CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: **074849**

Trade Name : CLOMIPRAMINE HCL CAPSULES

Generic Name: Clomipramine HCL Capsules 25mg, 50mg and 75mg

Sponsor : Novopharm N.C., Inc.

Approval Date: April 4, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074849

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074849

APPROVAL LETTERS

ANDA 74-849

APR 4 1997

Novopharm N.C. Inc.
Attention: Therese M. Ast, Ph.D., Esq.
U.S. Agent for Novopharm Limited
4700 Novopharm Blvd.
Wilson, NC 27893

Dear Dr. Ast:

This refers to your abbreviated new drug application dated February 6, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clomipramine Hydrochloride Capsules, 25, 50, and 75 mg.

Reference is also made to your amendments dated April 25 and 29, and November 1 and 7, 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 that your Clomipramine Hydrochloride Capsules 25 mg, 50 mg, and 75 mg are bioequivalent and, therefore therapeutically equivalent, to the listed drug (Anafranil® Capsules 25 mg, 50 mg, and 75 mg, respectively, of Basel Pharmaceuticals. 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 FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

4/4/97

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074849

FINAL PRINTED LABELING

NDC 55953-031-70 500 CAPSULES

Clomipramine Hydrochloride

Capsules

25 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm®

APR 4 1997

USUAL DOSAGE: See package insert for complete product information.

00000-0000 Printed in Canada Sub. 00

0 12899 03170 6

Each capsule contains:
Clomipramine Hydrochloride ..... 25 mg

Do not store above 30°C (86°F).
Protect from moisture.
Dispense in tight, light-resistant container (USP).

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

Area for Lot and Exp.

APPROVED

MAR 50

NDC 55953-031-40 100 CAPSULES

Clomipramine Hydrochloride

Capsules

25 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm®

APR 4 1997

USUAL DOSAGE: See package insert for complete product information.

00000-0000 Printed in Canada Sub. 00

0 12899 03140 9

Each capsule contains:
Clomipramine Hydrochloride ..... 25 mg

Do not store above 30°C (86°F).
Protect from moisture.
Dispense in tight, light-resistant container (USP).

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

Area for Lot and Exp.

APPROVED

MAR 50

NDC 55953-032-40 100 CAPSULES

Clomipramine Hydrochloride

Capsules

50 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm®

APR 4 1997

USUAL DOSAGE: See package insert for complete product information.

00000-0000 Printed in Canada Sub. 00

0 12899 03240 6

Each capsule contains:
Clomipramine Hydrochloride ..... 50 mg

Do not store above 30°C (86°F).
Protect from moisture.
Dispense in tight, light-resistant container (USP).

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

Area for Lot and Exp.

MAKE

NDC 55953-033-40 100 CAPSULES

Clomipramine Hydrochloride

Capsules

75 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm®

APR 4

USUAL DOSAGE: See package insert for complete product information.

00000-0000 Printed in Canada Sub. 00

0 12899 03340 3

Each capsule contains:
Clomipramine Hydrochloride ..... 75 mg

Do not store above 30°C (86°F).
Protect from moisture.
Dispense in tight, light-resistant container (USP).

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

Area for Lot and Exp.

NDC 55953-032-70 500 CAPSULES

Clomipramine Hydrochloride

Capsules

50 mg

Caution: Federal law prohibits dispensing without prescription.

novopharm®

APR 4 1997

USUAL DOSAGE: See package insert for complete product information.

00000-0000 Printed in Canada Sub. 00

0 12899 03270 3

Each capsule contains:
Clomipramine Hydrochloride ..... 50 mg

Do not store above 30°C (86°F).
Protect from moisture.
Dispense in tight, light-resistant container (USP).

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

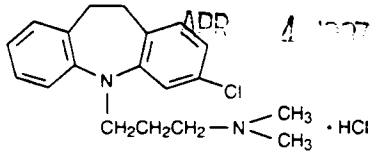
Area for Lot and Exp.

CLOMIPRAMINE HYDROCHLORIDE CAPSULES

DESCRIPTION

Clomipramine hydrochloride is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

Each capsule, for oral administration, contains 25, 50, or 75 mg of clomipramine hydrochloride. In addition, each capsule contains the following inactive ingredients: Colloidal silicon dioxide, D & C Red #28, D & C Yellow # 10, FD & C Blue #1 (50 mg capsules only), FD & C Red #40 (25 mg capsules only), gelatin, imprinting ink (contains D & C Yellow #10, FD & C Blue #1, FD & C Blue #2, FD & C Red #40, and synthetic black iron oxide,), lactose monohydrate, magnesium stearate, pregelatinized starch, silicon dioxide, sodium lauryl sulfate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but clomipramine's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.

Pharmacokinetics

Absorption/Bioavailability: Clomipramine from a capsule is as bioavailable as clomipramine from a solution. The bioavailability of clomipramine from capsules is not significantly affected by food.

In a dose proportionality study involving multiple clomipramine doses, steady-state plasma concentrations (C_{SS}) and area-under-plasma-concentration-time-curves (AUC) of clomipramine and clomipramine's major active metabolite, desmethylclomipramine, were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{SS} and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and clomipramine/desmethylclomipramine concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{SS} and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see **WARNINGS** and **PRECAUTIONS**, Drug Interactions).

After a single 50 mg oral dose, maximum plasma concentrations of clomipramine occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/mL to 154 ng/mL (mean, 92 ng/mL). After multiple daily doses of 150 mg of clomipramine hydrochloride, steady-state maximum plasma concentrations range from 94 ng/mL to 339 ng/mL (mean, 218 ng/mL) for clomipramine and from 134 ng/mL to 532 ng/mL (mean, 274 ng/mL) for desmethylclomipramine. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: Clomipramine distributes into cerebrospinal fluid (CSF) and brain and into breast milk. Desmethylclomipramine also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of clomipramine is approximately 97%, principally to albumin, and is independent of clomipramine concentration. The interaction between clomipramine and other highly protein-bound drugs has not been fully evaluated, but may be important (see **PRECAUTIONS**, Drug Interactions).

Metabolism: Clomipramine is extensively biotransformed to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of clomipramine in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of clomipramine and desmethylclomipramine were only about 0.8-1.3% of the dose administered. Clomipramine does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C_{SS} and AUC for clomipramine and desmethylclomipramine may increase disproportionately with increasing oral doses suggests that the metabolism of clomipramine and desmethylclomipramine may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of clomipramine and desmethylclomipramine are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, clomipramine and desmethylclomipramine may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see **WARNINGS**).

After a 150-mg dose, the half-life of clomipramine ranges from 19 hours to 37 hours (mean, 32 hr) and that of desmethylclomipramine ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for clomipramine. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for clomipramine is approximately 2.5 and for desmethylclomipramine is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of clomipramine and desmethylclomipramine (see **DOSAGE AND ADMINISTRATION**). The effects of hepatic and renal impairment on the disposition of clomipramine hydrochloride have not been determined.

Interactions: Coadministration of haloperidol with clomipramine increases plasma concentrations of clomipramine. Coadministration of clomipramine with phenobarbital increases plasma concentrations of phenobarbital (see **PRECAUTIONS**, Drug Interactions). Younger subjects (18-40 years of age) tolerated clomipramine better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of clomipramine were significantly lower in smokers than in nonsmokers.

INDICATIONS AND USAGE

Clomipramine hydrochloride capsules are indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of clomipramine for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking clomipramine experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. Clomipramine treated patients experienced a 2.5 unit decrement on the NIMH-OC. Patients on placebo showed no

Mania/Hypomania: During premarketing testing of clomipramine in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to clomipramine.

Hepatic Changes: During premarketing testing, clomipramine was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with clomipramine, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with clomipramine use. As is the case with tricyclic antidepressants to which clomipramine is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with clomipramine.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when clomipramine was used in combination with other drugs. When clomipramine and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with clomipramine in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving clomipramine, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving clomipramine had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving clomipramine and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of clomipramine with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with clomipramine hydrochloride should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use in Concomitant Illness: As with closely related tricyclic antidepressants, clomipramine should be used with caution in the following:
(1) Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity;
(2) Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug;
(3) Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises;
(4) Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of clomipramine have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see **DRUG ABUSE AND DEPENDENCE**).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe clomipramine hydrochloride:
(1) The risk of seizure (see **WARNINGS**);
(2) The relatively high incidence of sexual dysfunction among males (see ***Sexual Dysfunction***);
(3) Since clomipramine may impair the mental and/or physical abilities required for the performance of complex tasks, and since clomipramine is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see **WARNINGS**);
(4) Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since clomipramine may exaggerate their response to these drugs;
(5) Patients should notify their physician if they become pregnant or intend to become pregnant during therapy;
(6) Patients should notify their physician if they are breast-feeding.

Drug Interactions

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary). Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

The risks of using clomipramine in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of clomipramine, caution is advised in using it concomitantly with other CNS-active drugs (see **Information for Patients**). Clomipramine should *not* be used with MAO inhibitors (see **CONTRAINDICATIONS**).

Close supervision and careful adjustment of dosage are required when clomipramine is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with clomipramine because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of clomipramine has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of methylphenidate or hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin) and such an effect may be anticipated with clomipramine as well. Administration of clomipramine has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see **CLINICAL PHARMACOLOGY**, Interactions).

Because clomipramine is highly bound to serum protein, the administration of clomipramine to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clomipramine by other highly bound drugs (see **CLINICAL PHARMACOLOGY**, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

If the pharmacokinetics of clomipramine and desmethylclomipramine [illegible] doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, clomipramine and desmethylclomipramine may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see **WARNINGS**).

After a 150-mg dose, the half-life of clomipramine ranges from 19 hours to 37 hours (mean, 32 hr) and that of desmethylclomipramine ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for clomipramine. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for clomipramine is approximately 2.5 and for desmethylclomipramine is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of clomipramine and desmethylclomipramine (see **DOSAGE AND ADMINISTRATION**). The effects of hepatic and renal impairment on the disposition of clomipramine hydrochloride have not been determined.

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The effectiveness of clomipramine for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking clomipramine experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. Clomipramine treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of clomipramine for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use clomipramine for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Clomipramine hydrochloride capsules are contraindicated in patients with a history of hypersensitivity to clomipramine or other tricyclic antidepressants.

Clomipramine should not be given in combination, or within 14 days before or after treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Clomipramine is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

Seizures

During premarket evaluation, seizure was identified as the most significant risk of clomipramine hydrochloride use.

The observed cumulative incidence of seizures among patients exposed to clomipramine hydrochloride at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates correct the crude rate of 0.7% (25 of 3519 patients) for the variable duration of exposure in clinical trials.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of clomipramine greater than 250 mg is limited, given that the plasma concentration of clomipramine may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see **DOSAGE AND ADMINISTRATION**).

Caution should be used in administering clomipramine hydrochloride to patients with a history of seizures or other predisposing factors, e.g., brain damage or varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Rare reports of fatalities in association with seizures have been reported by foreign post-marketing surveillance, but not in U.S. clinical trials. In some of these cases, clomipramine has been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions. Thus a causal association between clomipramine treatment and these fatalities has not been established.

Physicians should discuss with patients the risk of taking clomipramine while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS

General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for clomipramine hydrochloride should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking clomipramine in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with clomipramine in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena: Patients treated with clomipramine have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with clomipramine. As with tricyclic antidepressants to which it is closely related, clomipramine may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

propatenone [illegible] (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6; they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary). Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

The risks of using clomipramine in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of clomipramine, caution is advised in using it concomitantly with other CNS-active drugs (see Information for Patients). Clomipramine should *not* be used with MAO inhibitors (see **CONTRAINDICATIONS**).

Close supervision and careful adjustment of dosage are required when clomipramine is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with clomipramine because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of clomipramine has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of methylphenidate or hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin) and such an effect may be anticipated with clomipramine as well. Administration of clomipramine has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see **CLINICAL PHARMACOLOLGY**, Interactions).

Because clomipramine is highly bound to serum protein, the administration of clomipramine to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clomipramine by other highly bound drugs (see **CLINICAL PHARMACOLOGY**, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

Pregnancy: Teratogenic Effects. Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses of up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken clomipramine hydrochloride until delivery. Clomipramine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Clomipramine has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received clomipramine for up to 8 weeks. In addition, 150 adolescent patients have received clomipramine in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see **ADVERSE REACTIONS**) is similar to that in adults, it is unknown what, if any, effects long-term treatment with clomipramine hydrochloride may have on the growth and development of children.

The safety and effectiveness in pediatric patients below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of clomipramine in pediatric patients under the age of 10.

