CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040207

Trade Name : PROCHLORPERAZINE MALEATE TABLETS USP 5MG AND 10MG (BASE)

Generic Name: Prochlorperazine Maleate Tablets USP 5mg and 10mg (Base)

Sponsor : Duramed Pharmaceuticals, Inc.

Approval Date: May 1, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040207

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040207

APPROVAL LETTER

ANDA 40-207

MAY 1 1997

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza, M.S., R.Ph.
5040 Lester Road
Cincinnati, OH 45213

Dear Sir:

This refers to your abbreviated new drug application dated August 28, 1996, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Prochlorperazine Maleate Tablets USP, 5 mg and 10 mg (base).

Reference is also made to your amendments dated November 7, 1996, February 27 and 28, March 14, and April 9, 1997.

We have completed the review of this abbreviated application and conclude that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Prochlorperazine Maleate Tablets USP, 5 mg and 10 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Compazine® Tablets, 5 mg and 10 mg of SmithKline Beecham 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 FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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

Sincerely yours,

for

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040207

FINAL PRINTED LABELING

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00507 ISS. 2/97

DURA med

NDC 51285-521-02

Prochlorperazine maleate *Tablets, USP*

5 mg *

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

***Each tablet contains** prochlorperazine maleate equivalent to 5 mg prochlorperazine.
Contains FD&C Yellow No. 5 (tartrazine) as a color additive.
Usual Dosage: 10 to 40 mg daily. See accompanying insert for complete prescribing information.
Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container.

Lot No.:

Exp. Date:

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00506 ISS. 2/97

DURA med

NDC 51285-522-02

Prochlorperazine maleate *Tablets, USP*

10 mg *

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

***Each tablet contains** prochlorperazine maleate equivalent to 10 mg prochlorperazine.
Usual Dosage: 10 to 40 mg daily. See accompanying insert for complete prescribing information.
Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container.

Lot No.:

Exp. Date:

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00508 ISS. 2/97

DURA med

NDC 51285-522-04

Prochlorperazine maleate *Tablets, USP*

10 mg *

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

***Each tablet contains** prochlorperazine maleate equivalent to 10 mg prochlorperazine.
Usual Dosage: 10 to 40 mg daily. See accompanying insert for complete prescribing information.
Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container.

Lot No.:

Exp. Date:

PROCHLORPERAZINE MALEATE TABLETS, USP

PRESCRIBING INFORMATION

I002970297

DESCRIPTION

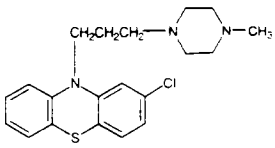
Prochlorperazine maleate is classified as an antiemetic and antipsychotic agent.

Each tablet, for oral administration, contains Prochlorperazine Maleate, USP (equivalent to 5 mg or 10 mg of prochlorperazine). In addition, each tablet contains the following inactive ingredients:

5 mg Tablets: lactose monohydrate, pregelatinized starch, povidone K-30, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80, FD&C Yellow No. 5 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake.

10 mg Tablets: lactose monohydrate, pregelatinized starch, povidone K-30, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80, D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake.

Prochlorperazine maleate is represented by the chemical formula: 2-Chloro-10-[3-(4-methyl-1-piperazinyl)propyl] phenothiazine maleate (1:2), and has the following structural formula:



• $2C_4H_4O_4$

$C_{20}H_{24}ClN_3S \cdot 2C_4H_4O_4$ Molecular Weight: 606.10
(Prochlorperazine base: 373.95; Maleate salt: 232.15)

Prochlorperazine Maleate, USP is a white or pale yellow, practically odorless crystalline powder that is practically insoluble in water and in alcohol and slightly soluble in warm chloroform.

CLINICAL PHARMACOLOGY

Prochlorperazine is a propylpiperazine derivative of phenothiazine. Like other phenothiazines, it exerts an antiemetic effect through a depressant action on the chemoreceptor trigger zone.

INDICATIONS AND USAGE

Prochlorperazine maleate tablets are indicated for control of severe nausea and vomiting.

Prochlorperazine maleate tablets are also indicated for the management of the manifestations of psychotic disorders.

Prochlorperazine is effective for the short-term treatment of generalized non-psychotic anxiety. However, *prochlorperazine* is not the first drug to be used in therapy for most patients with non-psychotic anxiety, because certain risks associated with its use are not shared by common alternative treatments (e.g., benzodiazepines).

When used in the treatment of non-psychotic anxiety, *prochlorperazine* should not be administered at doses of more than 20 mg per day or for longer than 12 weeks, because the use of *prochlorperazine* at higher doses or for longer intervals may cause persistent tardive dyskinesia that may prove irreversible (see WARNINGS).

The effectiveness of *prochlorperazine* as treatment for non-psychotic anxiety was established in 4-week clinical studies of outpatients with generalized anxiety disorder. This evidence does not predict that *prochlorperazine* will be useful in patients with other non-psychotic conditions in which anxiety, or signs that mimic anxiety, are found (e.g., physical illness, organic mental conditions, agitated depression, character pathologies, etc.).

Prochlorperazine has not been shown effective in the management of behavioral complications in patients with mental retardation.

CONTRAINDICATIONS

Do not use in comatose states or in the presence of large amounts of central nervous system depressants (alcohol, barbiturates, narcotics, etc.).

Do not use in pediatric surgery.

Do not use in children under 2 years of age or under 20 lbs. Do not use in children for conditions for which dosage has not been established.

WARNINGS

The extrapyramidal symptoms which can occur secondary to prochlorperazine may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy. The use of prochlorperazine and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process.

The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that: 1) is known to respond to neuroleptic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on PRECAUTIONS and ADVERSE REACTIONS.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Patients with bone marrow depression or who have previously demonstrated a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) with a phenothiazine should not receive any phenothiazine, including *prochlorperazine*, unless in the judgment of the physician the potential benefits of treatment outweigh the possible hazards.

Prochlorperazine may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, caution patients about activities requiring alertness (e.g., operating vehicles or machinery).

Phenothiazines may intensify or prolong the action of central nervous system depressants (e.g., alcohol, anesthetics, narcotics).

Usage in Pregnancy: Safety for the use of *prochlorperazine* during pregnancy has not been established. Therefore, *prochlorperazine* is not recommended for use in pregnant patients except in cases of severe nausea and vomiting that are so serious and intractable that, in the judgment of the physician, drug intervention is required and potential benefits outweigh possible hazards.

There have been reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

Nursing Mothers: There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

PRECAUTIONS

The antiemetic action of prochlorperazine may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see WARNINGS).

When *prochlorperazine* is used with cancer chemotherapeutic drugs, vomiting as a sign of the toxicity of these agents may be obscured by the antiemetic effect of *prochlorperazine*.

Because hypotension may occur, large doses and parenteral administration should be used cautiously in patients with impaired cardiovascular systems. To minimize the occurrence of hypotension after injection, keep patient lying down for at least 1/2 hour. If hypotension occurs after parenteral or oral dosing, place patient in head-low position with legs raised. If a vasoconstrictor is required, norepinephrine bitartrate and phenylephrine hydrochloride are suitable. Other pressor agents, including epinephrine, should not be used because they may cause a paradoxical further lowering of blood pressure.

Aspiration of vomitus has occurred in a few post-surgical patients who have received prochlorperazine as an antiemetic. Although no causal relationship has been established, this possibility should be borne in mind during surgical aftercare.

Deep sleep, from which patients can be aroused, and coma have been reported, usually with overdosage.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics.

As with all drugs which exert an anticholinergic effect, and/or cause mydriasis, prochlorperazine should be used with caution in patients with glaucoma.

Because phenothiazines may interfere with thermoregulatory mechanisms, use with caution in persons who will be exposed to extreme heat.

