1546.3 (30)	1602.8 (45)	1493.1 (35)	1.07	1.04
24	851.0 (25)	936.3 (31)	892.6 (27)	1.05	1.10
48	288.9 (51)	252.9 (50)	244.9 (41)	1.03	0.88
72	91.2 (112)	88.0 (120)	99.1 (118)	0.89	0.97
96	15.2 (284)	25.8 (225)	6.5 (412)	3.97	1.70

II. ARITHMETIC MEANS FOR PK PARAMETERS (CV%)

PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REF. TREATMENT C	B/C	B/A
AUC(T) [pg•hr/mL]	48960 (25)	49590 (34)	48310 (26)	1.03	1.01
AUC(I)[a] [pg•hr/mL]	53470 (23)	51590 (24)	52740 (27)	0.98	0.96
Cmax [pg/mL]	1962.4 (29)	2104.3 (40)	1945.2 (32)	1.08	1.07
Tmax [hr]	6.83 (36)	6.78 (39)	5.44 (43)	1.25	0.99
Kel[a] [1/hr]	0.0452 (23)	0.0409 (32)	0.0462 (31)	0.89	0.90
$T_{1/2}$[a] [hr]	16.21 (26)	19.44 (47)	16.26 (29)	1.20	1.20

[a] (N = 14-17 subjects)

TABLE 12
IN VIVO FOOD EFFECT STUDY NO. 940027; 18 SUBJECTS

I. METHAMPHETAMINE ARITHMETIC MEAN PLASMA LEVELS [PG/ML] VS. TIME (CV%)

TIME (HR)	FASTED TEST (TREATMENT A)	FED TEST (TREATMENT B)	FED REFERENCE (TREATMENT C)	RATIO (B/C)	RATIO (B/A)
0	0.0	0.0	0.0	-----	-----
0.25	0.0	0.0	77.7 (285)	-----	-----
0.5	371.6 (129)	746.5 (175)	2563.8 (121)	0.29	2.01
0.67	2239.7 (102)	1745.4 (133)	4436.2 (115)	0.39	0.78
0.83	3973.9 (74)	2598.2 (112)	4970.2 (92)	0.52	0.65
1	5565.6 (54)	3667.4 (93)	5462.8 (73)	0.67	0.66
1.5	7834.7 (45)	5872.4 (71)	7189.3 (60)	0.82	0.75
2	8832.1 (45)	7258.8 (64)	8511.9 (51)	0.85	0.82
2.5	9094.6 (41)	8372.9 (53)	8619.5 (48)	0.97	0.92
3	9428.3 (43)	8649.8 (50)	8789.2 (44)	0.98	0.92
4	8905.7 (40)	9467.1 (46)	9189.3 (42)	1.03	1.06
5	9776.2 (41)	9625.1 (41)	9389.4 (40)	1.02	0.98
6	8721.8 (38)	9198.2 (39)	8955.5 (42)	1.03	1.05
8	9042.6 (43)	8953.0 (42)	8504.2 (39)	1.05	0.99
12	7130.6 (37)	7616.8 (43)	6859.2 (40)	1.11	1.06
24	3696.6 (36)	3935.9 (41)	3588.9 (37)	1.10	1.06
48	1116.2 (73)	956.7 (59)	935.9 (52)	1.02	0.86
72	289.5 (134)	386.8 (119)	298.1 (168)	1.30	1.33
96	97.6 (229)	134.8 (190)	64.2 (286)	2.10	1.38

II. ARITHMETIC MEANS FOR PK PARAMETERS (CV%)

PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REF. TREATMENT C	B/C	B/A
AUC(T) [pg•hr/mL]	230600 (41)	238300 (43)	221600 (40)	1.08	1.03
AUC(I)[a] [pg•hr/mL]	248300 (38)	240800 (41)	237500 (38)	1.01	0.97
Cmax [pg/mL]	10692 (41)	11312 (38)	10786 (44)	1.05	1.06
Tmax [hr]	3.92 (45)	4.17 (37)	4.25 (46)	0.98	0.94
Kel[a] [1/hr]	0.0490 (30)	0.0498 (31)	0.0515 (33)	0.97	1.02
$T_{1/2}$[a] [hr]	15.25 (27)	15.08 (28)	14.95 (35)	1.01	0.99

[a] (N = 16-18 Subjects)