Use in Elderly

Clomipramine has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in the U.S. clinical trials received clomipramine for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

ADVERSE REACTIONS

Commonly Observed

The most commonly observed adverse events associated with the use of clomipramine and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3615 patients who received clomipramine in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primary somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received clomipramine in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving clomipramine (N=322) or placebo (N=319) or children treated with clomipramine (N=46) or placebo (N=44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials (Percentage of Patients Reporting Event)

Body System Adverse Event*	Adults: Clomipramine hydrochloride (N=322)	Adults: Placebo (N=319)	Children and Adolescents: Clomipramine hydrochloride (N=46)	Children and Adolescents: Placebo (N=44)
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7
Libido change	21	3	-	-
Nervousness	18	2	4	2
Myoclonus	13	-	2	-
Increased appetite	11	2	-	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	-
Twitching	7	1	4	5
Impaired concentration	5	2	-	-
Depression	5	1	-	-
Hypertonia	4	1	2	-
Sleep disorder	4	-	9	5
Psychosomatic disorder	3	-	-	-
Yawning	3	-	-	-
Confusion	3	-	2	-
Speech disorder	3	-	-	-
Abnormal dreaming	3	-	-	2
Agitation	3	-	-	-
Migraine	3	-	-	-
Depersonalization	2	-	2	-
Irritability	2	2	2	-
Emotional lability	2	-	-	2
Panic reaction	1	-	2	-
Aggressive reaction	-	-	2	-
Paresis	-	-	2	-
Skin and Appendages				
Increased sweating	29	3	9	-
Rash	8	1	4	2
Pruritus	6	-	2	2
Dermatitis	2	-	-	2
Acne	2	2	-	5
Dry skin	2	-	-	5
Urticaria	1	-	-	-
Abnormal skin odor	-	-	2	-
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	-	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	-
Flatulence	6	3	-	2
Tooth disorder	5	-	-	-
Gastrointestinal disorder	2	-	-	2
Dysphagia	2	-	-	-
Esophagitis	1	-	-	-
Eructation	-	-	2	2
Ulcerative stomatitis	-	-	2	-
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	-
Flushing	8	-	7	-
Hot flushes	5	-	2	-
Chest pain	4	4	7	-
Fever	4	-	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	-	-
Chills	2	1	-	-
Weight decrease	-	-	7	-
Otitis media	-	-	4	5
Asthenia	-	-	2	-
Halitosis	-	-	2	-
Cardiovascular System				
Postural hypotension	6	-	4	-
Palpitation	4	2	4	-
Tachycardia	4	-	2	-
Syncope	-	-	2	-
Respiratory System				
Pharyngitis	14	9	-	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	-	7	2
Epistaxis	2	-	-	2
Dyspnea	-	-	2	-
Laryngitis	-	1	2	-
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	-	-
Micturition frequency	5	3	-	-
Urinary retention	2	-	7	-
Dysuria	2	2	-	-
Cystitis	2	-	-	-
Female Patients Only	**(N=182)**	**(N=167)**	**(N=10)**	**(N=21)**
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	-	-	-
Menstrual disorder	4	2	-	-
Vaginitis	2	-	-	-
Leukorrhea	2	-	-	-
Breast enlargement	2	-	-	-
Breast pain	1	-	-	-
Amenorrhea	1	-	-	-
Male Patients Only	**(N=140)**	**(N=152)**	**(N=26)**	**(N=23)**
Ejaculation failure	42	2	6	-
Impotence	20	3	-	-
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	-	4	-
Tinnitus	6	-	4	-
Abnormal lacrimation	3	2	-	-
Mydriasis	2	-	-	-
Conjunctivitis	1	-	-	-
Anisocoria	-	-	2	-
Blepharospasm	-	-	2	-
Ocular allergy	-	-	2	-
Vestibular disorder	-	-	2	2
Musculoskeletal				
Myalgia	13	9	-	-
Back pain	6	6	-	-
Arthralgia	3	5	-	-
Muscle weakness	1	-	2	-
Hemic and Lymphatic				
Purpura	3	-	-	-
Anemia	-	-	2	2
Metabolic and Nutritional				
Thirst	2	2	-	2

* Events reported by at least 1% of clomipramine patients are included

DRUG ABUSE AND DEPENDENCE

Clomipramine has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with clomipramine discontinuation (see **PRECAUTIONS**, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential clomipramine abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received clomipramine for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for clomipramine in foreign marketing, it is not possible to predict the extent to which clomipramine might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with clomipramine either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of clomipramine overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, clomipramine's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of clomipramine may not reflect the severity of poisoning: they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation may be necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery.

In the alert patient, the stomach should be emptied promptly by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Instillation of activated charcoal slurry may help reduce absorption of clomipramine.

External stimulation should be minimized to reduce the tendency for convulsions. If anticonvulsants are necessary, diazepam and phenytoin may be useful. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, and, if necessary, a vasopressor agent by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of clomipramine in tissues.

The slow intravenous administration of physostigmine salicylate has been used as a last resort to reverse severe CNS anticholinergic manifestations of overdosage with tricyclic antidepressants; however, it should not be used routinely, since it may induce seizures and cholinergic crises.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of clomipramine in 520 adults, and 91 children and adolescents with OCD. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both clomipramine and its active metabolite, desmethylclomipramine, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see **CLINICAL PHARMACOLOGY**). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with clomipramine hydrochloride should be initiated at dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce the gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see **PRECAUTIONS**, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue clomipramine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of clomipramine after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Clomipramine Hydrochloride Capsules, 25 mg have an opaque orange cap and an opaque yellow body, and are size # 2 hard gelatin capsules, imprinted with black ink N and 25 on opposing cap and body portions of the capsules. 031

They are supplied as follows:

NDC 55953-031-40	Bottles of 100
NDC 55953-031-70	Bottles of 500

Clomipramine Hydrochloride Capsules, 50 mg have an opaque blue cap and an opaque yellow body, and are size # 1 hard gelatin capsules, imprinted with black ink N and 50 on opposing cap and body portions of the capsules. 032

They are supplied as follows:

NDC 55953-032-40	Bottles of 100
NDC 55953-032-70	Bottles of 500

Clomipramine Hydrochloride Capsules, 75 mg have an opaque yellow cap and body, and are size # 1 hard gelatin capsules, imprinted with black ink N and 75 on opposing cap and body portions of the capsules. 033

They are supplied as follows:

Female Patients Only	(N=182)	(N=167)	(N=10)	(N=21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	-	-	-
Menstrual disorder	4	2	-	-
Vaginitis	2	-	-	-
Leukorrhea	2	-	-	-
Breast enlargement	2	-	-	-
Breast pain	1	-	-	-
Amenorrhea	1	-	-	-
Male Patients Only	**(N=140)**	**(N=152)**	**(N=20)**	**(N=23)**
Ejaculation failure	42	2	6	-
Impotence	20	3	-	-
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	-	4	-
Tinnitus	6	-	4	-
Abnormal lacrimation	3	2	-	-
Mydriasis	2	-	-	-
Conjunctivitis	1	-	-	-
Anosocona	-	-	2	-
Blepharospasm	-	-	2	-
Ocular allergy	-	-	2	-
Vestibular disorder	-	-	2	2
Musculoskeletal				
Myalgia	13	9	-	-
Back pain	6	6	-	-
Arthralgia	3	5	-	-
Muscle weakness	1	-	2	-
Hemic and Lymphatic				
Purpura	3	-	-	-
Anemia	-	-	2	2
Metabolic and Nutritional				
Thirst	2	2	-	2

* Events reported by at least 1% of clomipramine patients are included.

Other Events Observed During the Premarketing Evaluation of Clomipramine

During clinical testing in the U.S., multiple doses of clomipramine were administered to approximately 3600 subjects. Unfoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of unfoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to clomipramine who experienced an event of the type cited on at least one occasion while receiving clomipramine. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with clomipramine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: *Infrequent* - general edema, increased susceptibility to infection, malaise. *Rare* - dependent edema, withdrawal syndrome.

Cardiovascular System: *Infrequent* - abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* - aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: *Infrequent* - abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* - cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: *Infrequent* - hypothyroidism. *Rare* - goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: *Infrequent* - lymphadenopathy. *Rare* - leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: *Infrequent* - dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare*- fat intolerance, glycosuria.

Musculoskeletal System: *Infrequent* - arthrosis. *Rare* - dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: *Frequent*- abnormal thinking, vertigo. *Infrequent* - abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare*- anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: *Infrequent* - bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* - cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: *Infrequent* - alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* - chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: *Infrequent* - abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* - blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: *Infrequent* - endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* - albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

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HOW SUPPLIED

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They are supplied as follows:

NDC 55953-031-40	Bottles of 100
NDC 55953-031-70	Bottles of 500

Clomipramine Hydrochloride Capsules, 50 mg have an opaque blue cap and an opaque yellow body, and are size # 1 hard gelatin capsules, imprinted with black ink N and 50 on opposing cap and body portions of the capsules. 032

They are supplied as follows:

NDC 55953-032-40	Bottles of 100
NDC 55953-032-70	Bottles of 500

Clomipramine Hydrochloride Capsules, 75 mg have an opaque yellow cap and body, and are size # 1 hard gelatin capsules, imprinted with black ink N and 75 on opposing cap and body portions of the capsules. 033

They are supplied as follows:

NDC 55953-033-40	Bottles of 100

Do not store above 30°C (86°F). Protect from moisture.
Dispense in a tight, light-resistant container (USP).

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with clomipramine. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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

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M1B 2K9

Manufactured for: Novopharm® USA Inc.
Schaumburg, IL 60173

Issued October 1996
Printed in U.S.A.
Sub. 00

70293

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074849

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-849

3. NAME AND ADDRESS OF APPLICANT

Novopharm Limited
30 Novopharm Court
Scarborough, Ontario, M1B 2K9 Canada

4. LEGAL BASIS FOR SUBMISSION

Novopharm Limited certifies that in their opinion and to the best of its knowledge, all patents for the reference product have expired.

The firm has indicated that the exclusivity for Anafranil has expired on December 29, 1994, and to the best of their knowledge, no extension has been registered.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Clomipramine Hydrochloride

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

N/A

9. AMENDMENTS AND OTHER DATES:

Original 2/6/96
Amendment 4/25/96
Amendment 11/1/96
Amendment 11/7/96

10. PHARMACOLOGICAL CATEGORY

Treatment of obsessions and compulsions

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

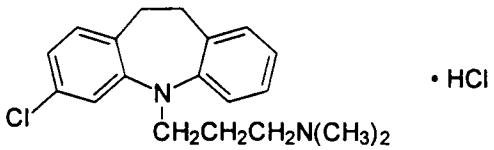
Capsules

14. POTENCY

25 mg, 50 mg, 75 mg

15. CHEMICAL NAME AND STRUCTURE

Clomipramine Hydrochloride. $C_{19}H_{23}ClN_2$•HCl. 351.3. 5*H* -Dibenz[*b,f*]azepine-5-propanamine, 3-chloro-10,11-dihydro-*N* ,*N* -dimethyl-, monohydrochloride. 17321-77-6. USAN 1993, page 159.



17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

3/24/97

Nashed E. Nashed, Ph.D. 3/21/97

Supervisor: Paul Schwartz, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074849

BIOEQUIVALENCE REVIEW(S)

D W

ANDA 74-849

Novopharm LTD
Attention: Thérèse Ast. Ph.D., Esq.
Authorized U.S. Agent
4409 Airport Drive N.W.
Wilson NC 27896

MAR 26 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Clomipramine Hydrochloride Capsules 25 mg, 50 mg and 75 mg.

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

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 500 ml of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   Not less than of the labeled amount of the drug in the capsule is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research-

MAR 20 1997

Clomipramine HCl
25 mg, 50 mg and 75 mg capsules
NDA #74-849
Reviewer: J. Lee
74849SA.N96

Novopharm Ltd.
Ontario, Canada
Submission date:
November 1, 1996

Review of a Study Amendment

This submission responds to deficiencies conveyed to the company on its fasting bio-study for clomipramine HCl 75 mg tablet.

1. Regarding vomiting subjects

   The laboratory has provided their rationale for (1) continuing to dose and collect blood samples for those subjects who vomited and (2) not assaying samples from the vomiting subjects.

2. Exclusion of subject #40's data

   The laboratory has provided, as requested, a more detailed reason for excluding subject #40's data from the statistical analysis.

3. Dissolution testing

   The sponsor utilized a non-current FDA method in their dissolution testing and was requested to retest using the current PF method. The summaries of the retest are attached (along with the results of a new test lot) and are satisfactory.

4. Re-request of waiver

   The sponsor is re-requesting waiver of in-vivo bioequivalence testing for their 25 mg and 50 mg test products based on 21 CFR 320.22 (d)(2). Waivers are granted per same.

Comment:

1. The responses to the deficiencies in the fasting study are sufficient.

Recommendation:

1. The bioequivalence studies (fasted and fed) conducted by . for Novopharm Ltd. on its clomipramine HCl 75 mg capsule, batch #PD2841, comparing it to Anafranil® 75 mg capsule has been found acceptable by the Division of Bioequivalence. The study demonstrates that Novopharm's clomipramine

HCl 75 mg capsule is bioequivalent to the reference product, Anafranil® 75 mg capsule manufactured by Basel Pharmaceuticals.

2. The in-vitro dissolution testing data on the 25 mg and 50 mg capsules using the current PF method is also acceptable. The formulation for the 25 mg and 50 mg capsules are proportionally similar to the 75 mg capsule, which underwent bioequivalence testing. The waivers of in-vivo study requirements for the 25 mg and 50 mg capsules are granted. Novopharm's clomipramine HCl 25 mg and 50 mg capsules are deemed bioequivalent to the like strengths of Anafranil® capsules manufactured by Burroughs-Wellcome.

3. The in-vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of 0.1N HCl at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than of the labeled amount of the drug in the capsule is dissolved in 30 minutes.

4. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

1/30/97

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

1/30/1997

Concur: _____ Date: 3/20/97

Rabi Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

JLee/jl/ 01-22-97

cc: NDA #74-849 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

USP XXIII Apparatus II Basket _____ Paddle X rpm 50

Medium: 0.1N HCl @ 37°C Volume: 500 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Anafranil® capsule

Assay Methodology: _____

75 mg

Results

Time (min)	Test Product Lot # PD2841 (Bio-lot) Mean % Dissolved	Range	(CV)	Reference Product Lot # 1T164487 (Bio-lot) Mean % Dissolved	Range	(CV)
10	92	-	(5.2)	89	-	(7.5)
20	97	-	(3.3)	96	-	(3.3)
30	99	-	(3.3)	100	-	(2.1)
40	100	-	(2.4)	100	-	(1.6)
50	102	-	(2.4)	101	-	(1.9)
60	102	-	(2.4)	102	-	(3.1)
	Lot # 3082PD (New lot)			Lot # _____		
10	88	-	(9.1)			( )
20	95	-	(2.7)			( )
30	97		(2.3)			( )
40	98	-	(3.7)			( )
50	98	-	(2.0)			( )
60	99	-	(2.8)			( )

USP XXIII Apparatus II Basket _____ Paddle X rpm 50

Medium: 0.1N HCl @ 37°C Volume: 500 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Anafranil® capsule

Assay Methodology: _____

50 mg

Results

Time (min)	Test Product Lot # PD2854 (Lot used in ANDA) Mean % Dissolved	Range	(CV)	Reference Product Lot # 1T003913 Mean % Dissolved	Range	(CV)
10	89	_	(7.8)	96	_	(4.2)
20	94	_	(3.6)	103	_	(1.4)
30	96	_	(3.0)	105	_	(1.5)
40	98	_	(2.2)	106	_	(1.7)
50	98	_	(2.9)	107	_	(1.5)
60	99	_	(1.8)	108	_	(1.4)
	Lot # 3081PD (New lot)			Lot # _____		
10	96	_	(5.0)	_____	_____	( )
20	100	_	(1.9)	_____	_____	( )
30	101	_	(1.8)	_____	_____	( )
40	102	_	(1.9)	_____	_____	( )
50	103	_	(1.7)	_____	_____	( )
60	103	_	(2.6)	_____	_____	( )

USP XXIII Apparatus __II__ Basket _____ Paddle __X__ rpm __50__

Medium: 0.1N HCl @ 37°C Volume: __500__ ml

Number of Tabs/Caps Tested: __12__

Reference Drug: Anafranil® capsule

Assay Methodology: _____

25 mg

Results

Time (min)	Test Product Lot # PD2896 (Lot used in ANDA) Mean % Dissolved	Range	(CV)	Reference Product Lot # 1T193025 Mean % Dissolved	Range	(CV)
10	83	_	(11)	104	_	(3.2)
20	93	_	(8.1)	111	_	(1.8)
30	99	_	(4.6)	113	_	(1.7)
40	102	_	(3.2)	114	_	(2.0)
50	103	_	(3.0)	115	_	(2.1)
60	104	_	(2.5)	115	_	(1.4)
	Lot # 3080PD (New lot)			Lot # _____		
10	86	_	(10)			( )
20	96	_	(4.9)			( )
30	99	_	(3.7)			( )
40	100	_	(2.8)			( )
50	101	_	(2.9)			( )
60	102	_	(2.7)			( )

PROPORTIONALITY DATA

CLOMIPRAMINE HYDROCHLORIDE CAPSULES 25 mg, 50 mg and 75 mg

DOSAGE STRENGTH			25 mg		50 mg		75 mg	
NO	INGREDIENT	STD	AMOUNT PER CAP (mg)	AMOUNT PER CAP (%)	AMOUNT PER CAP (mg)	AMOUNT PER CAP (%)	AMOUNT PER CAP (mg)	AMOUNT PER CAP (%)
	CAPSULE FILL MATERIAL							
1.	Clomipramine Hydrochloride	HOUSE	25.00	14.29	50.00	14.29	75.00	21.43
2.	Pregelatinized Starch	NF						
3.	Colloidal Silicon Dioxide	NF						
4.	Lactose Monohydrate	NF						
5.	Sodium Lauryl Sulfate	NF						
6.	Magnesium Stearate	NF						
7.	Talc (For Capsule Lubrication Only)	USP						
	Total Fill Material Weight		175 mg	100.0%	350 mg	100.0%	350 mg	100.0%
	CAPSULE SHELL							
8.	Gelatin	NF						
9.	Titanium Dioxide	USP						
10.	D&C Yellow #10	HOUSE						
11.	FD&C Blue #1	HOUSE						
12.	FD&C Red #40	HOUSE						
13.	D&C Red #28	HOUSE						
14.	Black Imprinting Ink	HOUSE						
15.	Silicon Dioxide	NF						
16.	Sodium Lauryl Sulfate	NF						
	Shell Weight		62 mg	100.0%	77 mg	100.0%	77 mg	100.0%
	Total Filled Capsule Weight		237 mg	100.0%	427 mg	100.0%	427 mg	100.0%

SEP 20 1996

Clomipramine HCl
25 mg, 50 mg and 75 mg capsules
NDA #74-849
Reviewer: J. Lee
74849SDW.496

Novopharm Ltd.
Ontario, Canada
Submission date:
April 26, 1996
April 29, 1996

Review of a Post-prandial Bioavailability Study

This submission is an amendment to the application to include the post-prandial study that was omitted in the original submission with the fasting study (2/6/96).

Objective:

To assess the effect of food on the rate and extent of absorption of two clomipramine HCl formulations (Novopharm product vs Anafranil®) after administration of single doses to healthy, non smoking, male volunteers.

Forty-eight non-smoking male volunteers from 18-44 yrs and within 10% of ideal body weight for their height and frame were enrolled in the study. The protocol stipulated that if less than eighteen subjects complete the study without vomiting during the first 24 hours post-dose, an additional group of volunteers would be enrolled in order to complete the study with 18 non-vomiters; dropouts would not be replaced.

The clinical and analytical facilities for this study were the same as that employed in the fasting study. The inclusion and exclusion criteria for subject selection were also the same.

The study (DP257) was designed as a randomized, open-label, three-way crossover study with a 21 day washout period between dosings. Treatments consisted of a single 75 mg dose of the same two batches of test and reference products (used in the fasting study).

Forty-eight subjects were dosed according to the following scheme:

	period I 10/29/95	period II 11/19/95	period III 12/10/95
sequence I	A	B	C
sequence II	B	C	A
sequence III	C	A	B

sequence I - subj #3, 4, 9, 12, 14, 16, 21, 24, 25, 28, 33, 34, 39, 41, 43, 47
sequence II - subj #1, 5, 7, 10, 15, 17, 19, 22, 26, 29, 31, 35, 37, 42, 44, 48
sequence III - subj #2, 6, 8, 11, 13, 18, 20, 23, 27, 30, 32, 36, 38, 40, 45, 46

Treatment A: 1 x 75 mg clomipramine capsule (Novopharm) following a standard breakfast*
Treatment B: 1 x 75 mg Anafranil® capsule (Basel) following a standard breakfast*
Treatment C: 1 x 75 mg clomipramine capsule (Novopharm) following an overnight fast.

*standard breakfast: 1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving of hash brown potatoes
180 ml oz of orange juice
240 ml oz of whole milk

Note: After consultation with a statistician in the Division of Biometrics on the merits of the 3-sequence design vs the usual 6-sequence design of food studies, the reviewer concluded that the 3-sequence design of this study is acceptable due to the insignificance of residual effects in this study.

Of the forty-eight enrollees, two subjects did not complete the study. Subj. #10 did not return for period II; subj. #16 could not return for period II.

Only the first 24 subjects who completed the study without vomiting in the first 24 hours after drug administration would have their samples analyzed per protocol. These were subj. #3, 4, 7, 9, 12, 13, 14, 15, 17, 18, 19, 22, 24, 25, 26, 27, 28, 29, 30, 32, 33, 35, 41 and 42. See appended adverse events summary.

After an overnight fast, subjects on treatment A or B were served a standard breakfast 30 minutes before dosing. Fasting continued for four hours post-dose. Blood samples (7 ml) were drawn in Vacutainers containing EDTA at 0 (pre-dose, 2 x 7 ml), 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168 and 240 hours. Subjects were released after the 24-hour blood draw and returned to the clinical facility for their subsequent blood draws. All blood samples were drawn within 2 minutes of the scheduled time through the first 24 hours, except those for 1 subject (page 459). The blood sampling deviation for that subject (#13) is considered insignificant. All samples from the 48-240 hour blood draws were taken within 2% of the scheduled times. Sample handling followed the procedure used in the fasting study.

There were many instances of protocol deviations reported (p. 149), centering mainly around dietary infractions. There were also many subjects who did not eat or complete at least half of their post-dose meals (p. 149-50) contravening the identical meal plan for both periods. All these deviations were, however, judged unlikely to affect bioavailability comparisons.

Analytical:

Data Analysis and Results:

Means, standard deviations and CV%s were calculated for AUC_{0-t}, AUC_{inf}, C_{max}, t_{max}, kel, $t_{½}$ and concentrations at each sampling time point (see attached tables). The elimination rate constant, Ke, could not be calculated for the following subjects: [CLO] subj. #14, 18, 25 (T, fed); subj. #24 (R, fed); [DMCLO] subj. #3, 22 (T, fed); subj. #19 (T, fasted) - consequently, the $t_{½}$ and AUC_{inf} could not be calculated for those subjects. Sample analysis and data analysis was performed only for the first 24 subjects who did not vomit in the first 24 hours after drug administration (p. 2020, Statistics report).

Areas under the curve showed ~5-11% difference for T/R (fed) and a 9-10% difference in C_{max} ratios for drug & metabolite. There was no food effect observed for T(fed)/T(fasted) in AUCs; however, a slight increase was noted in C_{max}. The results are summarized in appended tables.

Comment:

1. The same comments apply regarding non-assaying of the samples of vomiting subjects as was stated in the comment section of the review of the fasting study.

2. Responses to the deficiencies in the dissolution testing, waiver request, etc. from the fasting study have not been received at the present time. Therefore, from the bioequivalence standpoint, this application is still incomplete.

Recommendation:

1. The bioequivalence study (fed) conducted by for Novopharm, Ltd. on its clomipramine HCl 75 mg capsule, batch #PD2841, comparing it to Anafranil® 75 mg capsule, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Novopharm's clomipramine HCl 75 mg capsule is bioequivalent under fed conditions to the reference product, Analfranil® 75 mg capsule, manufactured by Basel Pharmaceuticals.

9/12/96

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 9/12/1996

Concur: for Date: 9/20/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

JLee/jl/ 08-19-96

cc: NDA #74-849 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

FED

TABLE 1
Protect DP187
SUMMARY OF RESULTS - CLOMIPRAMINE

OBSERVED & Ln-transformed DATA

BIOAVAILABILITY PARAMETERS
(N = 24)

	OBSERVED BIOAVAILABILITY PARAMETERS Means						Ln-TRANSFORMED PARAMETERS (Geometric Means)		
	AUC0-t (ng.hr/mL)	AUCinf (ng.hr/mL)	Cmax (ng/mL)	Tmax (hrs)	Kel (1/hr)	t½ (hrs)	AUC0-t (ng.hr/mL)	AUCinf (ng.hr/mL)	Cmax (ng/mL)
TREATMENT:									
A:									
NOVOPHARM (FED)	695.9	654.53	53.319	5.375	0.0349	24.401	601.04	590.66	50.977
C.V.:	(61%)	(43%)	(30%)	(22%)	(49%)	(45%)	(57%)	(48%)	(31%)
B:									
BASEL (FED)	629.81	679.43	48.646	5.5333	0.0339	25.47	540.09	583.77	46.254
C.V.:	(60%)	(58%)	(30%)	(32%)	(54%)	(43%)	(59%)	(59%)	(34%)
C:									
NOVOPHARM (FAST)	642.44	692.29	47.301	4.5	0.0324	25.634	542	591.59	44.81
C.V.:	(70%)	(68%)	(34%)	(23%)	(50%)	(40%)	(59%)	(56%)	(34%)
Ratio of Means									
(A/B%):	111	96	110	.	.	.	111	101	110
(B/C%):	98	98	103	.	.	.	100	99	103
(A/C%):	109	95	113	.	.	.	111	100	114
ANOVA p-value:	0.038	0.122	0.031	0.001	0.910	0.924	0.045	0.099	0.031
Treatment Factor	A>C,A>B	NS	A>C	A>C,B>C	NS	NS	A>C,A>B	NS	A>C
Minimum(%) Detectable Difference(α=.05,β=.2):									
A vs B:	14	14	15	.	.	.	16	16	16
B vs C:	14	14	16	.	.	.	16	16	17
A vs C:	14	14	16	.	.	.	16	16	17
POWER(%) to Detect 20% Difference(α=.05,β=.2):									
A vs B:	98	97	96				94	92	93
B vs C:	98	98	95				93	93	91
A vs C:	98	98	95				93	93	91
90% Confidence Intervals (Two One-Sided t-Test Method:									
A vs B:									
Lower Limit:	103.0	101.3	101.4	.	.	.	102.1	101.6	101.6
Upper Limit:	119.9	119.8	119.7	.	.	.	123.2	124.6	122.9
B vs C:									
Lower Limit:	91.6	90.2	94.3	.	.	.	92.6	90.4	94.4
Upper Limit:	108.5	107.6	113.3	.	.	.	111.7	109.7	114.2
A vs C:									
Lower Limit:	103.1	100.2	105.3	.	.	.	103.8	101.3	105.4
Upper Limit:	120.0	118.4	124.2	.	.	.	125.3	123.9	127.5

NS = Not Significant

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TABLE 2
Protect DP25*
MEAN PLASMA (C.V.%) CLOMIPRAMINE CONCENTRATIONS ng/mL
AT EACH SAMPLING TIME POINT
Observed Data
n = 24

TIME (hours)	A: NOVOPHARM (FED) mean(C.V.%)	B: BASEL (FED) mean(C.V.%)	C: NOVOPHARM (FAST) mean(C.V.%)	ANOVA° p-value Treatment factor	Statistically Significant Differences**
pre-dose	0.00	0.00	0.00		
1 hour	2.73 (344)	1.00 (291)	3.44 (114)	0.3056	NS
2 hours	9.23 (123)	5.81 (102)	24.46 (52)	0.0000	C>A,C>B
3 hours	26.57 (66)	15.28 (83)	36.84 (37)	0.0002	A>B,C>A,C>B
4 hours	37.43 (47)	30.93 (52)	42.36 (32)	0.0090	A>B,C>B
5 hours	50.93 (31)	43.59 (35)	43.50 (33)	0.0156	A>B,A>C
6 hours	46.88 (32)	43.32 (35)	40.61 (41)	0.0290	A>C
8 hours	39.60 (36)	35.16 (35)	33.85 (41)	0.0069	A>C,B>C
12 hours	28.49 (48)	26.29 (53)	23.03 (53)	0.0032	A>C,B>C
16 hours	19.23 (51)	18.17 (64)	16.66 (64)	0.0195	A>C
24 hours	14.14 (54)	13.00 (55)	12.24 (74)	0.0150	A>C
48 hours	6.70 (70)	6.10 (77)	5.68 (83)	0.0030	A>C,B>C
72 hours	3.86 (84)	3.46 (76)	3.34 (95)	0.1416	NS
96 hours	2.13 (99)	2.01 (104)	1.57 (72)	0.2642	NS
120 hours	1.14 (137)	1.16 (114)	0.94 (159)	0.0888	NS
144 hours	0.66 (167)	0.42 (164)	0.51 (196)	0.2558	NS
168 hours	0.41 (252)	0.19 (392)	0.20 (252)	0.0843	NS
240 hours	0.00	0.05 (490)	0.00	0.4516	NS

°The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S2).