Phenothiazines can diminish the effect of oral anticoagulants.

Phenothiazines can produce alpha-adrenergic blockade.

Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.

Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concomitantly.

Concomitant administration of propranolol with phenothiazines results in increased plasma levels of both drugs.

Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Potentiation of anticonvulsant effects does not occur. However, it has been reported that phenothiazines may interfere with the metabolism of phenytoin and thus precipitate phenytoin toxicity.

The presence of phen
results.

5 mg tablet contains FD
(including bronchial ast
of FD&C Yellow No. 5 (
seen in patients who als

Long-Term Therapy: G
neuroleptics will develop
s contemplated be give
patients and on their qua
and the competency of t

To lessen the likelihood
a history of long-term t
evaluated periodically to
therapy discontinued.

**Children with acute illne
or dehydration seem
particularly dystonias.
under close supervision**

Drugs which lower the s
used with metrizamide.
discontinued at least 48
hours postprocedure, a
occurring either prior to

ADVERSE REACTIONS

Drowsiness, dizziness,
occur.

Cholestatic jaundice has
studies should be conduc

If tests indicate an abno
changes in the livers of pa
has been established.

Leukopenia and agranu
appearance of sore throat
indicate leukocyte depres

Neuromuscular (Extrapy

These symptoms are see
be characterized by mo
parkinsonism.

Depending on the sever
therapy is reinstituted, i
children or pregnant pati
barbiturates by suitable r
hydrochloride may be
parkinsonism agent, ex
symptoms. Suitable supp
hydration should be emp

Motor Restlessness: S
insomnia. These symptom
similar to the original neu
these side effects have su

If these symptoms becom
dosage or change of dru
propranolol may be helpf

Dystonias: Symptoms m
torticollis; extensor rigi
carpopedal spasm, trism
tongue.

These usually subside wi
drug has been discontinu
In mild cases, reassuranc
will usually bring rapid
parkinsonism agent, ex
symptoms. *In children*,
injectable diphenhydram
hydrochloride prescribin
treatment with anti-parki
the signs and symptoms

Pseudo-parkinsonism:
pillrolling motion; cogw
important. In most cases
agent is administered co
required. Generally, ther
patients should be eva
Levodopa has not been f
to lower the dosage of p

Tardive Dyskinesia: As
patients on long-term th
syndrome can also deve
periods at low doses. T
appears to be highest a
rely upon prevalence es
patients are likely to de
patients appear to be irr
movements of the tongu
puckering of mouth, ch
involuntary movements
extremities are the only
tardive dystonia, has als

There is no known effecti
alleviate the symptoms
discontinued if these syn

Should it be necessary to
to a different antipsychot

It has been reported that
the syndrome and if the

Adverse Reactions Rep
Adverse reactions with d
occurrence, i.e., some a
Some adverse reactions

PROCHLORPERAZINE MALEATE TABLETS, USP
PRESCRIBING INFORMATION

RAZINE

I002970297

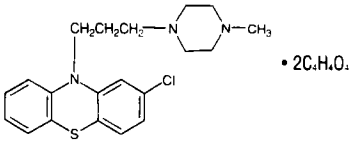
lassified as an antiemetic and antipsychotic agent.

ition, contains Prochlorperazine Maleate, USP (equivalent to 5 mg ne). In addition, each tablet contains the following inactive

5 mg Tablets: lactose monohydrate, pregelatinized starch, povidone K-30, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80, FD&C Yellow No. 5 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake.

10 mg Tablets: lactose monohydrate, pregelatinized starch, povidone K-30, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80, D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake.

Prochlorperazine maleate is represented by the chemical formula: 2-Chloro-10-[3-(4-methyl-1-piperazinyl)propyl] phenothiazine maleate (1:2), and has the following structural formula:



$C_{20}H_{24}ClN_3S \cdot 2C_4H_4O_4$ Molecular Weight: 606.10 (Prochlorperazine base: 373.95; Maleate salt: 232.15)

Prochlorperazine Maleate, USP is a white or pale yellow, practically odorless crystalline powder that is practically insoluble in water and in alcohol and slightly soluble in warm chloroform.

CLINICAL PHARMACOLOGY

Prochlorperazine is a propylpiperazine derivative of phenothiazine. Like other phenothiazines, it exerts an antiemetic effect through a depressant action on the chemoreceptor trigger zone.

INDICATIONS AND USAGE

Prochlorperazine maleate tablets are indicated for control of severe nausea and vomiting.

Prochlorperazine maleate tablets are also indicated for the management of the manifestations of psychotic disorders.

Prochlorperazine is effective for the short-term treatment of generalized non-psychotic anxiety. However, *prochlorperazine* is not the first drug to be used in therapy for most patients with non-psychotic anxiety, because certain risks associated with its use are not shared by common alternative treatments (e.g., benzodiazepines).

of non-psychotic anxiety, *prochlorperazine* should not be than 20 mg per day or for longer than 12 weeks, because the ner doses or for longer intervals may cause persistent tardive versible (see WARNINGS).

erazine as treatment for non-psychotic anxiety was established tpatients with generalized anxiety disorder. This evidence does *azine* will be useful in patients with other non-psychotic of signs that mimic anxiety, are found (e.g., physical illness, tated depression, character pathologies, etc.).

een shown effective in the management of behavioral mental retardation.

or in the presence of large amounts of central nervous system ates, narcotics, etc.).

2 years of age or under 20 lbs. Do not use in children for as not been established.

is which can occur secondary to prochlorperazine may be ervous system signs of an undiagnosed primary disease e.g., Reye's syndrome or other encephalopathy. The use of otential hepatotoxins should be avoided in children and symptoms suggest Reye's syndrome.

dyskinesia, a syndrome consisting of potentially irreversible, ments, may develop in patients treated with neuroleptic n the prevalence of the syndrome appears to be highest among women, it is impossible to rely upon prevalence estimates to euroleptic treatment, which patients are likely to develop the tic drug products differ in their potential to cause tardive

e syndrome and the likelihood that it will become irreversible he duration of treatment and the total cumulative dose of to the patient increase. However, the syndrome can develop, after relatively brief treatment periods at low doses. There is shed cases of tardive dyskinesia, although the syndrome may if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process.

The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that: 1) is known to respond to neuroleptic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on PRECAUTIONS and ADVERSE REACTIONS.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Patients with bone marrow depression or who have previously demonstrated a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) with a phenothiazine should not receive any phenothiazine, including *prochlorperazine*, unless in the judgment of the physician the potential benefits of treatment outweigh the possible hazards.

Prochlorperazine may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, caution patients about activities requiring alertness (e.g., operating vehicles or machinery).

Phenothiazines may intensify or prolong the action of central nervous system depressants (e.g., alcohol, anesthetics, narcotics).

Usage in Pregnancy: Safety for the use of *prochlorperazine* during pregnancy has not been established. Therefore, *prochlorperazine* is not recommended for use in pregnant patients except in cases of severe nausea and vomiting that are so serious and intractable that, in the judgment of the physician, drug intervention is required and potential benefits outweigh possible hazards.

There have been reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

Nursing Mothers: There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

PRECAUTIONS

The antiemetic action of prochlorperazine may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see WARNINGS).

When *prochlorperazine* is used with cancer chemotherapeutic drugs, vomiting as a sign of the toxicity of these agents may be obscured by the antiemetic effect of *prochlorperazine*.

Because hypotension may occur, large doses and parenteral administration should be used cautiously in patients with impaired cardiovascular systems. To minimize the occurrence of hypotension after injection, keep patient lying down for at least 1/2 hour. If hypotension occurs after parenteral or oral dosing, place patient in head-low position with legs raised. If a vasoconstrictor is required, norepinephrine bitartrate and phenylephrine hydrochloride are suitable. Other pressor agents, including epinephrine, should not be used because they may cause a paradoxical further lowering of blood pressure.