TABLE 13

IN VIVO FOOD EFFECT STUDY NO. 940027
LEAST SQUARES MEANS FOR PK PARAMETERS

I. SELEGILINE (N=17)

PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REF. TREATMENT C	B/C	B/A
AUC(T) [pg•hr/mL]	719.9	1759.6	1669.7	1.05	2.44
AUC(I)[a] [pg•hr/mL]	998.1	1958.6	1965.0	1.00	1.96
Cmax [pg/mL]	964.1	1117.2	1563.4	0.71	1.16
Tmax [hr]	0.84	1.47	0.76	1.93	1.75
Kel[a] [1/hr]	1.5338	0.8493	0.9128	0.93	0.55
$T_{1/2}$[a] [hr]	0.76	0.98	1.05	0.93	1.29

II. DESMETHYLSELEGILINE (N=18)

PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REF. TREATMENT C	B/C	B/A
AUC(T) [pg•hr/mL]	32325	37601	36423	1.03	1.16
AUC(I) [pg•hr/mL]	34139	39271	38665	1.02	1.15
Cmax [pg/mL]	14163	9834.3	10857	0.91	0.69
Tmax [hr]	0.99	1.77	1.11	1.59	1.79
Kel [1/hr]	0.2403	0.2392	0.2084	1.15	1.00
$T_{1/2}$ [hr]	3.78	3.65	4.50	0.81	0.97

[a] (N=9-13 Subjects)

TABLE 13 [CON'T.]

IN VIVO FOOD EFFECT STUDY NO. 940027
LEAST SQUARES MEANS FOR PK PARAMETERS

III. AMPHETAMINE (N=18)

PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REF. TREATMENT C	B/C	B/A
AUC(T) [pg•hr/mL]	48623	49235	48999	1.01	1.01
AUC(I)[a] [pg•hr/mL]	54776	50817	53497	0.95	0.93
Cmax [pg/mL]	1884.1	2135.5	1992.3	1.07	1.13
Tmax [hr]	6.59	7.06	5.41	1.30	1.07
Kel[a] [1/hr]	0.0442	0.0432	0.0463	0.93	0.98
$T_{1/2}$[a] [hr]	16.63	18.56	16.18	1.15	1.12

IV. METHAMPHETAMINE (N=18)

PARAMETER	FASTED TEST TREATMENT A	FED TEST TREATMENT B	FED REF. TREATMENT C	B/C	B/A
AUC(T) [pg•hr/mL]	230074	237030	223482	1.06	1.03
AUC(I)[b] [pg•hr/mL]	255473	234987	233203	1.01	0.92
Cmax [pg/mL]	10897	11305	10588	1.07	1.04
Tmax [hr]	3.88	4.28	4.17	1.03	1.10
Kel[b] [1/hr]	0.0483	0.0514	0.0519	0.99	1.06
$T_{1/2}$[b] [hr]	15.34	14.94	14.80	1.01	0.97

[a] (N = 14-17 subjects) [b] (N = 16-18 subjects)

Table 14 - In Vitro Dissolution Testing

Drug (Generic Name): Selegiline HCL Tablets
Dose Strength: 5 mg
ANDA No.: 74-537
Firm: Novopharm, Ltd.
Submission Date: 8/23/94
File Name: WP #74537.894

I. Conditions for Dissolution Testing: (No dissolution method in USP XXIII)

Apparatus: USP XXIII Paddle, 50 RPM
No. Units Tested: 12
Medium: 0.1N HCL
Volume: 900 mL
Reference Drug: Eldepryl® Tablets, 5 mg
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # PD2607 Strength: 5 mg			Reference Product Lot # 3Z011N Strength: 5 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	46.7		15.2	97.2		3.3
20	85.5		5.6	98.0		2.7
30	99.0		2.5	98.5		2.4
40	100.5		1.6	98.8		2.1

TABLE 15

PRODUCT FORMULATION - SELEGILINE TABLETS, 5 MG

(NOVOPHARM, LTD.)

INGREDIENT	STANDARD	AMOUNT (MG/TAB)	PERCENT TABLET WEIGHT
SELEGILINE HCL	HOUSE	5.0	3.33
LACTOSE	NF		
LACTOSE	NF		
STARCH	NF		
POVIDONE	USP		
STARCH	NF		
MAGNESIUM STEARATE	NF		
TALC	USP		
PURIFIED WATER	USP		
TABLET WEIGHT		150.0 MG	100.0%

Figure 1

Project No. 930491

Mean Human Plasma Selegiline Concentrations

(Linear Plot) (N=29)