**Not Sig.= (treatment effect) not significant at p=0.05 level. Differences based on Least Square Means test.

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FED

TABLE 3
Project DP257
SUMMARY OF RESULTS - N-DESMETHYLCLOMIPRAMINE

OBSERVED & Ln-transformed DATA

BIOAVAILABILITY PARAMETERS
(N = 24)

	OBSERVED BIOAVAILABILITY PARAMETERS (Means)						Ln-TRANSFORMED PARAMETERS (Geometric Means)		
	AUC0-t (ng.hr/mL)	AUCinf (ng.hr/mL)	Cmax (ng/mL)	Tmax (hrs)	Kel (1/hr)	t½* (hrs)	AUC0-t (ng.hr/mL)	AUCinf (ng.hr/mL)	Cmax (ng/mL)
TREATMENT:									
A:									
NOVOPHARM (FED)	811.29	863.92	9.6446	16.75	0.0185	47.2	507.57	617.91	8.845
C.V.:	(101%)	(88%)	(45%)	(80%)	(46%)	54%)	(102%)	(84%)	(42%)
B:									
BASEL (FED)	748.7	932.04	8.8883	15.25	0.0188	49.312	482.34	609.95	8.2912
C.V.:	(98%)	107%)	38%)	99%)	50%)	63%)	101%)	93%)	(39%)
C:									
NOVOPHARM (FAST)	843.56	1079.8	9.9546	13.333	0.0205	48.477	520.07	673.46	9.2024
C.V.:	(100%)	112%)	(41%)	77%)	(65%)	69%)	(106%)	(100%)	(41%)
Ratio of Means									
(A/B%):	108	93	109	.	.	.	105	101	107
(B/C%):	89	86	89	.	.	.	93	91	90
(A/C%):	96	80	97	.	.	.	98	92	96
ANOVA p-value:	0.017	0.029	0.014	0.474	0.066	0.436	0.292	0.252	0.016
Treatment Factor	A>B,C>B	B>A,C>B	A>B,C>B	NS	NS	NS	NS	NS	C>B
Minimum(%) Detectable Difference(α=.05,ß=.2):									
A vs B:	12	13	11	.	.	.	13	12	10
B vs C:	11	12	10	.	.	.	12	11	9.3
A vs C:	11	12	10	.	.	.	12	11	9.3
POWER(%) to Detect 20% Difference(α=.05,ß=.2):									
A vs B:	>99	99	>99				99	>99	>99
B vs C:	>99	>99	>99				>99	>99	>99
A vs C:	>99	>99	>99				>99	>99	>99
90% Confidence Intervals (Two One-Sided t-Test Method)									
A vs B:									
Lower Limit:	102.2	101.9	101.7	.	.	.	98.2	99.9	100.6
Upper Limit:	116.4	118.0	115.2	.	.	.	113.9	115.0	113.2
B vs C:									
Lower Limit:	82.9	82.0	83.4	.	.	.	87.1	89.4	85.0
Upper Limit:	95.7	96.2	95.4	.	.	.	101.0	102.8	95.6
A vs C:									
Lower Limit:	91.2	90.7	90.9	.	.	.	92.0	95.7	90.6
Upper Limit:	104.0	105.2	103.0	.	.	.	106.8	110.4	102.0

NS = Not Significant

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TABLE 4

Project DP057
MEAN PLASMA (C.V.%) N-DESMETHYLCLOMIPRAMINE CONCENTRATIONS (ng/mL)
AT EACH SAMPLING TIME POINT
Observed Data
(n = 24)

TIME (hours)	A: NOVOPHARM (FED) mean(C.V.%)	B: BASEL (FED) mean(C.V.%)	C: NOVOPHARM (FAST) mean(C.V.%)	ANOVA* p-value Treatment factor	Statistically Significant Differences**
pre-dose	0.05 (490)	0.00	0.05 (490)	0.3969	NS
1 hour	0.19 (340)	0.34 (384)	0.14 (340)	0.7598	NS
2 hours	0.39 (265)	0.14 (344)	2.18 (75)	0.0000	C>A,C>B
3 hours	1.95 (105)	1.51 (115)	4.31 (61)	0.0001	C>A,C>B
4 hours	3.60 (58)	3.08 (74)	5.95 (47)	0.0001	C>A,C>B
5 hours	6.15 (46)	5.23 (49)	7.56 (37)	0.0007	C>A,C>B
6 hours	6.85 (38)	6.54 (38)	8.49 (35)	0.0000	C>A,C>B
8 hours	7.81 (39)	7.56 (33)	8.63 (39)	0.0097	C>A,C>B
12 hours	8.96 (44)	8.19 (38)	9.08 (45)	0.0509	NS
16 hours	7.87 (45)	7.68 (43)	8.50 (49)	0.0183	C>B
24 hours	7.92 (55)	7.34 (52)	8.11 (59)	0.0229	A>B,C>B
48 hours	6.80 (80)	6.02 (71)	6.66 (78)	0.3150	NS
72 hours	5.19 (99)	4.50 (96)	5.14 (99)	0.0553	NS
96 hours	3.40 (126)	3.37 (121)	3.46 (122)	0.5938	NS
120 hours	2.76 (136)	2.29 (142)	2.72 (138)	0.0086	A>B,C>B
144 hours	1.90 (155)	1.71 (179)	2.05 (159)	0.4187	NS
168 hours	1.63 (166)	1.34 (214)	1.74 (166)	0.0312	C>B
240 hours	0.86 (217)	0.79 (226)	0.83 (237)	0.5376	NS

*The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S5).

**Not Sig.= (treatment effect) not significant at p=0.05 level. Differences based on Least Square Means test.

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TABLE C2

ADVERSE EVENTS

PERIOD 1

Subject #	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
01	B	Nausea	Probably	2hrs 32min	1hr 43min	mild
		Vomiting (intermittent)	Probably	2hrs 56min	46min	moderate
		Nervousness	Probably	3hrs 15min	1hr 15min	mild
		Sensation of trembling	Probably	2hrs 56min	1hr 34min	mild
		Fatigue	Probably	3hrs	5hrs	mild
		Headache	Remote	4hrs	1day 2hrs	mild
02	C	Nausea	Probably	1hr 8min	3hrs	mild
		Dry Mouth	Probably	1hr 28min	2hrs 40min	mild
		Vomiting	Probably	1hr 56min	1hr 3min	moderate
		Loss of coordination	Probably	3hrs 48min	1day 10min	mild
		Shaking	Probably	5hrs 3min	17hrs 35min	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 1

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
02	C	Fatigue	Probably	3hrs 8min	19hrs 30min	mild
06	C	Drowsy	Probably	3hrs 20min	19hrs 30min	mild
		Vomiting	Probably	4hrs	3min	moderate
08	C	Vomiting	Probably	1hr 52min	2min	moderate
		Drowsy	Probably	2hrs 7min	5hrs 39min	mild
		Spasm	Probably	2hrs 7min	2hrs 9min	mild
		Headache	Possibly	1day 3hrs 46min	8hrs	mild
10	B	Fatigue	Possibly	1day 6hrs 42min	1day 16hrs	mild
		Difficulty concentrating	Remote	2days 4hrs 42min	1day	mild
11	C	Vomiting	Probably	1hr 27min	5min	moderate

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 1

Subject #	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
11	C	Felt faint	Remote	2days	30min	mild
13	C	Loose stools	Probably	1hr 26min	1day 10hrs 10min	mild
20	C	Vomiting (intermittent)	Probably	1hr 7min	40min	moderate
23	C	Vomiting (intermittent)	Probably	56min	1hr 2min	moderate
		Feeling cold	Probably	1hr 14min	9hrs 32min	mild
25	A	Fatigue	Probably	2hrs 57min	9hrs 15min	mild
		Shock feelings in right upper arm	Remote	23hrs 57min	45min	mild
		Restlessness	Possibly	1day 3hrs 12min	12hrs	mild
		Loss of appetite	Possibly	1day 2hrs 57min	4days 1hr 15min	mild
		Yawns frequently	Probably	1hr 12min	1day 14hrs	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 1

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
27	C	Nausea	Probably	1hr 33min	5min	mild
		Loose stools	Possibly	2hrs 18min	2min	mild
		Headache	Remote	2days 2hrs 18min	1day 19hrs 50min	mild
		Pain right flank	Remote	1day 12hrs 8min	2days 14hrs	mild
		Pain left flank	Remote	3days 6hrs 8min	20hrs	mild
28	A	Fatigue	Probably	1hr 51min	2hrs 35min	mild
33	A	Dizziness	Probably	2hrs 41min	19hrs 45min	mild
		Nausea	Probably	2hrs 41min	19hrs 45min	mild
		Dizziness	Possibly	1day 1hr 56min	1day 12hrs	mild
		Nausea	Possibly	1day 1hr 56min	1day 3hrs	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 1

Subject #	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
34	A	Tightness in jaw muscles	Probably	2hrs 9min	20hrs 30min	mild
		Constricted throat	Possibly	2hrs 9min	9hrs 15min	mild
		Feels "stoned"	Probably	2hrs 9min	2hrs 45min	mild
35	B	Difficulty focusing	Probably	1hr 52min	21hrs 10min	mild
36	C	Drowsiness	Probably	2hrs 5min	1hr 45min	mild
37	B	Headache	Possibly	1day 5hrs 48min	22hrs	mild
		Nausea	Possibly	1day 5hrs 48min	16hrs	mild
38	C	Vomiting	Probably	2hrs 4min	2min	moderate
39	A	Feeling weak	Probably	2hrs 54min	5min	mild
		Headache	Probably	44min	9hrs	mild
		Drowsy	Probably	5hrs 44min	7days 3hrs	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 1

Subject #	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
39	A	Dizziness	Probably	29min	3days 4hrs 15min	mild
		Loose stools	Remote	1day 5hrs 29min	5days 15min	mild
		Burning sensation upper esophagus	Remote	2days 4hrs 4min	3min	mild
		Burning sensation upper esophagus	Remote	3days 22hrs 44min	15hrs	mild
		Nausea	Probably	1hr 59min	5min	mild
		Headache	Remote	6days 11hrs 14min	1hr 30min	mild
40	C	Pain in the chest upper left side	Remote	52min	1hr 20min	mild
		Vomiting (intermittent)	Probably	1hr 40min	18min	moderate
		Erection (intermittent)	Remote	2hrs 12min	18hrs 30min	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 1

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
41	A	Headache	Possibly	1day 6hrs 40min	16hrs 30min	mild
42	B	Chattering teeth	Probably	2hrs 3min	2hrs 5min	mild
		Feels "stoned"	Probably	1hr 38min	7hrs 3min	mild
43	A	Loose stools	Possibly	41min	46min	mild
		Nausea	Probably	1hr 26min	20min	mild
		Fatigue	Probably	3hrs 36min	1day 8hrs	mild
45	C	Vomiting	Probably	1hr 15min	1min	moderate
		Headache	Probably	1day 4hrs 32min	1day 4hrs	mild
46	C	Nausea	Probably	1hr 30min	2hrs	mild
		Trembling left hand	Possibly	2hrs	5min	mild
		Drowsiness	Probably	2hrs	1hr 30min	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 1

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
46	C	Loose stools	Possibly	2hrs 15min	3min	mild
		Headache	Possibly	1day 12hrs 30min	4hrs	mild
48	B	Dizziness	Possibly	3days 1hr 26min	1hr 30min	mild

*A Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 2

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
01	C	Nausea	Probably	30min	3hrs 30min	mild
		Vomiting (intermittent)	Probably	40min	1hr 14min	moderate
		Loose stools	Probably	1hr 4min	10hrs 59min	mild
		Nervous	Probably	1hr 47min	1hr 13min	mild
		Fatigue	Probably	2hrs	20hrs 30min	mild
		Twitching	Probably	2hrs	1hr	mild
		Dizziness	Probably	2hrs	12hrs	mild
		Headache around posterior aspect of head	Possibly	1day 2hrs	8hrs	mild
04	B	Fatigue	Probably	1hr 54min	2hrs	mild
		Trouble sleeping	Possibly	1day 15hrs 24min	1day 7hrs	moderate
05	C	Nausea	Probably	1hr 5min	47min	mild

*A - Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B - Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C - Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 2