Aspiration of vomitus has occurred in a few post-surgical patients who have received prochlorperazine as an antiemetic. Although no causal relationship has been established, this possibility should be borne in mind during surgical aftercare.

Deep sleep, from which patients can be aroused, and coma have been reported, usually with overdosage.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics.

As with all drugs which exert an anticholinergic effect, and/or cause mydriasis, prochlorperazine should be used with caution in patients with glaucoma.

Because phenothiazines may interfere with thermoregulatory mechanisms, use with caution in persons who will be exposed to extreme heat.

Phenothiazines can diminish the effect of oral anticoagulants.

Phenothiazines can produce alpha-adrenergic blockade.

Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.

Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concomitantly.

Concomitant administration of propranolol with phenothiazines results in increased plasma levels of both drugs.

Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Potentiation of anticonvulsant effects does not occur. However, it has been reported that phenothiazines may interfere with the metabolism of phenytoin and thus precipitate phenytoin toxicity.

The presence of phenothiazines may produce false-positive phenylketonuria (PKU) test results.

5 mg tablet contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the over-all incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Long-Term Therapy: Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

To lessen the likelihood of adverse reactions related to cumulative drug effect, patients with a history of long-term therapy with prochlorperazine and/or other neuroleptics should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

Children with acute illnesses (e.g., chickenpox, CNS infections, measles, gastroenteritis) or dehydration seem to be much more susceptible to neuromuscular reactions, particularly dystonias, than are adults. In such patients, the drug should be used only under close supervision.

Drugs which lower the seizure threshold, including phenothiazine derivatives, should not be used with metrizamide. As with other phenothiazine derivatives, prochlorperazine should be discontinued at least 48 hours before myelography, should not be resumed for at least 24 hours postprocedure, and should not be used for the control of nausea and vomiting occurring either prior to myelography with metrizamide, or postprocedure.

ADVERSE REACTIONS

Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions and hypotension may occur.

Cholestatic jaundice has occurred. If fever with grippe-like symptoms occurs, appropriate liver studies should be conducted.

If tests indicate an abnormality, stop treatment. There have been a few observations of fatty changes in the livers of patients who have died while receiving the drug. No causal relationship has been established.

Leukopenia and agranulocytosis have occurred. Warn patients to report the sudden appearance of sore throat or other signs of infection. If white blood cell and differential counts indicate leukocyte depression, stop treatment and start antibiotic and other suitable therapy.

Neuromuscular (Extrapyramidal) Reactions

These symptoms are seen in a significant number of hospitalized mental patients. They may be characterized by motor restlessness, be of the dystonic type, or they may resemble parkinsonism.

Depending on the severity of symptoms, dosage should be reduced or discontinued. If therapy is reinstituted, it should be at a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should be stopped and not reinstituted. In most cases barbiturates by suitable route of administration will suffice. (Or, injectable diphenhydramine hydrochloride may be useful.) In more severe cases, the administration of an anti-parkinsonism agent, except levodopa *(see PDR)*, usually produces rapid reversal of symptoms. Suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed.

Motor Restlessness: Symptoms may include agitation or jitteriness and sometimes insomnia. These symptoms often disappear spontaneously. At times these symptoms may be similar to the original neurotic or psychotic symptoms. Dosage should not be increased until these side effects have subsided.

If these symptoms become too troublesome, they can usually be controlled by a reduction of dosage or change of drug. Treatment with anti-parkinsonian agents, benzodiazepines or propranolol may be helpful.

Dystonias: Symptoms may include: spasm of the neck muscles, sometimes progressing to torticollis; extensor rigidity of back muscles, sometimes progressing to opisthotonos; carpopedal spasm, trismus, swallowing difficulty, oculogyric crisis and protrusion of the tongue.

These usually subside within a few hours, and almost always within 24 to 48 hours, after the drug has been discontinued.

In mild cases, reassurance or a barbiturate is often sufficient. *In moderate cases*, barbiturates will usually bring rapid relief. *In more severe adult cases*, the administration of an anti-parkinsonism agent, except levodopa *(see PDR)*, usually produces rapid reversal of symptoms. *In children*, reassurance and barbiturates will usually control symptoms. (Or, injectable diphenhydramine hydrochloride may be useful. Note: See diphenhydramine hydrochloride prescribing information for appropriate *children's* dosage.) If appropriate treatment with anti-parkinsonism agents or diphenhydramine hydrochloride fails to reverse the signs and symptoms, the diagnosis should be reevaluated.

Pseudo-parkinsonism: Symptoms may include: mask-like facies; drooling; tremors; pillrolling motion; cogwheel rigidity; and shuffling gait. Reassurance and sedation are important. In most cases these symptoms are readily controlled when an anti-parkinsonism agent is administered concomitantly. Anti-parkinsonism agents *should be used only when* required. Generally, therapy of a few weeks to 2 or 3 months will suffice. After this time patients should be evaluated to *determine their need* for continued treatment. (Note: Levodopa has not been found effective in pseudo-parkinsonism.) Occasionally it is necessary to lower the dosage of prochlorperazine or to discontinue the drug.

Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The syndrome can also develop, although much less frequently, after relatively brief treatment periods at low doses. This syndrome appears in all age groups. Although its prevalence appears to be highest among elderly patients, especially elderly women, it is impossible to rely upon prevalence estimates to predict at the inception of neuroleptic treatment which patients are likely to develop the syndrome. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. In rare instances, these involuntary movements of the extremities are the only manifestations of tardive dyskinesia. A variant of tardive dyskinesia, tardive dystonia, has also been described.

There is no known effective treatment for tardive dyskinesia; anti-parkinsonism agents do not alleviate the symptoms of this syndrome. It is suggested that all anti-psychotic agents be discontinued if these symptoms appear.

Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Adverse Reactions Reported with prochlorperazine or other phenothiazine derivatives: Adverse reactions with different phenothiazines vary in type, frequency and mechanism of occurrence, i.e., some are dose-related, while others involve individual patient sensitivity. Some adverse reactions may be more likely to occur, or occur with greater intensity, in

patients with special medical problems, e.g., patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses of certain phenothiazines.

Not all of the following adverse reactions have been observed with every phenothiazine derivative, but they have been reported with 1 or more and should be borne in mind when drugs of this class are administered: extrapyramidal symptoms (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) some of which have lasted months and even years—particularly in elderly patients with previous brain damage; grand mal and petit mal convulsions, particularly in patients with EEG abnormalities or history of such disorders; altered cerebrospinal fluid proteins; cerebral edema; intensification and prolongation of the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol), atropine, heat, organophosphorus insecticides; autonomic reactions (dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis); reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia, hemolytic anemia, aplastic anemia); liver damage (jaundice, biliary stasis); endocrine disturbances (hyperglycemia, hypoglycemia, glycosuria, lactation, galactorrhea, gynecomastia, menstrual irregularities, false positive pregnancy tests); skin disorders (photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed in some patients receiving phenothiazine tranquilizers.

Although phenothiazines cause neither psychic nor physical dependence, sudden discontinuance in long-term psychiatric patients may cause temporary symptoms, e.g., nausea and vomiting, dizziness, tremulousness.

Note: There have been occasional reports of sudden death in patients receiving phenothiazines. In some cases, the cause appeared to be cardiac arrest or asphyxia due to failure of the cough reflex.

OVERDOSAGE

(See also ADVERSE REACTIONS.)

SYMPTOMS—Primarily involvement of the extrapyramidal mechanism producing some of the dystonic reactions described above.

Symptoms of central nervous system depression to the point of somnolence or coma. Agitation and restlessness may also occur. Other possible manifestations include convulsions, EKG changes and cardiac arrhythmias, fever and autonomic reactions such as hypotension, dry mouth and ileus.