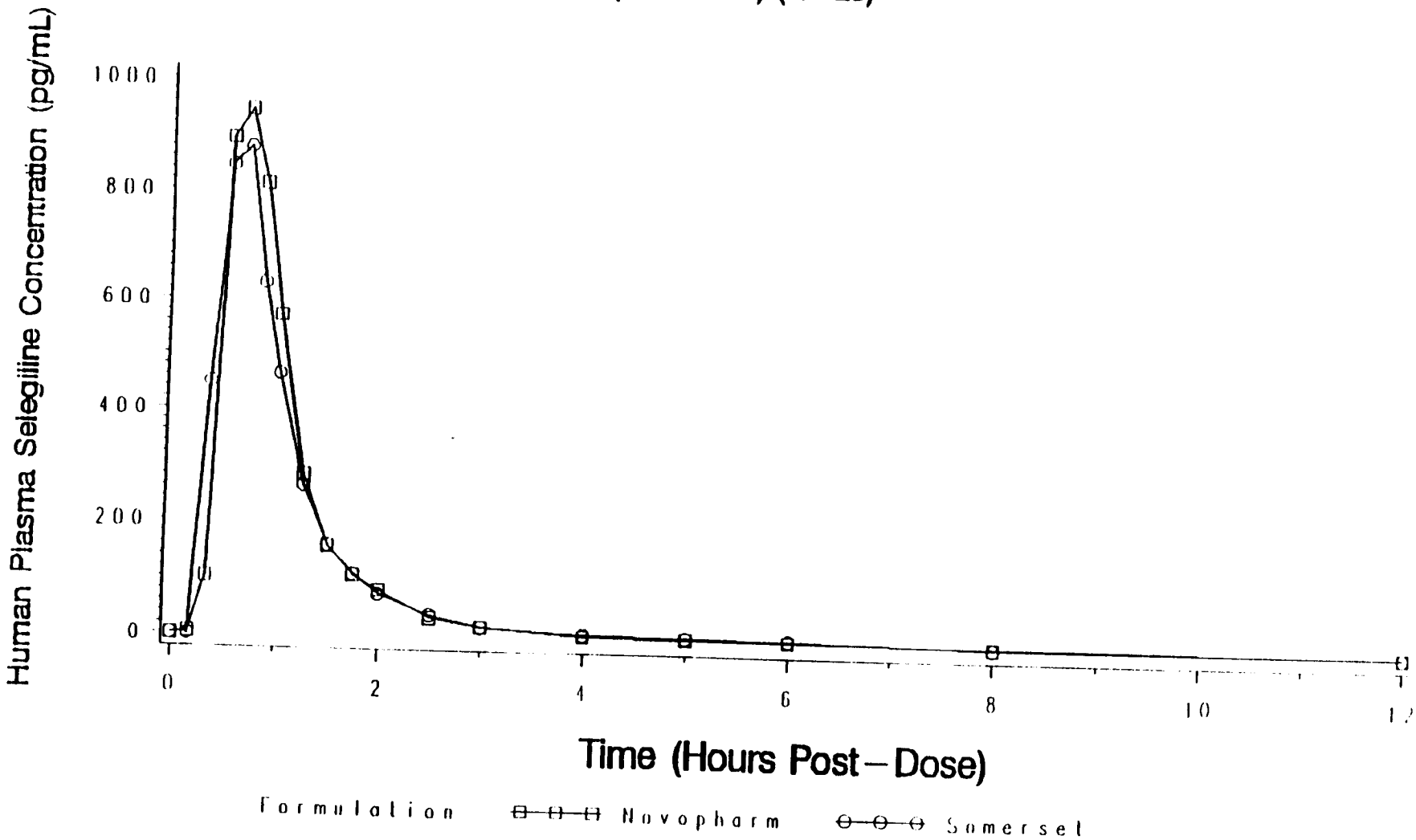


Figure 2

Project No. 930491

Mean Human Plasma Desmethylselegiline Concentrations

(Linear Plot)