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
05	C	Trouble sleeping	Possibly	1day 13hrs 52min	1day 7hrs 30min	moderate
06	A	Fatigue	Probably	1hr 50min	4days 12hrs	mild
		Trouble urinating	Possibly	2hrs 50min	1day 6hrs	moderate
		Trouble sleeping	Remote	2days 18hrs 50min	1day 19hrs	moderate
07	C	Fatigue	Probably	1hr 28min	1day 13hrs 20min	mild
		Trouble sleeping	Remote	2days 16hrs 33min	2days 15min	moderate
08	A	Fatigue	Probably	1hr 46min	21hrs 30min	mild
		Fatigue	Possibly	1day 1hr 46min	12hrs 30min	mild
13	A	Difficulty to sleep	Possibly	1day 15hrs 36min	2days 6hrs 30min	moderate
		Pain in frontal region of head	Remote	2days 17hrs 36min	10hrs	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 2

Subject #	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
14	B	Fatigue	Probably	1hr 4min	2days 21hrs 30min	mild
15	C	Fatigue	Probably	1hr 2min	1day 21hrs 30min	mild
17	C	Nausea	Probably	1hr 58min	1hr	mild
20	A	Nausea	Probably	1hr 37min	2hrs 15min	mild
23	A	Fatigue	Probably	1hr 31min	6hrs 15min	mild
25	B	Loss of appetite	Possibly	3hrs 12min	2days 10hrs 30min	mild
		Frontal headache	Remote	6days 7hrs 12min	9hrs	mild
26	C	Headache	Probably	40min	1day 30min	mild
27	A	Headache	Possibly	1day 8hrs 8min	3hrs	mild
		Nose bleed	Remote	1day 22hrs 28min	5min	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 2

Subject #	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
27	A	Runny nose	Remote	10hrs 8min	6days	mild
30	A	Sleepy	Probably	2hrs 2min	21hrs	mild
		Blurred vision	Probably	7hrs 2min	2hrs	mild
31	C	Vomiting	Probably	3hrs 10min	1min	moderate
		Ringing right ear	Remote	1day 8hrs	1min	mild
33	B	Nausea	Probably	2hrs 41min	1hr 59min	mild
		Dizzy	Probably	2hrs 41min	1hr 59min	mild
34	B	Headache	Probably	3hrs 34min	50min	mild
		Tightness of throat	Probably	3hrs 34min	1day 7hrs 50min	mild
		Shaky jaw	Probably	3hrs 34min	50min	mild
		Headache	Possibly	1day 3hrs 54min	1hr 30min	mild
37	C	Vomiting	Probably	1hr 48min	1min	moderate

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 2

Subject #	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
39	B	Nausea	Probably	2hrs 24min	36min	mild
		Vomiting	Probably	2hrs 53min	2min	moderate
		Headache	Probably	44min	3days 7hrs	mild
		Sleepy	Probably	44min	3days 7hrs	mild
		Coldness	Possibly	4hrs 41min	18hrs 33min	mild
		Diarrhea	Probably	4hrs 54min	1day 21hrs 20min	mild
		Blurry vision	Probably	9hrs 44min	13hrs 30min	mild
		Heartburn	Remote	1day 22hrs 4min	23hrs 50min	mild
		Diarrhea	Remote	4days 2hrs 14min	19hrs 30min	mild
40	A	Anxiety	Probably	1hr 43min	1day 20hrs 12min	mild
		Lightheaded	Probably	3hrs 47min	56min	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 2

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
40	A	Rash left side of base of neck	Remote	11hrs 57min	45min	mild
42	C	Headache	Probably	1hr 8min	1hr 15min	mild
		Dizzy	Probably	1hr 8min	7hrs 30min	mild
		Nausea	Probably	2hrs 8min	2hrs 20min	mild
		Chattering of teeth	Probably	1hr 8min	4days 8hrs 30min	mild
48	C	Dizzy	Probably	51min	2hrs 43min	mild
		Vomiting	Probably	1hr 17min	1min	moderate

*A - Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B - Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C - Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 3

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
01	A	Nausea	Probably	1hr 9min	2hrs 21min	mild
		Vomiting (intermittent)	Probably	1hr 11min	1hr 17min	moderate
		Dizziness	Probably	2hrs 27min	6hrs 33min	mild
		Headache	Probably	2hrs 27min	6hrs 33min	mild
04	C	Trouble sleeping	Possibly	1day 15hrs 24min	1day	moderate
06	B	Trouble sleeping	Possibly	1day 19hrs 50min	1day 18hrs	moderate
08	B	Nausea	Probably	5hrs 14min	32min	mild
		Vomiting	Probably	5hrs 18min	1min	moderate
12	C	Nausea	Probably	3hrs 8min	1hr	mild
17	A	Nausea	Probably	2hrs 48min	1hr 30min	mild
20	B	Nausea	Probably	2hrs 27min	55min	mild

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C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 3

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
21	C	Vomiting	Probably	2hrs	1min	moderate
27	B	Pressure left side of chest	Remote	1day 14hrs 38min	2days 19hrs 30min	moderate
30	B	Sleepiness	Probably	1hr 2min	2hrs	mild
		Upset stomach	Probably	1hr 2min	7hrs 15min	mild
34	C	Vomiting	Probably	1hr 59min	1min	moderate
		Shaky jaws	Probably	1hr 44min	7hrs 40min	mild
		Sleepiness	Probably	1hr 44min	18min	mild
		Dizziness	Probably	1hr 44min	18min	mild
		Headache	Possibly	1day 4hrs 24min	4hrs 45min	mild
		Trouble sleeping	Remote	1day 17hrs 54min	1day 5hrs 10min	moderate

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil *) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

TABLE C2

ADVERSE EVENTS (cont'd)

PERIOD 3

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
36	B	Headache	Probably	3hrs 55min	11hrs 40min	mild
		Nauseous	Probably	4hrs 10min	11hrs 25min	mild
		Vomited	Probably	8hrs 40min	10min	moderate
		Tingling both arms	Possibly	8hrs 40min	19min	mild
37	A	Shaky jaws	Probably	30min	5hrs 18min	mild
38	B	Vomit	Probably	4hrs 26min	2min	moderate
39	C	Nauseous	Probably	1hr 12min	1hr 55min	mild
		Dizzy	Probably	1hr 14min	21hrs	mild
		Vomiting	Probably	2hrs 57min	2min	moderate
		Blurry vision	Probably	3hrs 7min	1day 1hr 37min	mild
		Headache	Probably	14min	14hrs 30min	mild
		Diarrhea	Possibly	5hrs 15min	19hrs 24min	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
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C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

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TABLE C2

PERIOD 3

ADVERSE EVENTS (cont'd)

Subject#	Regimen*	Complaint	Relationship	Onset (post-dose)	Duration	Severity
40	B	Anxiety	Probably	22min	19hrs 18min	mild
		Runny nose	Possibly	2hrs 5min	5hrs 57min	mild
		Dry throat	Possibly	2hrs 5min	5hrs 57min	mild
		Erection (intermittent)	Probably	2hrs 37min	5hrs 25min	mild
		Yellow stools	Remote	1day 11hrs 2min	1day 9hrs 54min	mild
41	C	Headache	Possibly	2days 11hrs 40min	11hrs	mild
42	A	Shaky jaws	Probably	58min	3days 6hrs 40min	mild
		Tired	Probably	58 min	1day 20hrs 40min	mild
43	C	Numbness in fingertips	Possibly	1hr 3min	4hrs 3min	mild
		Tired	Probably	1hr 3min	4hrs 3min	mild
		Shaky hands	Probably	1hr 3min	4hrs 3min	mild
		Vomiting	Probably	1hr 21min	1min	moderate
48	A	Dizziness	Probably	1hr 21min	35min	mild

*A = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fed)
B = Single oral 75 mg dose of Basel (U.S.) 75 mg clomipramine HCL capsules (Anafranil ®) (fed)
C = Single oral 75 mg dose of Novopharm Limited 75 mg clomipramine HCL capsules (fasted)

MAY 28 1996

Clomipramine HCl
25mg, 50 mg and 75 mg capsules
NDA #74-849
Reviewer: J. Lee
74849SDW.296

Novopharm Ltd.
Ontario, Canada
Submission date:
February 6, 1996

Review of an in-vivo Bioavailability Study, Dissolution Testing Data and Two Requests for Waiver

Objective:

To assess the rate and extent of absorption of two clomipramine HCl formulations (Novopharm product vs Anafranil®) after administration of single doses to healthy, non smoking, male volunteers under fasted conditions.

Study Design:

The clinical study (DP256) was conducted at , under the supervision of Principal Investigator.

Sixty non-smoking male volunteers between the ages of 18-45 years and within 10% of ideal body weight for his height and frame were enrolled in the study. The protocol stipulated that if less than thirty subjects complete the study without vomiting during the first 24 hours post-dose, an additional group of volunteers would be enrolled in order to complete the study with 36 non-vomiters; dropouts would not be replaced.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests [hematology, serum chemistry and urinalysis].

Those with any of the following conditions were excluded:

History or presence of:

- significant cardiovascular, hepatic, renal, CNS, hematological or GI disease
- alcohol or drug abuse with the last year
- depression or anti-depressant therapy, convulsive or seizure disorders
- psychosis
- glaucoma
- prostatic hypertropy or urinary retention
- thryroid disease
- hypersensitivity or idiosyncratic reaction to clomipramine or any other tricyclic antipressants belonging to the dibenzazepine class
- personality disorders which would preclude valid informed consent or compliance with

protocol requirements

Persons who have used any tobacco product in the previous 3 months were also excluded.

Rx and OTC medications (especially MAO inhibitor drugs) were not allowed within 14 days of the first drug administration. There was to be no alcohol or caffeine consumption at least 24 and 12 hours, respectively, prior to drug administration.

Alcohol and xanthine-containing beverages and foods were prohibited for 48 hours before and throughout the sample collection period.

The study was designed as a randomized, open-label, two-way crossover study with a 21 day washout period between dosings. Treatments consisted of a single 75 mg dose of the following:

A. Clomipramine HCl
   75 mg Capsule, batch #PD2841
   Novopharm Limited
   expiry date: not given

B. Anafranil®
   75 mg Capsule, batch #1T164487
   Basel Pharmaceuticals
   expiry date: December, 1996

Sixty subjects were dosed according to the following scheme:

	Period I 07/22/95	Period II 08/12/95
sequence I	A	B
sequence II	B	A

sequence I - subj. #3, 4, 7, 8, 10, 12, 14, 15, 19, 20, 22, 24, 26, 28, 30, 31, 35, 36, 38, 40, 42, 43, 45, 46, 49, 52, 53, 54, 58, 59

sequence II - subj. #1, 2, 5, 6, 9, 11, 13, 16, 17, 18, 21, 23, 25, 27, 29, 32, 33, 34, 37, 39, 41, 44, 47, 48, 50, 51, 55, 56, 57, 60

Of the sixty enrollees, four subjects did not complete the study. Subject #52 was withdrawn from the study due to the number of adverse events and possible hypersensitivity to the drug; subj. #58 withdrew in period I for being unable to comply with return blood draws; subj. #25 and 36 withdrew prior to period II dosing. A total of 56 subjects were reported to have completed the study.

Twenty subjects vomited after dosing in period I and seventeen subjects vomited after dosing in period II for a total of twenty-eight subjects vomiting in either or both periods; thus, a total of

thirty-two subjects completed the study without vomiting. Although the protocol specified that those subjects who vomit within 24 hours post-dose would be excluded from the statistical analyses, all subjects who did vomit did so within approximately three hours after drug administration (see clinical complaints summary, attached).

After an overnight fast, volunteers were given a 75 mg dose of clomipramine HCl with 240 ml of water. Fasting continued for four hours post-dose. Blood samples (7 ml) were drawn in Vacutainers containing EDTA at 0 (pre-dose, 2 x 7 ml), 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168 and 240 hours. Subjects were released after the 24-hour blood draw and returned to the clinical facility for their subsequent blood draws. All blood samples were drawn within 2 minutes of the scheduled time through the first 24 hours, except those for 4 subjects (page 341). The blood sampling deviations for those 4 subjects are considered insignificant. All samples from the 48-240 hour blood draws were taken within 2% of the scheduled times.

The samples were cooled in an ice bath and cold centrifuged soon after collection. Plasma samples were split into two portions and stored in tubes ≤ 10°C, pending assay.

There were 18 instances of protocol deviations reported (p. 342), centering mainly around infractions of the ban on alcohol and xanthine-containing beverages. There were also many subjects who did not eat or complete at least half of their post-dose meals (p. 343) contravening the identical meal plan for both periods. All these deviations were, however, judged unlikely to affect bioavailability comparisons.

Analytical: [Not for release under FOI]

Data Analysis:

Plasma data (for clomipramine and metabolite) was analyzed by an analysis of variance procedure (SAS, version 6.04) to determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and plasma level concentrations at each sampling time. The eliminate rate constant, Ke, for subject #40 could not be calculated for both clomipramine and DMCLO since there didn't appear to be a terminal log-linear phase in his conc-time profile; consequently, the $t_{½}$ and AUC_{inf} could not be calculated for that subject. Similarly, no Ke could be calculated for subj. #24 (clomipramine, Ref.) and subj. #29 (DMCLO, Test). Of the original sixty subjects enrolled in the study, four did not complete the crossover; twenty-four subjects (#1, 2, 3, 8, 9, 10, 11, 14, 16, 18, 21, 26, 28, 32, 33, 37, 38, 44, 47, 53, 55, 56, 59 and 60) vomited during periods I and/or II. Since their samples were not analyzed, those subjects were excluded from the primary statistical analyses. The data for subject #40 was excluded from a secondary analysis, the laboratory having provided a reason and having performed a statistical test. The reviewer has further examined the data.