TREATMENT—It is important to determine other medications taken by the patient since multiple-dose therapy is common in overdosage situations. Treatment is essentially symptomatic and supportive. Early gastric lavage is helpful. Keep patient under observation and maintain an open airway, since involvement of the extrapyramidal mechanism may produce dysphagia and respiratory difficulty in severe overdosage. **Do not attempt to induce emesis because a dystonic reaction of the head or neck may develop that could result in aspiration of vomitus.** Extrapyramidal symptoms may be treated with anti-parkinsonism drugs, barbiturates or diphenhydramine hydrochloride. See prescribing information for these products. Care should be taken to avoid increasing respiratory depression.

If administration of a stimulant is desirable, amphetamine, dextroamphetamine or caffeine with sodium benzoate is recommended.

Stimulants that may cause convulsions (e.g., picrotoxin or pentylenetetrazol) should be avoided.

If hypotension occurs, the standard measures for managing circulatory shock should be initiated. If it is desirable to administer a vasoconstrictor, norepinephrine bitartrate and phenylephrine hydrochloride are most suitable. Other pressor agents, including epinephrine, are not recommended because phenothiazine derivatives may reverse the usual elevating action of these agents and cause a further lowering of blood pressure.

Limited experience indicates that phenothiazines are *not* dialyzable.

DOSAGE AND ADMINISTRATION

DOSAGE AND ADMINISTRATION—ADULTS

(For children's dosage and administration, see below.) Dosage should be increased more gradually in debilitated or emaciated patients.

Elderly Patients: In general, dosages in the lower range are sufficient for most elderly patients. Since they appear to be more susceptible to hypotension and neuromuscular reactions, such patients should be observed closely. Dosage should be tailored to the individual, response carefully monitored and dosage adjusted accordingly. Dosage should be increased more gradually in elderly patients.

1. To Control Severe Nausea and Vomiting: Adjust dosage to the response of the individual. Begin with the lowest recommended dosage.

Oral Dosage—Tablets: Usually one 5 mg or 10 mg tablet 3 or 4 times daily. Daily dosages above 40 mg should be used only in resistant cases.

2. In Adult Psychiatric Disorders: Adjust dosage to the response of the individual and according to the severity of the condition. Begin with the lowest recommended dose. Although response ordinarily is seen within a day or 2, longer treatment is usually required before maximal improvement is seen.

Oral Dosage: *Non-Psychotic Anxiety*—Usual dosage is 5 mg 3 or 4 times daily. Do not administer in doses of more than 20 mg per day or for longer than 12 weeks.

Psychotic Disorders—In relatively mild conditions, as seen in private psychiatric practice or in outpatient clinics, dosage is 5 or 10 mg 3 or 4 times daily.

In moderate to severe conditions, for hospitalized or adequately supervised patients, usual starting dosage is 10 mg 3 or 4 times daily. Increase dosage gradually until symptoms are controlled or side effects become bothersome. When dosage is increased by small increments every 2 or 3 days, side effects either do not occur or are easily controlled. Some patients respond satisfactorily on 50 to 75 mg daily.

In more severe disturbances, optimum dosage is usually 100 to 150 mg daily.

DOSAGE AND ADMINISTRATION—CHILDREN

Do not use in pediatric surgery.

Children seem more prone to develop extrapyramidal reactions, even on moderate doses. Therefore, use lowest effective dosage. Tell parents not to exceed prescribed dosage, since the possibility of adverse reactions increases as dosage rises.

Occasionally the patient may react to the drug with signs of restlessness and excitement; if this occurs, do not administer additional doses. Take particular precaution in administering the drug to children with acute illnesses or dehydration (see ADVERSE REACTIONS, *Dystonias*).

1. Severe Nausea and Vomiting in Children: Prochlorperazine should not be used in children under 20 pounds in weight or 2 years of age. It should not be used in conditions for which children's dosages have not been established. Dosage and frequency of administration should be adjusted according to the severity of the symptoms and the response of the patient. The duration of activity following intramuscular administration may last up to 12 hours. Subsequent doses may be given by the same route if necessary.

Oral Dosage: More than 1 day's therapy is seldom necessary.

Weight	Usual Dosage	Not to Exceed
under 20 lbs not recommended		
20 to 29 lbs	2½ mg 1 or 2 times a day	7.5 mg per day
30 to 39 lbs	2½ mg 2 or 3 times a day	10 mg per day
40 to 85 lbs	2½ mg 3 times a day or 5 mg 2 times a day	15 mg per day

2. In Psychotic Children:

Oral Dosage: For children 2 to 12 years, starting dosage is 2½ mg 2 or 3 times daily. Do not give more than 10 mg the first day. Then increase dosage according to patient's response.

FOR AGES 2 to 5, total daily dosage usually does not exceed 20 mg.

FOR AGES 6 to 12, total daily dosage usually does not exceed 25 mg.

HOW SUPPLIED

Prochlorperazine Maleate Tablets, USP, are available as follows:

5 mg Tablets: Each round, orange, unscored tablet contains prochlorperazine maleate equivalent to 5 mg prochlorperazine, and is debossed with "ϕ" on one side and "521" on the other.

10 mg Tablets: Each round, yellow, unscored tablet contains prochlorperazine maleate equivalent to 10 mg prochlorperazine, and is debossed with "ϕ" on one side and "522" on the other.

5 mg and 10 mg tablets, in bottles of 100, 10 mg tablets in bottles of 500.

5 mg 100's: NDC 51285-521-02

10 mg 100's: NDC 51285-522-02

10 mg 500's: NDC 51285-522-04

Dispense in a tight, light-resistant container.

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

CAUTION: Federal law prohibits dispensing without prescription.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OHIO 45213 USA

I00297 ISS. 02/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040207

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-207

3. NAME AND ADDRESS OF APPLICANT

Duramed Pharmaceuticals, Inc.
5040 Lester Rd
Cincinnati, OH 45213

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that in their opinion and to the best of their knowledge, there are no active patents or periods of exclusivity in effect for the listed drug Compazine Tablets or that claim a use of the listed drug.

7. NONPROPRIETARY NAME

Prochlorperazine Maleate Tablets USP, 5 mg and 10 mg (base)

9. AMENDMENTS AND OTHER DATES:

Original 8/28/96
Amendment 11/7/96
Amendment 2/27/97
Amendment 2/27/97
Amendment 4/9/97

10. PHARMACOLOGICAL CATEGORY

Control of severe nausea and vomiting, management of the mainfestations of psychotic disorders

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

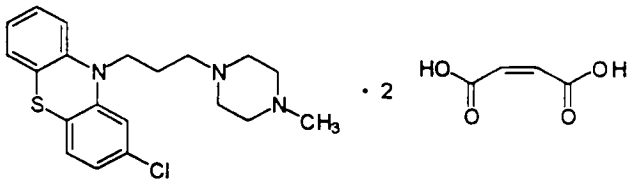
Tablets

14. POTENCY

5, 10 mg

15. CHEMICAL NAME AND STRUCTURE

Prochlorperazine Maleate. $C_{20}H_{24}ClN_3S \cdot 2C_4H_4O_4$. 606.1. 10*H*-Phenothiazine, 2-Chloro-10-[3-(4-methyl-1-piperazinyl)-propyl]-, (*Z*)-2-butenedioate (1:2). 84-02-6. USP 23, page 1304.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is APPROVABLE.

19. REVIEWER: DATE COMPLETED:

4/15/97

Nashed E. Nashed, Ph.D. 4/14/97

Supervisor: Paul Schwartz, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040207

BIOEQUIVALENCE REVIEW(S)

ANDA 40-207

Durmed Pharmaceuticals, Inc.
Attention: John Rapoza, M.S., R.Ph.
5040 Lester Road
Cincinnati OH 45213

MAR 31 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Prochlorperazine Maleate Tablets USP, 10 mg and 5 mg.