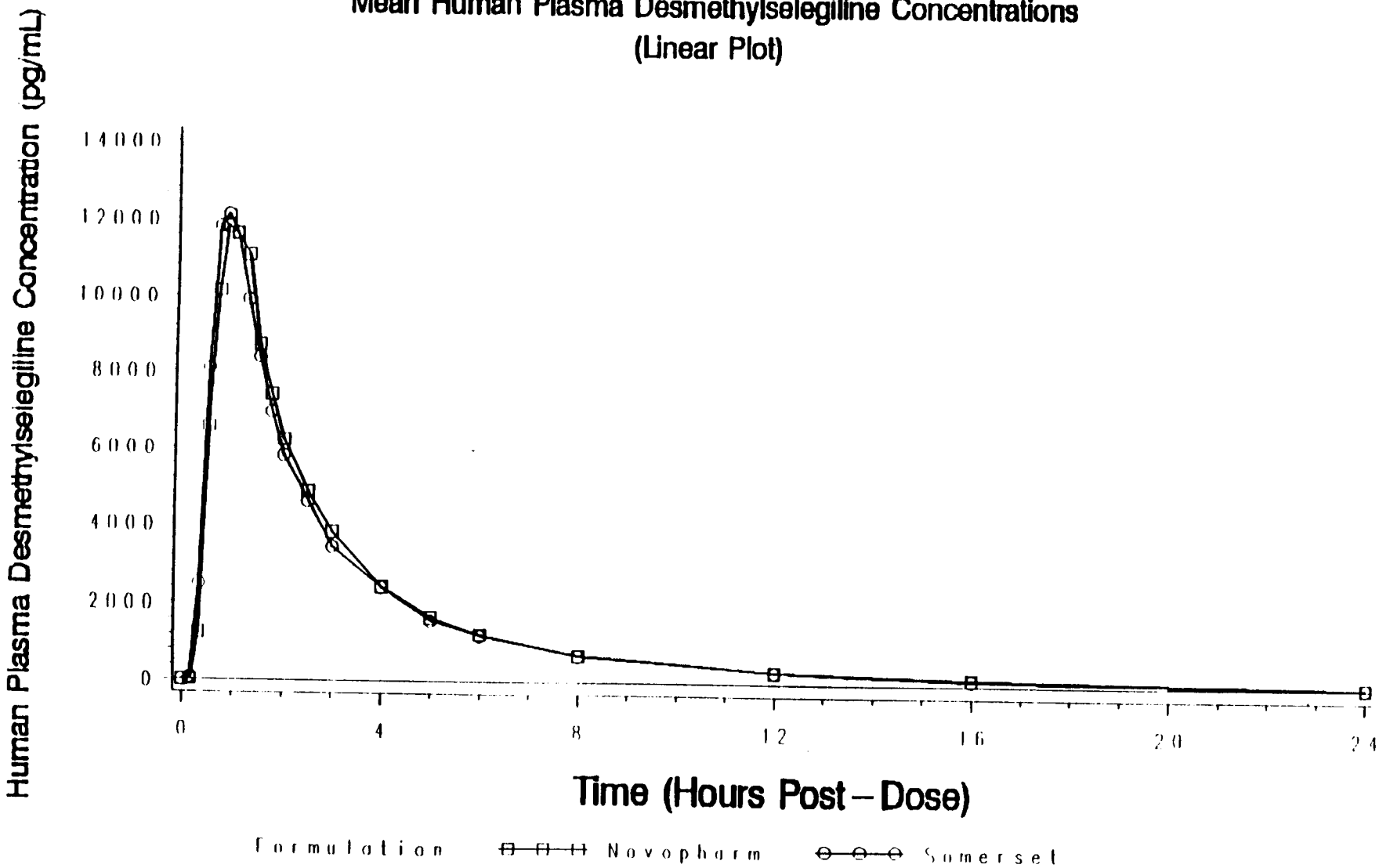


Figure 3

Project No. 930491

Mean Human Plasma Amphetamine Concentrations

(Linear Plot)