Results:

No statistically significant differences were found in any of the pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed for the bioavailability parameters. There was ≤ 2% difference between the test and reference formulations for plasma levels of clomipramine in AUC_{0-t}, AUC_{inf} and C_{max}. For DMCLO there was ≤ 3% difference between the test/reference products in the major bioavailability parameters. The study results are appended.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the following dissolution method:

USP Apparatus II (paddle) @ 50 rpm
900 ml water @ 37°C;

The above method is an in-house validated method. The Agency currently has an official PF

method (Mar-Apr, 1995). [see comment # 3.]

Batch Size:

The executed batch record for the bio-batch of Novopharm's 75 mg clomipramine shows a yield of approximately

Waiver Request:

The sponsor has requested a waiver of in-vivo requirements for their 25 mg and 50 mg clomipramine capsule. A quantitative formulation comparison between the 25 mg, 50 mg and 75 mg capsule was submitted, and comparative dissolution testing results were provided between the company's 25 mg and 50 mg test product vs Anafranil[R] 25 mg and 50 mg capsule.

Note: The sponsor has also conducted a post-prandial study on their test product, but submitted it at a date later than this submission. The Division of Bioequivalence will review that study at the appropriate time.

Comment:

1. Re: Vomiting subjects

   The laboratory has reported that 56 out of 60 originally enrolled subjects completed the study. Presumably, this means that the vomiting subjects completed their blood draws, but did not have their samples assayed (page 9, Analytic Report Section).

   a. If this is the case, the laboratory should explain why the blood draws continued for those subjects, after vomiting.
   b. The laboratory should explain why those subjects who vomited in period I were dosed in period II if they did not intend to assay the samples from those subjects and were not going to use their data in the statistical analyses.

2. The laboratory should provide a more detailed reason for excluding subject #40 from the statistical analyses; i.e. attempts to find a medical reason for 'non-absorption' of the drug, analytical error, non-reported adverse event, etc. (See attached guidance)

3. The dissolution testing conducted in this application utilized a non-FDA method. The Division of Bioequivalence in recent years has adopted the USP/PF method as official. The sponsor should repeat all dissolution testing in this application employing the following methodology: [Ref. pages 240-1 of the Mar-Apr 1995 PF]

   USP apparatus II (paddle) at 50 rpm
   500 ml 0.1N HCl at 37°C
   Tolerance: NLT (Q) in 30 minutes

4. The sponsor should resubmit the waiver request for the 25 mg and 50 mg capsules after

both the fasting and fed studies have been found acceptable and the dissolution testing has been repeated using the USP/PF method outlined above.

Recommendation:

1. The fasting bioequivalence study conducted by Novopharm Ltd. on its clomipramine HCl 75 mg capsule, batch #PD2841, comparing it to Anafranil 75 mg capsule has been found incomplete per comments #1-3.

All comments should be transmitted to the company.

5/28/96

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 5/28/96

Concur: Date: 5/28/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

Jlee/jl/05-23-96

cc: NDA # 74-849 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Lee, Patnaik), HFD-130 (JAllen), HFD-344 (Vish), Drug File, Division File

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TABLE 1
PROJECT DP156
SUMMARY OF STATISTICAL ANALYSIS - CLOMIPRAMINE
MEAN (C.V.%) BIOAVAILABILITY PARAMETERS
Observed Data
(n=30)*

BIOAVAILABILITY PARAMETERS	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	Ratio of Means	ANOVA° p-value Treatment Factor	90% CI limits (%) Lower	Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. α=.05,β=.2
AUC0-t(ng.hr/mL)	1017.99 (42)	1006.33 (39)	1.01	.8470 NS**	91	112	18	88
AUCinf(ng.hr/mL)	1074.94 (41)	1088.66 (34)	0.99	.7886 NS	90	108	18	95
Cmax(ng/mL)	48.23 (37)	47.72 (35)	1.01	.8178 NS	90	113	19	83
Tmax(hours)	4.62 (28)	5.00 (34)	0.93	.2400 NS				
Kel(1/hours)	0.03 (42)	0.03 (34)	0.97	.4330 NS				
t½(hours)	30.68 (32)	29.16 (32)	1.05	.1624 NS				

Observed (ln-transformed) Data
(geometric means)

BIOAVAILABILITY PARAMETERS	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	Ratio of Means	ANOVA° p-value Treatment Factor	90% CI limits (%) Lower	Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. α=.05,β=.2
AUC0-t(ng.hr/mL)	911.21 (52)	864.98 (77)	1.05	.7744 NS	82	132	41	74
AUCinf(ng.hr/mL)	971.67 (49)	1024.39 (37)	0.95	.3651 NS	84	105	19	84
Cmax (ng/mL)	44.36 (45)	43.18 (36)	1.03	.8474 NS	84	124	33	60

°The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S1 & S3).

*Except for AUCinf, KEL and Halflife, where n=30 for treatment B.

**NS = (treatment effect) not significant at p=0.05 level. Differences based on Least Square Means test.

CI = Confidence Interval.

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TABLE 1
Project DP086
MEAN PLASMA (C.V.%) CLOMIPRAMINE CONCENTRATIONS (ng/ml)
AT EACH SAMPLING TIME POINT
Observed Data
(n=33)

TIME (hours)	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	ANOVA* p-value Treatment Factor	Statistically Significant Differences**
pre-dose	0.00	0.00		
1 hour	4.44 (196)	3.56 (133)	0.6219	NS
2 hours	25.08 (76)	23.33 (78)	0.4620	NS
3 hours	39.10 (50)	36.30 (56)	0.3762	NS
4 hours	43.92 (42)	40.64 (46)	0.3026	NS
5 hours	44.74 (36)	42.99 (37)	0.5127	NS
6 hours	41.29 (32)	40.63 (35)	0.7389	NS
8 hours	35.54 (35)	34.79 (32)	0.7102	NS
12 hours	23.01 (39)	22.95 (36)	0.9874	NS
16 hours	16.58 (34)	16.69 (38)	0.8090	NS
24 hours	12.55 (36)	13.25 (41)	0.4287	NS
48 hours	5.79 (47)	5.79 (49)	0.9634	NS
72 hours	3.31 (55)	3.38 (55)	0.7663	NS
96 hours	2.01 (63)	1.92 (63)	0.4845	NS
120 hours	1.15 (111)	1.10 (102)	0.4185	NS
144 hours	0.58 (149)	0.37 (195)	0.2627	NS
168 hours	0.23 (246)	0.18 (277)	0.4217	NS
240 hours	0.03 (566)	0.00	0.3866	NS

*The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S2).

**NS = not significant at p=0.05 level.
Differences based on Least Square Means test.

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TABLE 3
PROJECT 17256
SUMMARY OF STATISTICAL ANALYSIS - N-DESMETHYLCLOMIPRAMINE
MEAN (C.V.%) BIOAVAILABILITY PARAMETERS
Observed Data
(n=32)*

BIOAVAILABILITY PARAMETERS	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	Ratio of Means	ANOVA* p-value Treatment factor	90% CI Limits (%) Lower	Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. α=.05,β=.2
AUC0-t(ng.hr/mL)	996.51 (102)	977.47 (102)	1.02	.6926 NS**	93	111	15	95
AUCinf(ng.hr/mL)	1287.41 (116)	1358.37 (125)	0.95	.5256 NS	86	106	17	91
Cmax(ng/mL)	10.01 (51)	10.04 (55)	1.00	.9396 NS	91	108	14	98
Tmax(hours)	16.69 (104)	16.52 (72)	1.01	.8268 NS				
Kel(1/hours)	0.01 (46)	0.01 (38)	1.01	.7688 NS				
t½(hours)	61.67 (59)	60.34 (69)	1.02	.7273 NS				

Observed (ln-transformed) Data
(geometric means)

BIOAVAILABILITY PARAMETERS	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	Ratio of Means	ANOVA* p-value Treatment factor	90% CI Limits (%) Lower	Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. α=.05,β=.2
AUC0-t(ng.hr/mL)	616.63 (101)	666.25 (93)	0.93	.3520 NS	84	105	18	86
AUCinf(ng.hr/mL)	765.93 (100)	830.93 (94)	0.92	.3242 NS	86	104	15	95
Cmax (ng/mL)	8.76 (55)	9.14 (52)	0.96	.3975 NS	87	105	15	96

*The ANOVA model has treatment, period, sequence and subject(sequence, as factors (see Appendix S4 & S6).

*Except for AUCinf, KEL and Halflife, where n=31 for treatments A and B.

**NS = (treatment effect) not significant at p=0.05 level. Differences based on Least Square Means test.

CI = Confidence Interval.

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TABLE 5
Project DP056
MEAN PLASMA (C.V.%) N-DESMETHYLCLOMIPRAMINE CONCENTRATIONS (ng/mL)
AT EACH SAMPLING TIME POINT
Observed Data
(n=30)

TIME (hours)	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	ANOVA* p-value Treatment factor	Statistically Significant Differences**
pre-dose	0.13 (420)	0.09 (566)	0.5700	NS
1 hour	0.28 (349)	0.09 (566)	0.2756	NS
2 hours	1.87 (116)	1.94 (109)	0.5675	NS
3 hours	3.97 (76)	3.82 (77)	0.7000	NS
4 hours	5.46 (61)	5.25 (71)	0.5934	NS
5 hours	6.78 (50)	6.44 (58)	0.5450	NS
6 hours	7.90 (47)	7.62 (54)	0.6624	NS
8 hours	8.85 (46)	8.46 (52)	0.4287	NS
12 hours	9.05 (48)	8.82 (53)	0.6172	NS
16 hours	8.90 (51)	8.36 (52)	0.2625	NS
24 hours	8.31 (57)	8.44 (57)	0.7210	NS
48 hours	7.20 (78)	7.26 (79)	0.9550	NS
72 hours	5.79 (101)	5.70 (90)	0.6860	NS
96 hours	4.47 (113)	4.33 (110)	0.6124	NS
120 hours	3.53 (139)	3.76 (131)	0.7896	NS
144 hours	3.03 (149)	2.96 (153)	0.4172	NS
168 hours	2.33 (162)	2.17 (177)	0.3779	NS
240 hours	1.32 (201)	1.28 (225)	0.7817	NS

*The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S5).

**NS = not significant at p=0.05 level.
Differences based on Least Square Means test.

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TABLE 3
PROJECT 02086
SUMMARY OF STATISTICAL ANALYSIS - CLOMIPRAMINE
MEAN (C.V.%) BIOAVAILABILITY PARAMETERS
Observed Data
(n=31)*

BIOAVAILABILITY PARAMETERS	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	Ratio of Means	ANOVA* p-value Treatment factor	90% CI Limits (%) Lower	Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. α=.05,β=.2
AUC0-t(ng.hr/mL)	1019.64 (43)	1038.11 (34)	0.98	.7835 NS**	89	108	16	95
AUCinf(ng.hr/mL)	1076.97 (42)	1088.66 (34)	0.99	.7866 NS	90	108	16	95
Cmax(ng/mL)	47.97 (38)	49.15 (30)	0.98	.7493 NS	89	108	16	94
Tmax(hours)	4.61 (25)	4.97 (35)	0.93	.0816 NS				
Kel(1/hours)	0.03 (43)	0.03 (34)	0.96	.4330 NS				
t½(hours)	30.97 (32)	29.16 (32)	1.06	.1624 NS				

Observed (ln-transformed) Data
(geometric means)

BIOAVAILABILITY PARAMETERS	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	Ratio of Means	ANOVA* p-value Treatment factor	90% CI Limits (%) Lower	Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. α=.05,β=.2
AUC0-t(ng.hr/mL)	909.46 (53)	975.21 (37)	0.93	.3341 NS	83	105	19	83
AUCinf(ng.hr/mL)	970.39 (50)	1024.39 (37)	0.95	.3651 NS	84	105	19	84
Cmax (ng/mL)	44.02 (46)	46.94 (31)	0.94	.3562 NS	84	105	19	88

*The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S7 & S9).

*Except for AUCinf, KEL and HalfLife, where n=30 for treatment B.

**NS = (treatment effect) not significant at p=0.05 level. Differences based on Least Square Means test.

CI = Confidence Interval.

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TABLE 6
Project D2036
MEAN PLASMA (C.V.%) CLOMIPRAMINE CONCENTRATIONS (ng/mL)
AT EACH SAMPLING TIME POINT
Observed Data
(n=31)

TIME (hours)	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	ANOVA* p-value Treatment factor	Statistically Significant Differences**
pre-dose	0.00	0.00		
1 hour	4.58 (182)	3.67 (130)	0.6102	NS
2 hours	25.53 (75)	24.11 (74)	0.5516	NS
3 hours	39.15 (51)	37.43 (50)	0.5419	NS
4 hours	43.64 (43)	41.88 (42)	0.4975	NS
5 hours	44.37 (37)	44.28 (33)	0.8589	NS
6 hours	41.08 (33)	41.88 (30)	0.8665	NS
8 hours	35.58 (36)	35.83 (27)	0.9658	NS
12 hours	23.04 (39)	23.65 (32)	0.7219	NS
16 hours	16.55 (35)	17.23 (33)	0.4728	NS
24 hours	12.51 (37)	13.67 (36)	0.1680	NS
48 hours	5.79 (48)	5.96 (45)	0.6055	NS
72 hours	3.32 (55)	3.49 (51)	0.4219	NS
96 hours	2.03 (63)	1.99 (60)	0.6786	NS
120 hours	1.19 (108)	1.14 (99)	0.4313	NS
144 hours	0.60 (145)	0.38 (191)	0.2737	NS
168 hours	0.23 (242)	0.18 (272)	0.4340	NS
240 hours	0.03 (557)	0.00	0.3731	NS

*The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S9).