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

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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 26 1997

Prochlorperazine Maleate
10 and 5 mg, Tablets
ANDA #40-207
Reviewer: F. Nouravarsani
40207SDW.297

Duramed pharmaceuticals, Inc.
Cincinnati, Ohio
Submission Date:
February 28, 1997

Review of a Study Amendment, and
Recommendations for Approval

Firm has responded to the agency's deficiencies letter dated February 05, 1997 summarized as follows:

Deficiency #1:

The data were analyzed using ANOVA to check for a period or group effect before pooling the data. Subjects #1-10, 12-27, and 29 were in group I, and subjects #30 to 40 were in group II. Statistical model [Sequence, Subject(Sequence), Period, Drug Formulation] was used with the pooled data from all of the subjects. The model included 2 periods. The firm was advised that, since period 2 of group I was period 1 of group II, therefore there was no need to check GROUP or GROUP*FORMULATION effects. However, the firm was requested to use a three periods model, and recalculate the 90% CI.

Response to Deficiency #1:

The firm reanalyzed the data statistically using a three periods model. The 90% CI was recalculated for the ln-transformed and un-transformed parameters.

	90% CI	Ratio of Least-Squares Means (A/B)%
ln AUC(0-T)	92.4-105.7	98.8
ln AUC(0-Inf)	91.5-104.2	97.6
ln C(Max)	94.8-108.6	101.5

The firm's response is acceptable.

Deficiency #2:

Subject #23 had vomited at 3.3 hours after the test product dose. The Division of Bioequivalence requested results of the statistical data analyses to be submitted by excluding this subject.

Response to Deficiency #2:

The firm submitted mean of the parameters of AUC(0-T), AUC(0-Inf), and C(Max) excluding the subject #23. The mean values of the parameters were found to be almost identical to those calculated by including this subject.

Deficiency #3:

Statistical data analysis comparing test and reference products plasma concentrations of Prochlorperazine at various times was not submitted. The firm was requested to submit the information.

Response to Deficiency #3:

The firm submitted results of the analysis, and there was not a significant difference between the plasma concentrations of the test and reference products at each sampling time (alpha = 0.05).

The firm's response is acceptable.

Deficiency #4:

The firm was requested to submit values of the repeated assay for the samples "lost in processing", "poor chromatography", "H/L standard missing from the regression", and "not reportable" .

Response to Deficiency #4:

The requested information was submitted. The response is acceptable.

Deficiency #5:

Twenty-two samples were reported with code "D" (anomalous sample value) in Table T5.1, but report in Table T6.1 showed 24 samples with this code. The firm was requested to explain.

Response to Deficiency #5:

The firm explained that two samples (39, 0.5, 1 and 39, 48, 1)

which were originally coded "D" (anomalous sample value) were removed from Table T5.1, because the repeated assay values for these samples were not valid. Therefore, the samples were coded "B" (lost in processing).

The response is acceptable.

Deficiency #6:

Chromatograms for subjects #1, 2, 3, 4, 5, 6, 9, and 10 were submitted. The firm was requested to submit also the chromatograms for subjects #7 and #8.

Response to Deficiency #6:

The chromatograms for subjects #7 and #8 were submitted. The firm explained that the chromatograms submitted for subjects #1, 2, 3, 4, 5, 6, 9, and 10 were from the first four acceptable analytical runs.

The response is acceptable.

WAIVER REQUEST:

The firm had requested (August 28, 1996) for a waiver of bioequivalence study requirements for its 5 mg Prochlorperazine Maleate Tablets based on the followings:

a. Bioequivalence study conducted on higher strength of the test product, 10 mg Prochlorperazine Maleate Tablets.

b. Comparative dissolution testing conducted on 5 and 10 mg Prochlorperazine Maleate Tablets, and 5 and 10 mg Compazine Tablets (Tables 1 and 2).

c. Formulations similarity of 5 and 10 mg Prochlorperazine Maleate Tablets (Table 3).

COMMENTS:

1. The 90% confidence intervals calculated using ln-transformed parameters of the AUC(0-T), AUC(0-Inf), and C(Max) fall within the required range by the Division of Bioequivalence.

2. Lots #C-0017 (test product) and #905C67J (reference product) were used for both, the bioequivalence study and the dissolution testing. The test product batch size was [redacted] Tablets.

DEFICIENCY: None

RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Duramed Pharmaceuticals, Inc. on its Prochlorperazine Maleate Tablets, 10 mg (lot #C-0017) comparing it to Compazine Tablets, 10 mg (lot #905C67J) by SmithKline Beecham has been found acceptable by the Division of Bioequivalence. The study demonstrates that Duramed's Prochlorperazine Maleate Tablets, 10 mg is bioequivalent to the reference product, Compazine Tablets, 10 mg manufactured by SmithKline Beecham.

2. The dissolution testing conducted by Duramed Pharmaceuticals, Inc. on its Prochlorperazine Maleate Tablets, 10 mg (lot #C-0017) and 5 mg (lot #S-0013) ~~are~~ is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.1 N HCl acid at 37°C using USP 23 apparatus 2 (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the Prochlorperazine in the dosage form is dissolved in 60 minutes.

4. The waiver of bioequivalence study requirements for 5 mg Prochlorperazine Maleate Tablets may be granted.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE

3/21/97

Concur: _____ Date: 3/26/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/03-21-97/40207SDW.297

CC: ANDA #40-207 (original, duplicate), Nouravarsani, HFD-658, Drug File, Division File

Table 1: In Vitro Dissolution Testing

Drug (Generic Name): Prochlorperazine Maleate Tablets
Dose Strength: 10 mg
ANDA: #40-207
Firm: Duramed Pharmaceuticals, Inc.
Submission Date: August 28, 1996
USP 23 Specifications: Not less than (Q) of the labeled amount of Prochlorperazine in 60 minutes.

I. Conditions for Dissolution Testing:

USP XXII Basket___ Paddle X RPM 75 No. Units Tested 12

Medium: 0.1N Hydrochloric Acid Volume: 500 mL

Reference Drug: Compazine

Assay Methodology: _____

II. Results of In Vitro Dissolution Testing:

Sampling Times minutes	Test Product: Lot #C-0017 Strength (mg) 10			Reference Product: Lot #905C67J Strength (mg) 10		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	59.9		(10.8)	70.2		(12.1)
30	101.0		(01.6)	83.9		(08.3)
45	100.9		(01.5)	90.1		(06.6)
60	101.0		(01.3)	93.8		(05.4)
75	100.8		(01.4)	97.2		(03.7)

Table 2: In Vitro Dissolution Testing

Drug (Generic Name): Prochlorperazine Maleate Tablets
Dose Strength: 5 mg
ANDA: #40-207
Firm: Duramed Pharmaceuticals, Inc.
Submission Date: August 28, 1996
USP 23 Specifications: Not less than (Q) of the labeled amount of Prochlorperazine in 60 minutes.

I. Conditions for Dissolution Testing:

USP XXII Basket___ Paddle X RPM 75 No. Units Tested 12

Medium: 0.1N Hydrochloric Acid Volume: 500 mL

Reference Drug: Compazine

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times minutes	Test Product: Lot #S-0013 Strength (mg) 5			Reference Product: Lot #123C66J Strength (mg) 5		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	51.6		(06.2)	71.3		(10.5)
30	91.7		(03.9)	85.6		(11.1)
45	99.5		(02.9)	91.8		(11.5)
60	98.4		(03.2)	93.9		(11.0)
75	98.7		(02.2)	95.9		(09.9)

Table 3: Formulations Comparison of the Test and Reference products:

Ingredients	5 mg	10 mg
Prochlorperazine Maleate	8.10 (a)	16.21 (a)
Lactose Monohydrate		
Magnesium Stearate		
Pregelatinized Starch		
Povidone		
Color Coat:		
Yellow Orange		
Clear Coat:		
Clear		
Theoretical Total Weight	110.29	220.58

(a): One mg of Prochlorperazine Maleate is equal to 0.617 mg of Prochlorperazine.