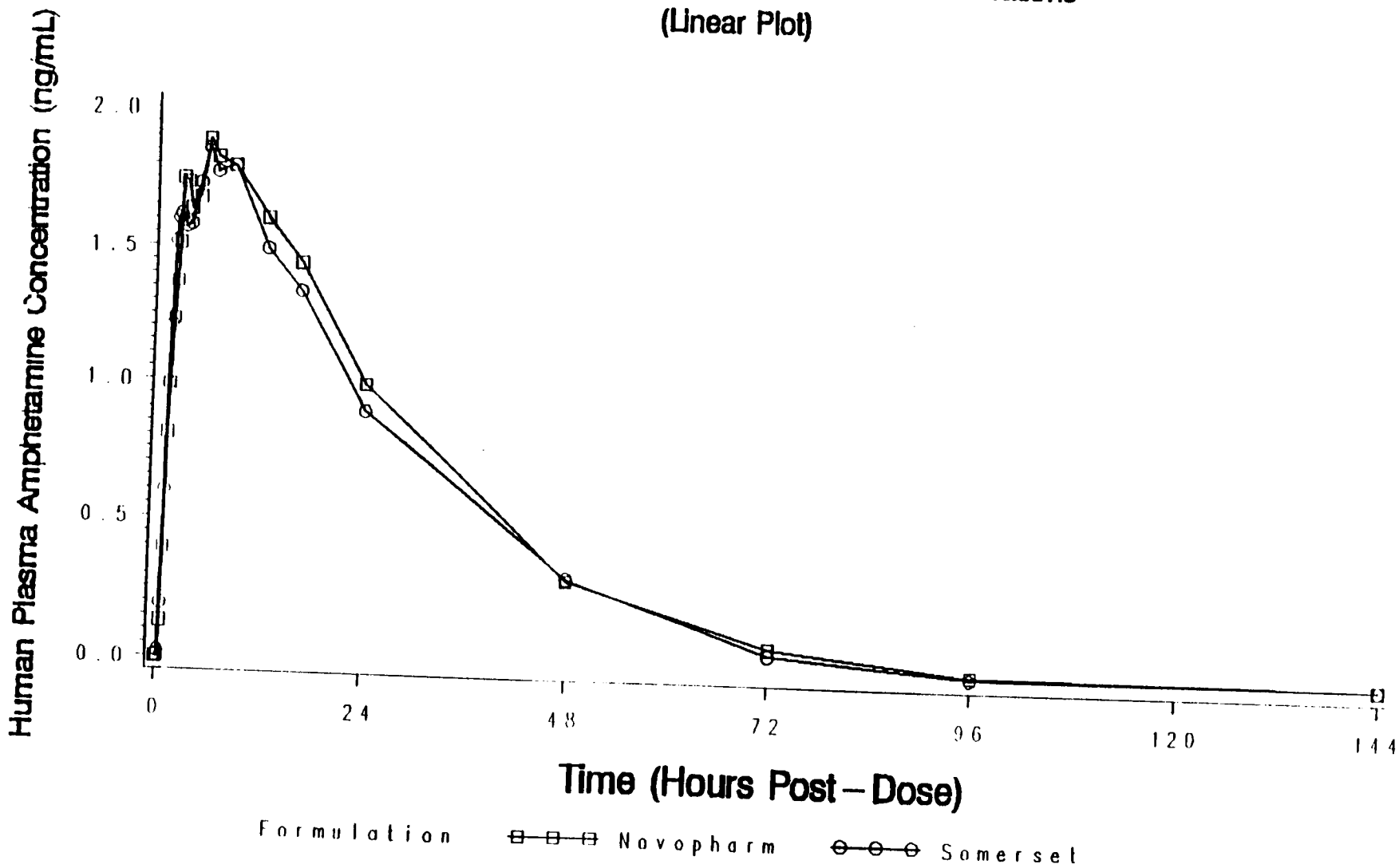


Figure 4

Project No. 930491

Mean Human Plasma Methamphetamine Concentrations

(Linear Plot)