**NS = not significant at p=0.05 level.
Differences based on Least Square Means test.

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TABLE 7
PROJECT 19036
SUMMARY OF STATISTICAL ANALYSIS - N-DESMETHYLCLOMIPRAMINE
MEAN (C.V.%) BIOAVAILABILITY PARAMETERS
Observed Data
(n=31)*

BIOAVAILABILITY PARAMETERS	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	Ratio of Means	ANOVA* p-value Treatment factor	90% CI Limits (%) Lower	Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. α=.05,β=.2
AUC0-t(ng.hr/mL)	1017.94 (101)	1009.01 (99)	1.01	.8326 NS**	92	110	15	96
AUCinf(ng.hr/mL)	1317.10 (115)	1355.37 (125)	0.97	.8256 NS	86	106	17	92
Cmax(ng/mL)	10.08 (51)	10.36 (51)	0.97	.8257 NS	91	104	12	>99
Tmax(hours)	16.84 (105)	16.50 (72)	1.02	.8268 NS				
Kel(1/hours)	0.01 (47)	0.01 (38)	1.00	.7688 NS				
t½(hours)	62.61 (59)	60.34 (69)	1.04	.7273 NS				

Observed (ln-transformed) Data
(geometric means)

BIOAVAILABILITY PARAMETERS	A: Novopharm mean(C.V.%)	B: Basel mean(C.V%)	Ratio of Means	ANOVA* p-value Treatment factor	90% CI Limits (%) Lower	Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. α=.05,β=.2
AUC0-t(ng.hr/mL)	628.87 (102)	666.25 (93)	0.94	.3520 NS	84	105	15	86
AUCinf(ng.hr/mL)	782.91 (101)	830.93 (94)	0.94	.3242 NS	86	104	15	95
Cmax (ng/mL)	8.79 (56)	9.14 (52)	0.96	.3975 NS	87	105	15	96

*The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S10 & S12).

*Except for AUCinf, KEL and Halflife, where n=30 for treatment A.

**NS = (treatment effect) not significant at p=0.05 level. Differences based on Least Square Means test.

CI = Confidence Interval.

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TABLE 8
Project DP256
MEAN PLASMA (C.V.%) N-DESMETHYLCLOMIPRAMINE CONCENTRATIONS (ng/mL)
AT EACH SAMPLING TIME POINT
Observed Data
(n=31)

TIME (hours)	A: Novopharm mean(C.V.%)	B: Basel mean(C.V.%)	ANOVA* p-value Treatment factor	Statistically Significant Differences**
pre-dose	0.14 (413)	0.09 (557)	0.6039	NS
1 hour	0.29 (343)	0.10 (557)	0.2927	NS
2 hours	1.89 (116)	1.90 (106)	0.6638	NS
3 hours	4.02 (76)	3.94 (74)	0.8119	NS
4 hours	5.50 (61)	5.42 (67)	0.7725	NS
5 hours	6.76 (51)	6.64 (54)	0.7816	NS
6 hours	7.93 (48)	7.86 (50)	0.8999	NS
8 hours	8.90 (47)	8.73 (48)	0.6539	NS
12 hours	9.08 (49)	9.10 (49)	0.9337	NS
16 hours	8.97 (51)	8.63 (48)	0.4191	NS
24 hours	8.42 (56)	8.72 (53)	0.4706	NS
48 hours	7.33 (77)	7.49 (76)	0.7235	NS
72 hours	5.92 (99)	5.89 (87)	0.8145	NS
96 hours	4.57 (111)	4.47 (107)	0.7058	NS
120 hours	3.65 (136)	3.89 (128)	0.7701	NS
144 hours	3.13 (145)	3.06 (150)	0.4119	NS
168 hours	2.40 (159)	2.24 (173)	0.3809	NS
240 hours	1.36 (197)	1.33 (221)	0.7698	NS

*The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S11).

**NS = not significant at p=0.05 level.
Differences based on Least Square Means test.

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TABLE C2
SUMMARY OF CLINICAL COMPLAINTS

Number of Complaints Recorded (by Relationship to Formulation)

Complaint	Novopharm Limited Formulation A		Basel U.S .Formulation B		Total Number of Subjects
	Possibly/ Probably	Remote	Possibly/ Probably	Remote	
Nausea	18	-	14	-	26
Vomiting	18	-	20	-	26
Drowsiness/sleepiness	7	-	9	-	16
Dizziness	10	-	8	1	16
Headache	7	2	5	1	9
Insomnia/unable to sleep	6	-	3	-	6
Loose stools	3	2	4	-	6
Tired	2	-	3	2	6
Hot	-	3	-	2	5
Chills	2	-	4	-	4
Cold	-	4	1	-	4
Trembling	1	-	2	-	3
Weakness	2	-	1	-	3
Numbness	2	-	1	-	3
Difficulty to urinate	2	-	1	-	3
Nervous/agitated	1	-	2	-	2
Teeth chattering	2	-	1	-	2
Sore throat	-	1	-	1	2
Stuffy nose	-	1	-	1	2
Throat feels tight/paralyzed	1	-	-	1	2
Dry mouth	2	-	-	-	2
Constipation	2	-	-	-	2
Trouble breathing/shortness of breath	2	-	1	1	2
Loss of erection/unable to ejaculate	1	1	2	-	2
Feeling stoned	1	-	1	-	2
Fainted	1	-	-	-	1
Perspiration	2	-	-	-	1
Unsteady gait	-	-	1	-	1
Claustrophobic	-	-	1	-	1
Shaking left leg	1	-	-	-	1
Feeling aggressive	1	-	-	-	1
Difficulty swallowing	1	-	-	-	1
Feeling hot and cold	-	-	1	-	1
Blurred vision	1	-	-	-	1
Left groin pain	-	1	-	-	1
Jaw muscle tightness	1	-	1	-	1
Anxious	1	-	-	-	1
Pain right arm biceps	-	-	-	-	1
Warm neck	-	1	-	-	1
Lump in front of anus	-	-	-	1	1
Mentally slower	-	-	-	-	1

BEST POSSIBLE C

Complaint	Novopharm Limited Formulation A		Basel U.S Formulation B		Total Number of Subjects
	Possibly/ Probably	Remote	Possibly/ Probably	Remote	
Tingling in fingers and toes	1	-	-	-	1
Stomach burning	-	1	-	-	1
Anal irritation	-	1	-	-	1
Squeezing feeling left side of chest	-	1	-	-	1
Pimples on back	-	-	-	1	1
Runny nose	-	1	-	-	1
Difficulty digesting	1	-	-	-	1
Crossing of the eyes	1	-	-	-	1
Trembling jaw	1	-	-	-	1
Diarrhea	1	-	-	-	1
Reduced appetite	-	1	-	-	1
Lightheaded	1	-	-	-	1
Lethargic	1	-	-	-	1
Palpitations	-	-	1	-	1
Retching	-	-	1	-	1
Itching eyes	-	-	-	1	1
Red pinpoint (rash like) on eye lids	-	-	1	-	1
Burping	-	1	-	-	1
Upset stomach	-	1	-	-	1
Aching bones	-	1	-	-	1
Dilated pupils	-	-	1	-	1
	Total of 133 complaints in 43 subjects.		Total of 104 complaints in 38 subjects.		

BEST POSSIBLE COPY

TABLE 03
CLINICAL COMPLAINTS

Subject No.	Period	Treatment*	Complaint	Relationship	Approx. Onset (post-dose)	Approx. Duration
1	1	B	Vomiting	Probable	1 hr, 9 mins	20 mins
			Feels nervous	Probable	1 hr, 9 mins	15 hrs, 21 mins
			Nauseated	Probable	1 hr, 47 mins	1 hr, 58 mins
			Teeth chattering	Probable	1 hr, 54 mins	7 hrs, 6 mins
			Headache	Probable	2 hrs, 10 mins	1 hr, 35 mins
			Unsteady gait	Probable	3 hrs, 20 mins	13 hrs, 10 mins
			Headache	Remote	14 days, 22.5 hrs	18 hrs
	2	A	Vomiting	Probable	1 hr, 28 mins	31 mins
			Dizzy	Probable	1 hr	8 hrs
			Chattering of teeth	Probable	4 hrs	12 hrs
			Feels anxious	Probable	4 hrs	1 day, 1 hr
			Headache	Possible	2 days, 3 hrs	10 hrs
2	1	B	Feeling claustrophobic	Possible	10 hrs, 55 mins	2 hrs
			Vomited	Probable	20 mins	3 mins
3	1	A	Vomiting	Probable	1 hr, 20 mins	1 hr, 3 mins
	2	B	Vomiting	Probable	1 hr, 50 mins	2 mins
4	1	A	Sore throat	Remote	2 days, 11 hrs	1 day, 18 hrs
			Stuffy nose	Remote	3 days, 12 hrs	13 days, 11 hrs
	2	B	Dizzy	Probable	2 hrs, 9 mins	2 hrs
6	1	B	Dizziness	Probable	1 hr	1 day, 21.25 hrs
			Nausea	Probable	1 hr	1 day, 21.25 hrs
	2	A	Dizziness	Probable	1 hr	21 hrs, 50 mins
8	1	A	Unable to sleep	Possible	2 days, 14.75 hrs	7 hrs
	2	B	Vomiting	Probable	2 hrs	1 min
9	1	B	Vomiting	Probable	1 hr, 7 mins	2 hrs, 47 mins
			Feeling hot	Remote	1 hr, 35 mins	35 mins
			Experienced a chill	Probable	3 hrs, 59 mins	< 1 min
			Sore throat	Remote	1 day, 2.75 hrs	19 hrs
			Stuffy nose	Remote	3 days, 22.75 hrs	30 mins
			Dizziness	Remote	5 days, 2.75 hrs	2 hrs, 30 mins
	2	A	Vomiting	Probable	54 mins	2 hrs, 7 mins
			Cold upper extremities	Remote	1 hr, 24 mins	2 hrs
			Warm neck	Remote	1 hr, 24 mins	28 mins
			Feeling cold	Remote	1 hr, 52 mins	1 hr, 32 mins
			Shaking left leg	Probable	1 hr, 52 mins	5 mins
			Sleepiness	Probable	1 hr, 14 mins	2 days, 13 hrs
			Weakness	Possible	1 day, 21.75 hrs	16 hrs, 30 mins
			Insomnia	Possible	3 days, 14.25 hrs	2 days, 0.5 hr
			Pain right arm biceps	Remote	3 days, 1.75 hrs	24 days, 21.5 hrs
10	1	A	Nauseated	Probable	2 hrs, 4 mins	1 hr, 38 mins
			Vomiting	Probable	2 hrs, 10 mins	58 mins
	2	B	Vomiting	Probable	1 hr, 46 mins	1 hr, 1 min
			Nausea	Probable	1 hr, 42 mins	1 day

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BEST POSSIBLE CO

TABLE 03
CLINICAL COMPLAINTS

Subject No.	Period	Treatment*	Complaint	Relationship	Approx. Onset (post-dose)	Approx. Duration
10	2	B	Drowsiness	Probable	4 hrs. 42 mins	4 hrs
11	1	B	Nauseated	Probable	1 hr	1 hr. 29 mins
			Vomiting	Probable	1 hr. 52 mins	10 mins
			Insomnia	Probable	1 day. 15.75 hrs	23 hrs
	2	A	Trouble sleeping	Possible	16 hrs. 10 mins	1 day. 21.5 hrs
			Feeling aggressive	Possible	22 hrs. 40 mins	4 hrs
14	1	A	Vomiting	Probable	3 hrs. 2 mins	4 mins
15	1	A	Throat feels paralyzed	Probable	1 hr. 54 mins	9 mins
			Nausea	Probable	1 hr. 54 mins	1 hr
			Difficulty swallowing	Possible	1 hr. 54 mins	9 mins
			Teeth chattering	Probable	12 hrs. 21 mins	12 hrs. 41 mins
			Feels nervous	Probable	12 hrs. 32 mins	20 hrs
			Dry mouth	Possible	3 days. 5.5 hrs	21 hrs
	2	B	Feeling agitated	Probable	55 mins	21 hrs. 37 mins
			Feeling hot and cold	Possible	55 mins	3 hrs. 22 mins
			Loose stools	Probable	1 hr. 13 mins	6 hrs. 29 mins
16	1	B	Nauseated	Probable	1 hr. 5 mins	1 hr. 10 mins
	2	A	Vomiting	Probable	1 hr. 30 mins	2 mins
			Feeling hot	Remote	1 hr. 30 mins	1 hr. 30 mins
			Nausea	Probable	1 hr	21 hrs. 30 mins
17	2	A	Headache	Possible	1 day. 8.5 hrs	14 hrs. 15 mins
18	1	B	Nausea	Probable	1 hr. 9 mins	3 hrs. 17 mins
			Vomiting	Probable	1 hr. 55 mins	33 mins
	2	A	Vomiting	Probable	2 hrs	2 mins
			Nausea	Probable	3 hrs. 46 mins	1 hr. 25 mins
			Cold hands and face	Remote	1 hr. 35 mins	3 hrs. 35 mins
			Sleepy	Probable	1 hr. 25 mins	10 hrs. 30 mins
			Dry mouth	Possible	1 day. 3.5 hrs	11 hrs
20	2	B	Sleep disturbance	Possible	2 days. 18.75 hrs	1 day. 3.5 hrs
21	1	B	Nauseated	Probable	2 hrs. 2 mins	15 mins
			Chills	Probable	2 hrs. 2 mins	15 mins
			Vomiting	Probable	2 hrs. 9 mins	1 min
			Loose stools	Probable	2 hrs. 55 mins	5 mins
22	1	A	Nausea	Possible	1 day. 4.25 hrs	18 hrs. 30 mins
23	1	B	Sleepy	Possible	1 day. 0.25 hrs	2 hrs
	2	A	Headache	Probable	1 hr. 36 mins	3 hrs. 53 mins
			Headache	Possible	22 hrs. 16 mins	11 hrs
24	1	A	Blurred vision	Possible	4 hrs. 14 mins	1 day 19 hrs
			Constipation	Possible	2 hrs. 14 mins	22 hrs
			Difficulty to urinate	Probable	2 hrs. 14 mins	1 day. 15.25 hrs
			Left groin pain	Remote	3 days. 3.25 hrs	2 days. 19.75 hrs
	2	B	Headache	Probable	1 hr. 49 mins	1 day. 4.5 hrs
25	1	B	Vomiting	Probable	52 mins	1 hr. 18 mins
			Difficulty urinating	Probable	1 day. 19.25 hrs	15 hrs
26	1	A	Nauseated	Probable	1 hr. 55 mins	2 hrs. 9 mins