JAN 29 1997 29 1997

Prochlorperazine Maleate
10 and 5 mg, Tablets
ANDA #40-207
Reviewer: F. Nouravarsani
40207SDW.896

Duramed pharmaceuticals, Inc.
Cincinnati, Ohio
Submission Date:
August 28, 1996

Review of a Bioequivalence Study, Dissolution Testing, and a Waiver Request

INTRODUCTION:

Duramed Pharmaceuticals, Inc. submitted a single dose, fasting bioequivalence study, and dissolution testing conducted on its test product, Prochlorperazine Tablets, 10 mg and the listed reference product, Compazine Tablets, 10 mg (N#10571-002) manufactured by SmithKline Beecham.

The firm has also submitted dissolution testing data for its 5 mg Prochlorperazine Maleate Tablets, and have requested a waiver of bioequivalence study requirements.

Prochlorperazine has been indicated for use in severe nausea, vomiting, and management of the manifestations of psychotic disorders. The recommended dose for adults is usually one 5 or 10 mg tablets three or four times per day. Dosage above 40 mg per day should only be used in resistant cases (PDR, 49th Edition, 1995).

The onset of action of prochlorperazine maleate from a tablet formulation was approximately 30-40 minutes with a duration of 3-4 hours (AHFS Drug Information, Page 1824, 1993).

The oral bioavailability of prochlorperazine was reported to be low following a single oral dose of 50 mg capsule in healthy young male subjects (Br. J. Clin. Pharmacol., 32(6), 677, 1991).

Duramed's products of Prochlorperazine Maleate Tablets, 5 mg (N89484), 10 mg (N89485), and 25 mg (N89486) are listed under the discontinued products in the Orange Book, 1995.

OBJECTIVES:

1. Determine single dose, fasting bioequivalency of the test product, Prochlorperazine Maleate Tablets, 10 mg, and the reference product, Compazine Tablets, 10 mg.

2. Compare dissolution testing conducted on the test and reference

products.

3. Waiver request for bioequivalence study requirements of Prochlorperazine Maleate Tablets, 5 mg.

BIOEQUIVALENCE STUDY:

Sponsor: Duramed Pharmaceuticals, Inc., Cincinnati, Ohio
Investigator:

Analytical Laboratory:

Principal Monitor:

Study Design:

A randomized, open label, single dose, two-treatment crossover study was conducted using normal, healthy male subjects. Two groups were used because of recruitment difficulties. Washout period was 14 days.

Clinical Study Dates:

Group	Period	Started	Completed	Dates
I	1	29	28	May 04 - 07, 1996
I	2	27	27	May 18 - 21, 1996
II	1'	11	11	May 18 - 21, 1996
II	2'	11	11	June 01 - 04, 1996

Treatments:

Treatment A (test Product): A single dose of Prochlorperazine Maleate Tablets, 2X10 mg, lot #C-0017. Batch size of tablets, Expiration date: 11/97.

Treatment B (reference Product): A single dose of Compazine tablets, 2X10 mg, lot #905C67J, expiration date: 10/97.

Subjects:

Two groups of normal, healthy, male subjects participated in the study. The first group included 29 subjects, and the second groups

consisted of 11 subjects. Two subjects in group one did not complete the study. Subject #11 dropped during period 1, and subject #28 dropped after period one. Therefore, thirty-eight (38) subjects completed the study.

The range of subject's age, weight, and height are summarized as follows:

Age: 19 - 53 years
Weight: 60.2 - 86.6 kg
Height: 169 - 189 cm

Housing, Fasting, Food and Fluid Intake:

All subjects were housed from evening before the dose administration until after blood draw at 72 hour. They fasted overnight for at least 10 hours prior to the dosing and 4 hours after the dose. Standard meals were served at each period. Except for 240 mL of water at room temperature taken with the dose, the subjects were not allowed to drink water for 2 hours before and after the dose, then ad libitum.

Blood Samples:

Blood samples were collected for each subject at each period at predose, and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, 30.0, 36.0, 48.0, 60.0, and 72.0 hours postdose. The plasma samples were stored frozen at -80° until analysis.

Vital Signs:

Blood pressure, pulse rate, respiratory rate, and temperature were measured within one hour before each dose (sitting), and were repeated at about 1, 2, and 4 hours (semi-reclining), and at 8, 12, 24, 48, and 72 hours (sitting) after the dose. Subjects had a physical examination before discharge from the study.

Analytical Procedures:

Statistical Analysis:

The data were analyzed using ANOVA to check for a period or group effect befor pooling the data. Subjects #1-10, 12-27, and 29 were in group I, and subjects #30 to 40 were in group II. There was no significant period effect observed for any group. Then, the data from all of the subjects were used, choosing the model [Group, Sequence, Subject(Sequence*Group), Period, Drug Formulation] to check if there was a significant group effect using Subject(Sequence*Group) as the error term. There was no significant group effect. Therefore, statistical model [Sequence, Subject(Sequence), Period, Drug Formulation] was used with the pooled data from all of the subjects.

The two one sided t-test procedure (90% confidence intervals) was used to compare the ln-transformed parameters of AUC(0-T), AUC(0-Inf), and C(Max) obtained from the test and reference products.

RESULTS:

The mean plasma Prochlorperazine concentrations are summarized in Table 1. Linear and Ln Plots of the mean plasma concentrations of Prochlorperazine versus time for both test and reference products are shown in Figures 1 and 2. The pharmacokinetic parameters are compared in Table 2.

The AUC(0-T) for the test product, 18406 hr*pg/mL, is comparable with the AUC(0-T) of 17806 hr*pg/mL for the reference product.

The AUC(0-Inf) for the test product, 20095 hr*pg/mL, is comparable with the one obtained for the reference product, 20058 hr*pg/mL.

The C(Max) for the test product, 1143.3 pg/mL, is comparable with the C(Max) of 1135 pg/mL for the reference product.

There are neither product, nor period (Ln-transformed, p=0.05), nor sequence effect (Ln-transformed, p=0.1) for the above parameters. The 90% confidence interval calculated for Ln-transformed (least-squares means) AUC(0-T), AUC(0-Inf), and C(Max) are summarized in Table 2.

Medical Events:

No serious medical events were reported. The following table

summarizes the drug related adverse effects.

Complaint	Subject #	Treatment
Headache	4	A
Nausea	4	A
	23	A
Lightheaded	8	A
Vomiting	23	A
Stiff Neck	2	B

IN - VITRO STUDIES:

Dissolution Testing:

The firm submitted dissolution testing (using USP 23 method) results conducted on 12 units each of the test and reference products in 500 mL of 0.1N HCl, using paddle at 75 rpm.

The mean dissolutions of Prochlorperazine Maleate Tablets, 10 mg were 101% and 93.8% of the labeled amount for the test and reference products, respectively, at 60 minutes (Table 3).

The mean dissolutions of Prochlorperazine Maleate Tablets, 5 mg were 98.4% and 93.9% of the labeled amount for the test and reference products, respectively, at 60 minutes (Table 4).

Assay Potency:

The potencies were 100.2% and 99.1% for the test and reference products, respectively.

Content Uniformity:

The mean content uniformities were 100.2% (CV%=0.8, N=10) for the test product, and 99.8% (CV%=2.6, N=10) for the reference product.

COMMENTS:

1. Lots C-0017 (test product) and #905C67J (reference product) were used for the bioequivalence study and the dissolution testing. The test product batch size was tablets.