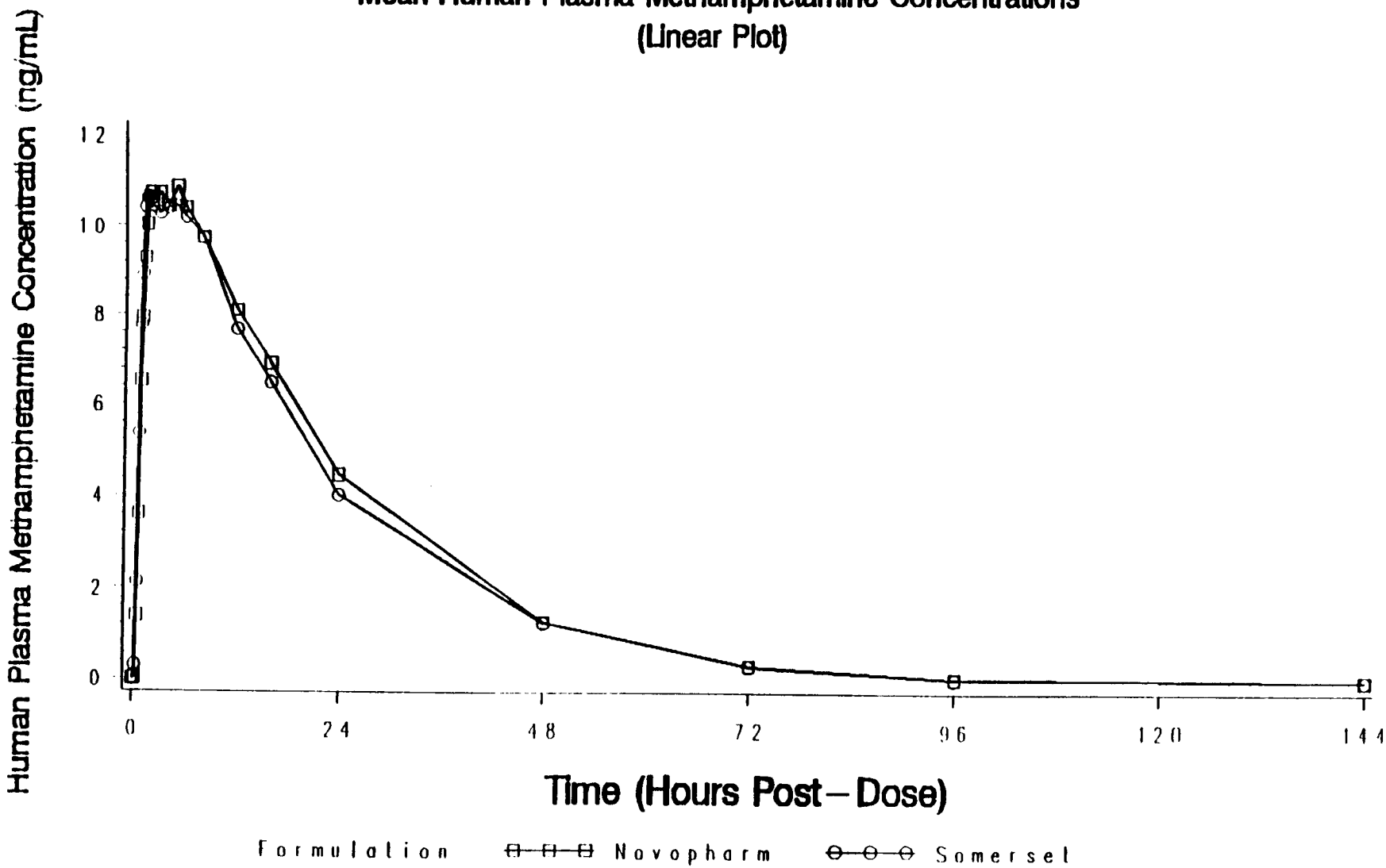


Figure 5

Project No. 940027

Mean Human Plasma Selegiline Concentrations

(Linear Plot) (N=17)