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TABLE 03
CLINICAL COMPLAINTS

Subject No.	Period	Treatment*	Complaint	Relationship	Approx. Onset (post-dose)	Approx. Duration
26	1	A	Vomiting	Probable	2 hrs. 2 mins	2 mins
			Trouble breathing	Probable	2 hrs. 5 mins	19 hrs. 35 mins
	2	B	Chills	Probable	39 mins	17 mins
			Shortness of breath	Probable	1 hr. 35 mins	15 mins
			Vomiting	Probable	1 hr. 38 mins	2 mins
			Nausea	Probable	4 hrs. 10 mins	1 hr. 17 mins
			Shortness of breath	Remote	7 days. 12.25 hrs	44 mins
28	1	A	Vomiting	Probable	1 hr. 11 mins	1 min
			Vomited	Probable	6 hrs. 28 mins	1 min
29	1	B	Lump in front of anus	Remote	9 days	1 day. 23 hrs
30	1	A	Fainted	Probable	1 hr. 2 mins	1 min
			Tingling in fingers and toes	Probable	1 hr. 16 mins	1 hr. 16 mins
			Chills	Probable	1 hr. 16 mins	1 hr. 16 mins
			Loose stools	Probable	4 hrs. 49 mins	5 hrs. 13 mins
			Constipated	Probable	10 hrs. 2 mins	1 day. 2 hrs
			Chills	Possible	23 hrs. 32 mins	2 days. 23 hrs
			Mentally slower	Probable	1 hr. 12 mins	4 days. 20.75 hrs
			Loose stools	Possible	1 day. 22.5 hrs	4 days. 15 hrs
			Stomach burning	Remote	3 days. 22.5 hrs	1 day. 16 hrs
			Anal irritation	Remote	1 day 22.5 hrs	6 days. 11.5 hrs
	2	B	Headache	Probable	1 hr. 17 mins	9 days. 2.75 hrs
			Chills	Possible	17 mins	2 days. 9.75 hrs
			Weakness	Possible	17 mins	1 day. 11.75 hrs
			Fatigue	Remote	5 days. 5 hrs	4 hrs
			Fatigue	Possible	6 days. 3.5 hrs	3 days. 0.5 hrs
31	1	A	Feeling sleepy	Probable	2 hrs. 40 mins	2 hrs. 20 mins
32	1	B	Vomiting	Probable	1 hr. 18 mins	2 mins
			Dizziness	Probable	2 hrs. 1 min	1 hr. 42 mins
			Numbness in legs	Possible	1 hr. 53 mins	1 hr. 50 mins
	2	A	Tiredness	Possible	28 mins	8 hrs. 30 mins
			Nausea	Probable	1 hr. 28 mins	2 hrs
			Squeezing feeling left side of chest	Remote	3 days. 8 hrs	5 mins
33	1	B	Nausea	Probable	1 hr. 26 mins	2 hrs. 33 mins
			Feeling tired	Probable	3 hrs. 59 mins	1 day. 6 hrs
			Pimples on back	Remote	1 day. 23 hrs	Unavailable
	2	A	Vomiting	Probable	1 hr. 41 mins	1 min
			Runny nose	Remote	2 days. 5 hrs	14 days. 18 hrs
35	1	A	Nausea	Probable	1 hr. 25 mins	1 hr. 27 mins
			Difficulty digesting	Probable	1 day. 4.75 hrs	23 hrs
	2	B	Drowsiness	Probable	52 mins	2 hrs
36	1	A	Feeling hot	Remote	1 hr. 28 mins	1 hr. 24 mins
37	1	B	Headache	Probable	1 hr. 3 mins	1 day. 21 hrs
			Vomiting	Probable	48 mins	2 mins

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TABLE 03
CLINICAL COMPLAINTS

Subject No.	Period	Treatment*	Complaint	Relationship	Approx. Onset (post-dose)	Approx. Duration
37	1	B	Tightness in jaw muscles	Possible	53 mins	2 days, 3 hrs
	2	A	Nausea	Probable	1 hr, 55 mins	2 hrs, 53 mins
			Crossing of the eyes	Probable	2 hrs, 14 mins	2 hrs, 34 mins
			Trembling jaw	Probable	2 hrs, 14 mins	20 hrs, 4 mins
			Muscle tightness of jaw	Possible	2 hrs, 14 mins	1 day, 20.5 hrs
			Headache	Probable	1 day, 2.75 hrs	1 day, 10 hrs
38	1	A	Vomiting	Probable	1 hr, 2 mins	55 mins
			Nausea	Probable	57 mins	2 hrs, 19 mins
			Dizziness	Probable	1 hr, 41 mins	1 hr, 35 mins
			Cold all over	Remote	1 hr, 53 mins	1 hr, 23 mins
			Numb legs	Possible	3 hrs, 11 mins	20 hrs, 5 mins
	2	B	Vomiting	Probable	1 hr, 25 mins	36 mins
			Drowsiness	Probable	2 hrs, 1 min	1 hr, 25 mins
39	1	B	Tired	Possible	5 hrs, 44 mins	1 day, 15 hrs
	2	A	Diarrhea	Probable	1 hr, 44 mins	3 hrs
			Nausea	Probable	2 hrs, 4 mins	6 hrs, 40 mins
41	1	B	Feeling hot	Remote	1 hr, 25 mins	30 mins
			Unable to sleep	Possible	2 days, 14.75 hrs	4 days, 8.25 hrs.
	2	A	Loose stools	Probable	1 hr, 10 mins	1 hr, 30 mins
			Difficulty urinating	Possible	1 day, 5.75 hrs	5 hrs
42	1	A	Nausea	Probable	55 mins	3 hrs, 30 mins
			Feeling hot	Remote	1 hr, 20 mins	3 hrs, 5 mins
	2	B	Drowsiness	Probable	38 mins	6 hrs
43	1	A	Reduced appetite	Remote	3 days, 11.5 hrs	1 day, 10 hrs
			Altered sleep pattern	Possible	3 days, 17.5 hrs	1 day, 4 hrs
44	1	B	Vomiting	Probable	1 hr, 34 mins	5 mins
			Nausea	Possible	3 days, 0.5 hr	12 hrs
	2	A	Vomiting	Probable	1 hr, 36 mins	2 hrs, 51 mins
			Light head	Probable	4 hrs, 4 mins	18 hrs, 30 mins
			Dizzy	Probable	4 hrs, 4 mins	18 hrs, 30 mins
			Headache	Possible	5 hrs, 34 mins	1 day, 13.5 hrs
			Dizziness	Probable	2 days, 3.5 hrs	7 hrs, 30 mins
45	1	A	Sleepiness	Probable	1 hr, 6 mins	1 day, 20.5 hrs
	2	B	Dizziness	Probable	10 hrs, 32 mins	1 day
47	1	B	Nausea	Probable	1 hr, 13 mins	1 hr, 15 mins
			Vomiting	Probable	1 hr, 15 mins	1 min
	2	A	Vomiting	Probable	1 hr, 3 mins	2 mins
			Sleepiness	Probable	1 hr, 28 mins	7 hrs
48	1	B	Loose stools	Probable	2 hrs, 26 mins	2 hrs, 20 mins
			Feeling cold	Possible	4 hrs, 46 mins	55 mins
			Loose stools	Probable	2 days, 2.5 hrs	6 hrs 5 mins
			Loss of erection	Possible	1 day, 2.5 hrs	3 days, 3 hrs
	2	A	Lethargic	Possible	1 hr, 56 mins	2 hrs

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TABLE 03
CLINICAL COMPLAINTS

Subject No.	Period	Treatment	Complaint	Relationship	Approx. Onset (post-dose)	Approx. Duration
48	2	A	Dizzy	Probable	1 hr, 56 mins	2 hrs
			Trouble sleeping	Probable	14 hrs, 56 mins	9 days, 6.5 hrs
			Unable to ejaculate	Remote	2 days, 5.5 hrs	4 days, 4 hrs
			Tired during the day	Possible	2 hrs, 26 mins	11 days, 21.5 hrs
49	1	A	Feeling sleepy	Probable	2 hrs, 1 min	2 hrs, 23 mins
			Feeling nauseated	Probable	4 hrs, 19 mins	20 mins
50	1	B	Feeling dizzy	Probable	1 hr	4 hrs, 57 mins
			Feeling sleepy	Probable	1 hr	4 hrs, 57 mins
			Feeling nauseated	Probable	2 hrs, 52 mins	10 mins
			Trembling	Probable	2 hrs, 52 mins	1 hr, 15 mins
	2	A	Trouble sleeping	Probable	14 hrs, 52 mins	1 day, 8.25 hrs
52	1	A	Nausea	Probable	1 hr, 16 mins	3 hrs, 7 mins
			Dizziness	Probable	1 hr, 23 mins	9 hrs, 55 mins
			Trembling	Probable	1 hr, 23 mins	9 hrs, 55 mins
			Numbness	Probable	1 hr, 39 mins	5 days, 12.5 hrs
			Difficulty breathing	Probable	1 hr, 43 mins	2 hrs, 35 mins
53	2	B	Vomiting	Probable	2 hrs, 11 mins	2 mins
			Drowsiness	Possible	16 mins	22 hrs
54	1	A	Nausea	Probable	44 mins	1 day, 10.5 hrs
			Perspiring	Possible	8 hrs	16 mins
			Weakness	Probable	29 mins	8 days, 4.75 hrs
			Excessive perspiration	Possible	1 day, 23.5 hrs	4 days, 3.75 hrs
			Headache	Possible	2 days, 1.25 hrs	6 hrs
			Headache	Remote	5 days, 21.75 hrs	13 hrs, 30 mins
	2	B	Dizziness	Probable	54 mins	5 days, 8.25 hrs
			Palpitations	Probable	44 mins	5 days, 0.5 hr
			Nausea	Probable	1 hr, 14 mins	1 day
			Retching	Probable	2 hrs, 1 min	1 min
			Drowsiness	Probable	2 hrs, 14 mins	8 days, 20 hrs
			Itchy eyes	Remote	2 days, 4.25 hrs	4 hrs
			Headache	Possible	1 day, 1.25 hrs	13 hrs, 59 mins
55	1	B	Trembling hands	Probable	1 hr, 5 mins	52 mins
	2	A	Vomiting	Probable	1 hr, 10 mins	2 mins
			Nausea	Probable	1 hr, 2 mins	1 hr, 10 mins
			Dizziness	Probable	1 hr, 2 mins	1 hr, 10 mins
56	1	B	Dizziness	Probable	1 hr, 29 mins	2 hrs, 26 mins
			Nausea	Probable	2 hrs, 2 mins	1 hr, 53 mins
			Vomiting	Probable	2 hrs, 24 mins	2 mins
			Tight throat	Remote	11 hrs, 40 mins	10 hrs, 30 mins
			Red pinpoint (rash like) on eye lids	Possible	12 hrs, 40 mins	4 days, 8 hrs
			Unable to have erection	Probable	1 hr, 10 mins	3 days, 1 hr
	2	A	Dizziness	Probable	1 hr, 10 mins	7 hrs
			Nausea	Probable	1 hr, 10 mins	8 hrs

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TABLE C3
CLINICAL COMPLAINTS

Subject No.	Period	Treatment*	Complaint	Relationship	Approx. Onset (post-dose)	Approx. Duration
56	2	A	Vomiting	Probable	2 hrs, 35 mins	2 mins
			Feels stoned	Possible	12 hrs, 10 mins	1 day, 10 hrs
			Unable to have erection	Probable	1 hr, 10 mins	2 days, 5 hrs
58	1	A	Vomiting	Probable	2 hrs, 21 mins	2 mins
59	1	A	Dizziness	Probable	49 mins	3 days, 21.75 hrs
			Burping	Remote	2 days, 12 hrs	1 day, 10.5 hrs
			Upset stomach	Remote	2 days, 11 hrs	1 day, 11.5 hrs
			Aching bones	Remote	2 days, 11.25 hrs	12 hrs
			Headache (frontal)	Remote	3 days, 10 hrs	1 day, 12.5 hrs
	2	B	Vomiting	Probable	1 hr, 15 mins	50 mins
			Drowsiness	Probable	2 hrs, 4 mins	20 hrs
			Dilated pupils	Possible	6 hrs, 4 mins	2 days, 16 hrs
			Feeling stoned	Possible	1 day, 20 hrs	1 day, 2.5 hrs
60	1	B	Vomiting	Probable	59 mins	1 min
			Dizziness	Probable	1 hr	5 mins
			Feeling tired	Remote	2 days, 5 hrs	4 hrs
	2	A	Vomiting	Probable	1 hr, 52 mins	2 mins
			Drowsiness	Possible	2 mins	5 hrs
			Loose stools	Remote	7 days, 3 hrs	6 hrs
			Loose stools	Remote	9 days, 13 hrs	15 mins

* A = Novopharm Limited 1 x 75 mg clomipramine HCl capsule
B = Basel U.S. (Anafranil®) 1 x 75 mg clomipramine HCl capsule