3. The firm has submitted a copy of letter (dated May 12, 1994) from the OGD, that permits use of 10 mg Prochlorperazine Tablets for bio-study. The firm may request a waiver for its lower strength, 5 mg Tablets, but not for its 25 mg product.

4. The dissolution testing method and specifications used by the firm are the same as the one reported in USP 23, 1995.

DEFICIENCIES:

1. The data were analyzed using ANOVA to check for a period or group effect before pooling the data. Subjects #1-10, 12-27, and 29 were in group I, and subjects #30 to 40 were in group II. Statistical model [Sequence, Subject(Sequence), Period, Drug Formulation] was used with the pooled data from all of the subjects. The model included 2 periods. The firm should be advised that, since period 2 of group I is period 1 of group II, therefore there is no need to check GROUP or GROUP*FORMULATION effects. However, the model should have three period, and the 90% CI should be recalculated.

2. Subject #23 vomited at 3.3 hours after the test product dose. The Division of Bioequivalence requests results of the statistical analyses to be submitted for data by including and excluding this subject.

3. Statistical data analysis comparing test and reference products plasma concentrations of Prochlorperazine at various times should be submitted.

4. The firm should submit values of the repeated assay for the samples "lost in processing", "poor chromatography", "H/L standard missing from the regression", and "not reportable" .

5. Twenty-two samples were reported with code "D" (anomalous sample value) in Table T5.1, but report in Table T6.1 shows 24 samples with this code. The firm should explain.

6. Chromatograms for subjects #1, 2, 3, 4, 5, 6, 9, and 10 were submitted. The chromatograms for subjects #7 and #8 should also be submitted.

RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Duramed Pharmaceuticals, Inc. on its Prochlorperazine Tablets, 10 mg (lot #C-0017) comparing it to Compazine Tablets, 10 mg (lot #905C67J) by SmithKline Beecham has been found incomplete by the Division of Bioequivalence.

2. The dissolution testings conducted by Duramed Pharmaceuticals, Inc. on its Prochlorperazine Maleate Tablets, 10 mg (lot #C-0017) and 5 mg (lot #S-0013) are acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.1 N HCl acid at 37°C using USP 23 apparatus 2 (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than , of the labeled amount of the Prochlorperazine in the dosage form is dissolved in 60 minutes.

4. The waiver of bioequivalence study requirements for 5 mg Prochlorperazine Tablets may not be granted, since the firm does not have an acceptable bio-study on its higher strength.

The firm should be informed of the DEFICIENCIES #1-6, and COMMENT #2.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE 1/29/97

Concur: Date: 1/29/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Table 1:

Mean (CV%) Plasma Concentrations (pg/mL) of Prochlorperazine, Dose = 2X10 mg, N = 38:

Time, hr	Test Product	Reference Product
0.00	0.00 (---)	2.96 (616)
0.50	103.49 (73.8)	121.60 (78.8)
1.00	264.47 (45.5)	269.29 (54.7)
1.50	381.71 (45.4)	398.57 (48.8)
2.00	542.17 (58.8)	549.98 (53.9)
2.50	629.14 (53.8)	634.89 (62.4)
3.00	716.61 (60.6)	729.70 (58.7)
4.00	866.08 (67.3)	828.03 (64.2)
5.00	1056.3 (83.2)	1007.5 (68.8)
6.00	1044.9 (87.1)	1042.4 (78.1)
8.00	964.56 (93.2)	958.78 (85.3)
10.0	773.44 (93.5)	753.38 (91.2)
12.0	662.48 (95.3)	639.52 (95.6)
18.0	405.35 (156)	385.79 (133)
24.0	269.82 (103)	257.41 (88.7)
30.0	198.19 (113)	177.40 (108)
36.0	127.40 (125)	123.69 (117)
48.0	64.78 (166)	63.94 (159)
60.0	28.94 (231)	27.21 (222)
72.0	22.76 (270)	16.38 (266)

Table 2:

Comparison of Mean (CV%) Prochlorperazine Pharmacokinetic Parameters, and 90% CI Obtained for the Test and Reference Products, Dose = 2X10 mg, N = 38:

Parameters	Test	Reference	90% CI Ln-trans.
AUC(0-T) hr*pg/mL	18,406 (104)	17,806 (94)	93.6-107.4
AUC(0-Inf) hr*pg/mL	20,095 (102)	20,058 (87)a	92.6-105.2
C(Max) pg/mL	1,143.3 (79)	1,134.9(75)	94.9-108.4
T(Max) hr	5.54 (34)	5.24 (41)	
K(Elm) 1/hr	0.0522 (35)	0.0482 (24)a	
T(1/2) hr	14.71 (32)	15.11 (22)a	

a: N = 35

Table 3: In Vitro Dissolution Testing

Drug (Generic Name): Prochlorperazine Maleate Tablets
Dose Strength: 10 mg
ANDA: #40-207
Firm: Duramed Pharmaceuticals, Inc.
Submission Date: August 28, 1996
USP 23 Specifications: Not less than (Q) of the labeled amount of Prochlorperazine in 60 minutes.

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X RPM 75 No. Units Tested 12

Medium: 0.1N Hydrochloric Acid Volume: 500 mL

Reference Drug: Compazine

Assay Methodology: _____

II. Results of In Vitro Dissolution Testing:

Sampling Times minutes	Test Product: Lot #C-0017 Strength (mg) 10			Reference Product: Lot #905C67J Strength (mg) 10		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	59.9		(10.8)	70.2		(12.1)
30	101.0		(01.6)	83.9		(08.3)
45	100.9		(01.5)	90.1		(06.6)
60	101.0		(01.3)	93.8		(05.4)
75	100.8		(01.4)	97.2		(03.7)

Table 4: In Vitro Dissolution Testing

Drug (Generic Name): Prochlorperazine Maleate Tablets
Dose Strength: 5 mg
ANDA: #40-207
Firm: Duramed Pharmaceuticals, Inc.
Submission Date: August 28, 1996
USP 23 Specifications: Not less than (Q) of the labeled amount of Prochlorperazine in 60 minutes.

I. Conditions for Dissolution Testing:

USP XXII Basket____ Paddle X RPM 75 No. Units Tested 12

Medium: 0.1N Hydrochloric Acid Volume: 500 mL

Reference Drug: Compazine

Assay Methodology: _____

II. Results of In Vitro Dissolution Testing:

Sampling Times minutes	Test Product: Lot #S-0013 Strength (mg) 5			Reference Product: Lot #123C66J Strength (mg) 5		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	51.6		(06.2)	71.3		(10.5)
30	91.7		(03.9)	85.6		(11.1)
45	99.5		(02.9)	91.8		(11.5)
60	98.4		(03.2)	93.9		(11.0)
75	98.7		(02.2)	95.9		(09.9)

Table 5: Formulations Comparison of the Test and Reference products:

Ingredients	5 mg	10 mg
Prochlorperazine Maleate	8.10 (a)	16.21 (a)
Lactose Monohydrate		
Magnesium Stearate		
Pregelatinized Starch		
Povidone		
Color Coat:		
Yellow		
Orange		
Clear Coat:		
Clear		
Theoretical Total Weight	110.29	220.58

(a): One mg of Prochlorperazine Maleate is equal to 0.617 mg of Prochlorperazine.