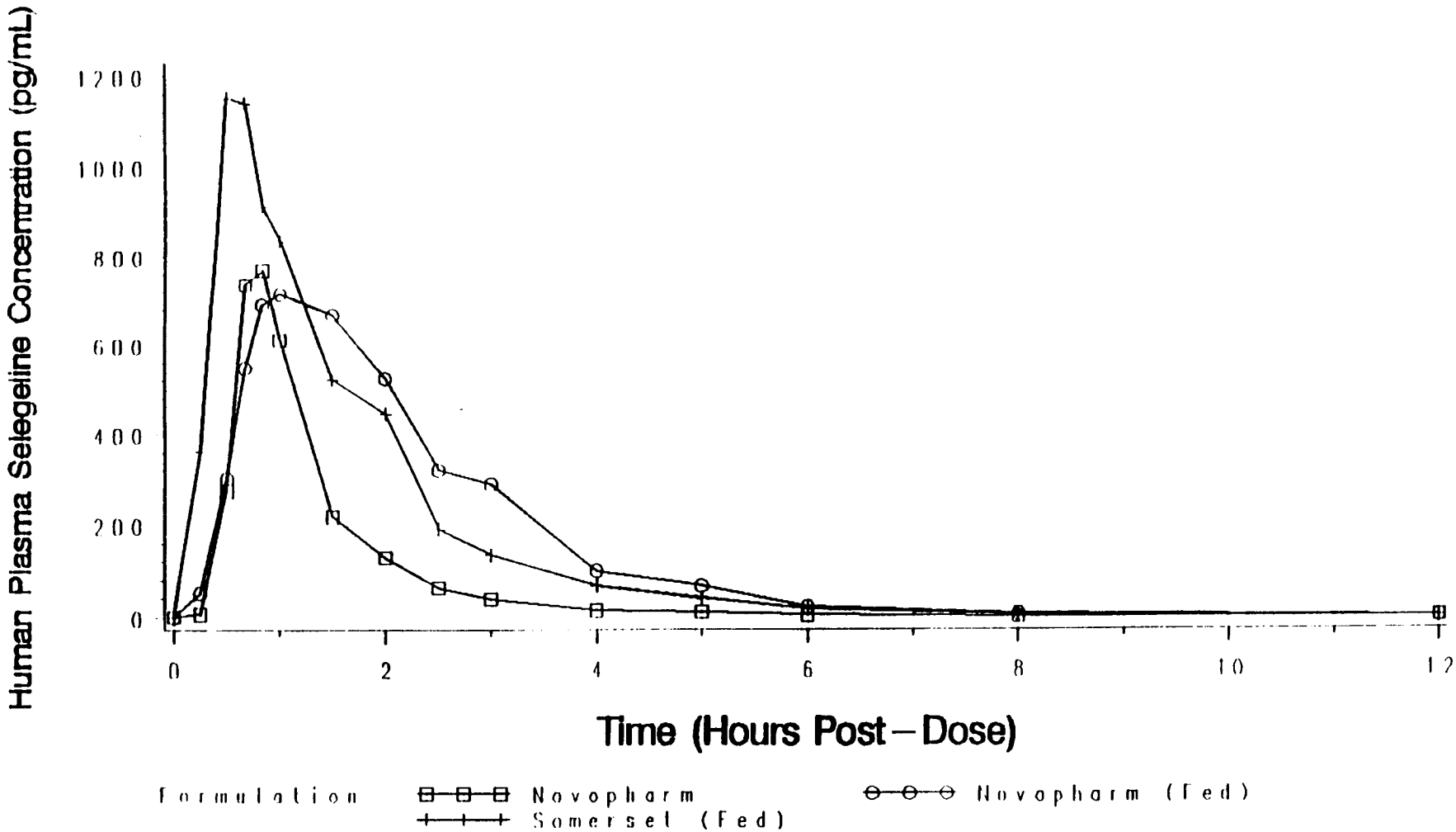


Figure 6

Project No. 940027

Mean Human Plasma Desmethylselegiline Concentrations

(Linear Plot)