Figure 1

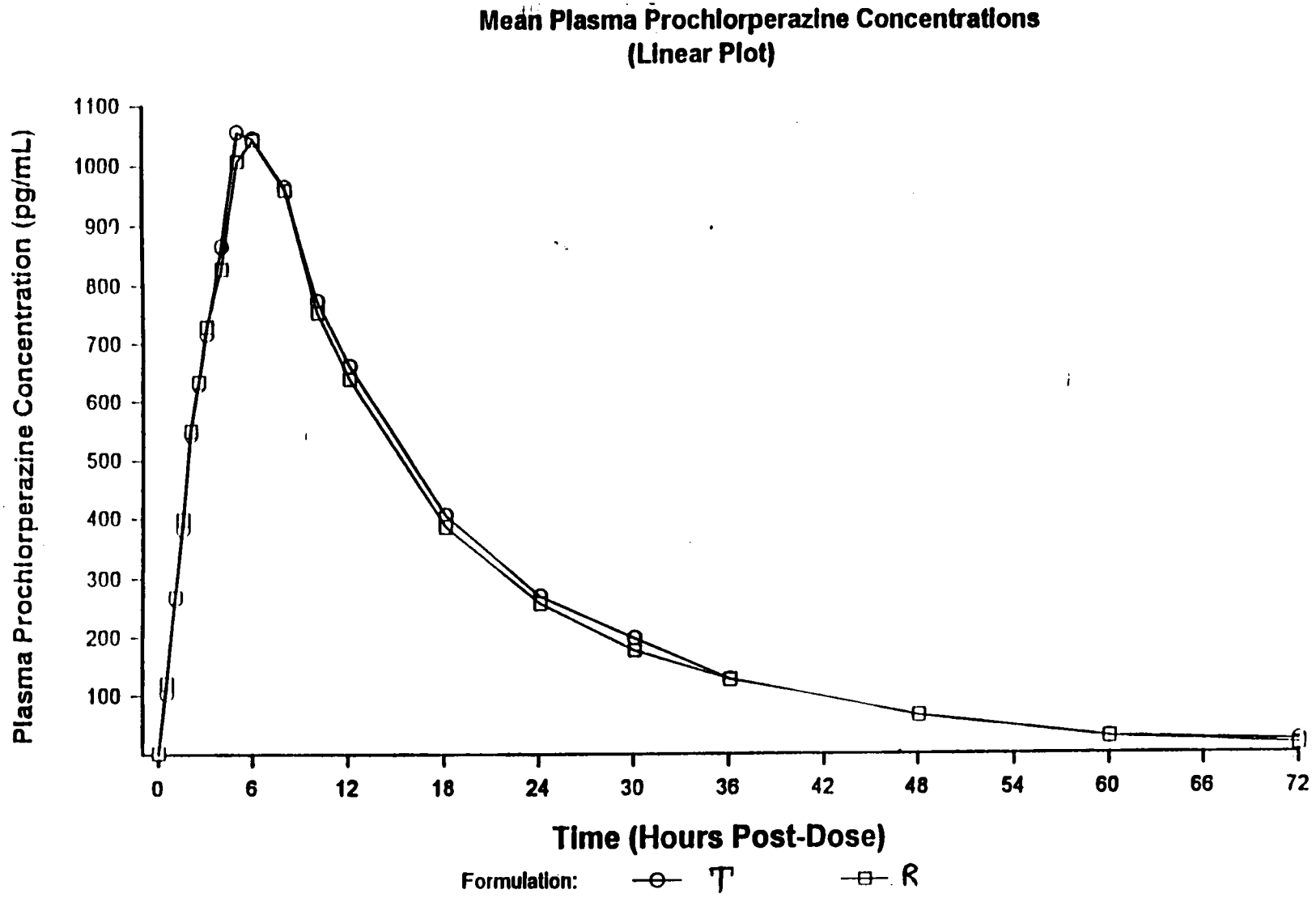
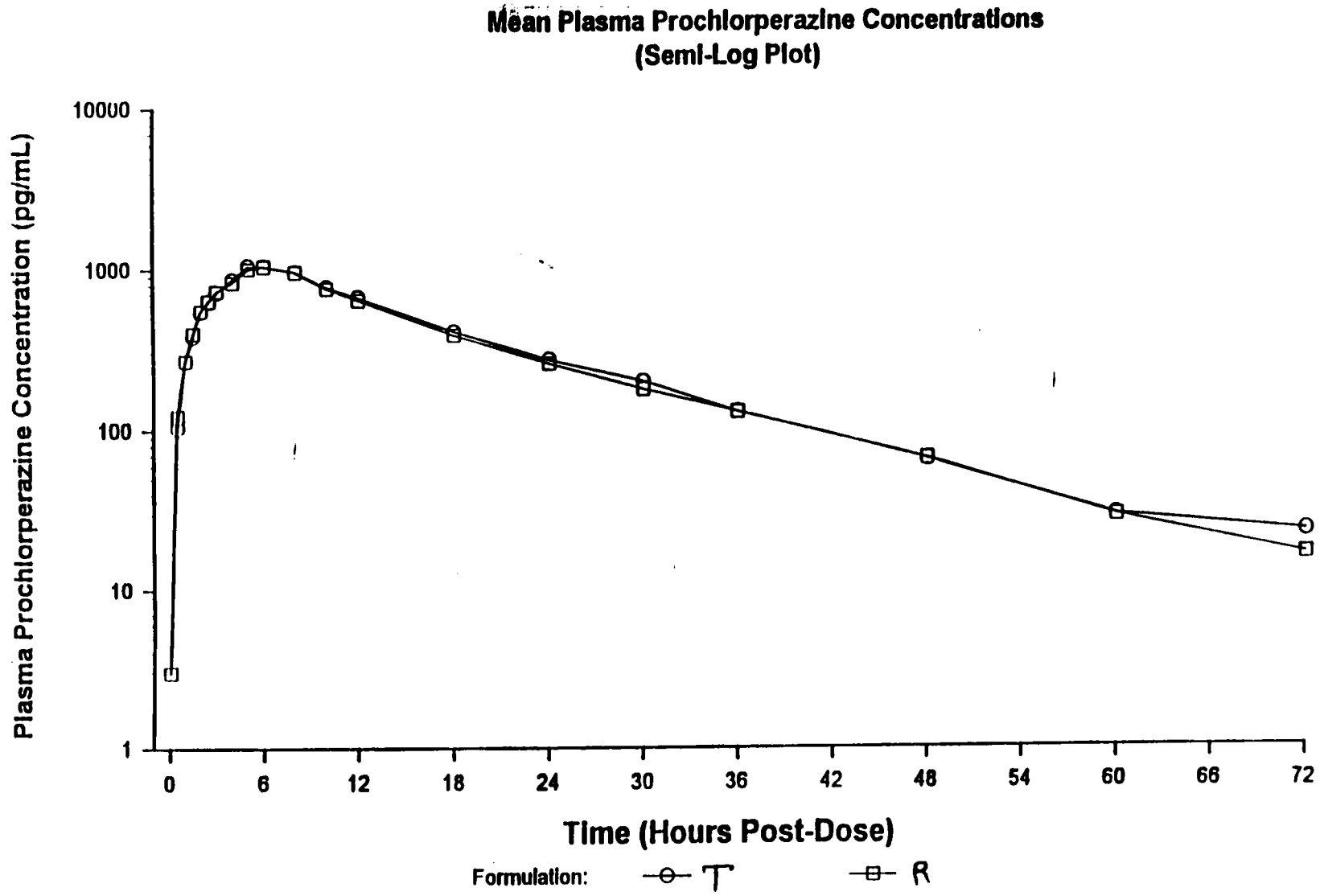

Mean Plasma Prochlorperazine Concentrations
(Linear Plot)
Plasma Prochlorperazine Concentration (pg/mL)
1100
1000
900
800
700
600
500
400
300
200
100
0
6
12
18
24
30
36
42
48
54
60
66
72
Time (Hours Post-Dose)
Formulation:
T
R

Figure 2


Mean Plasma Prochlorperazine Concentrations
(Semi-Log Plot)
Plasma Prochlorperazine Concentration (pg/mL)
10000
1000
100
10
1
0
6
12
18
24
30
36
42
48
54
60
66
72
Time (Hours Post-Dose)
Formulation:
T
R