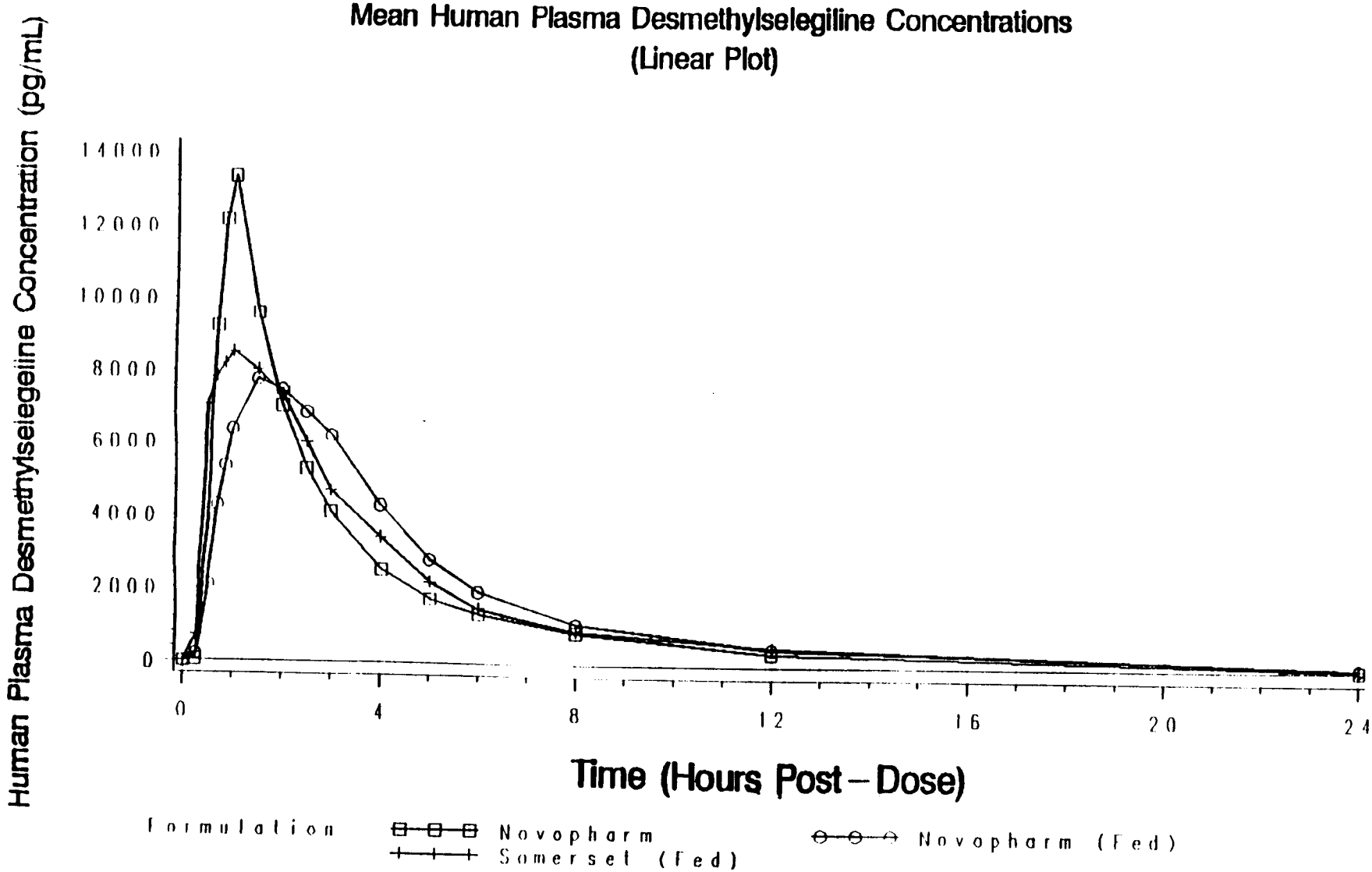
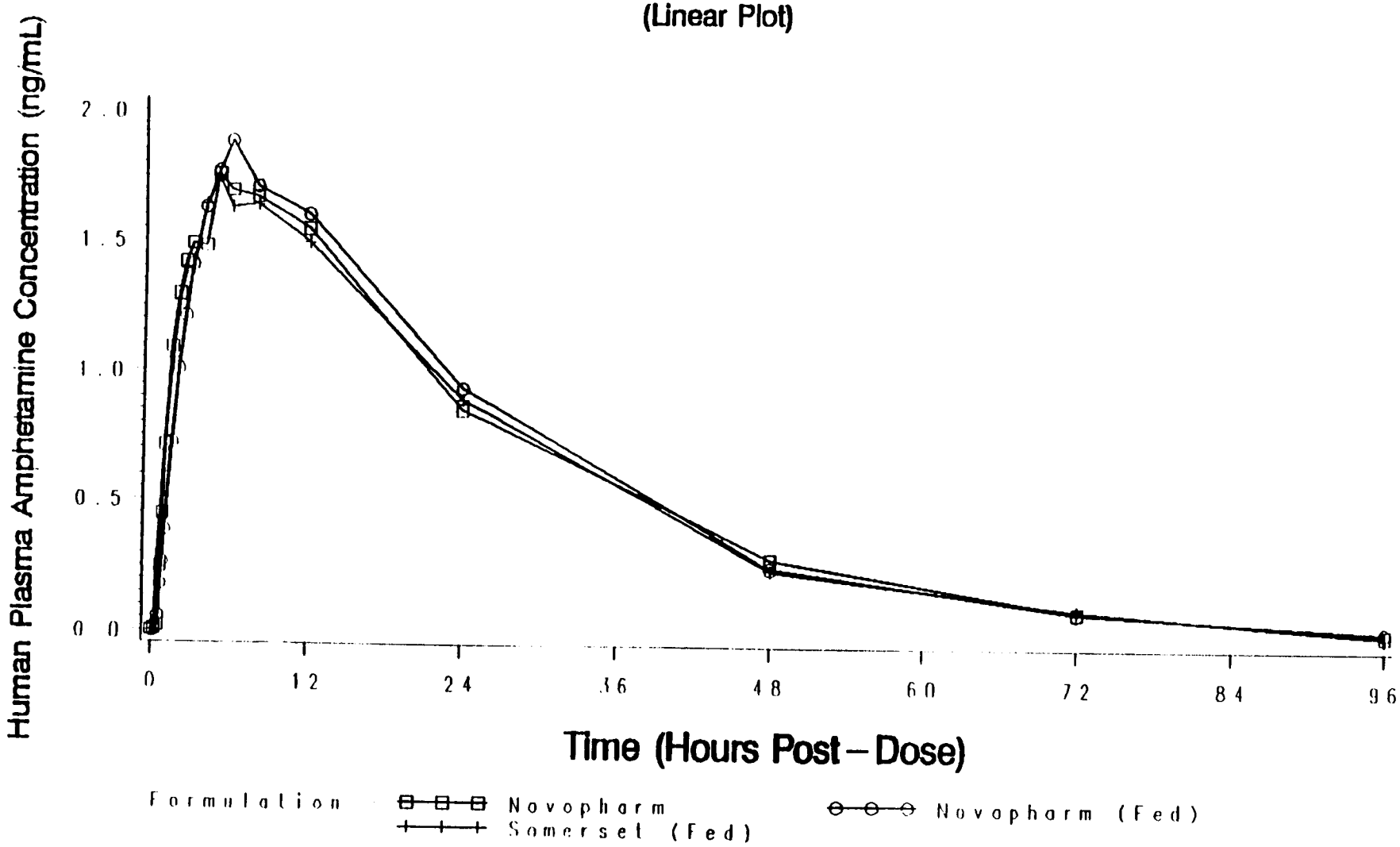


Figure 7

Project No. 940027

Mean Human Plasma Amphetamine Concentrations

(Linear Plot)