CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 40268

Trade Name Prochlorperazine Maleate Tablets USP 5mg (base) and 10mg (base)

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

Sponsor Trigen Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 40268

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Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40268

APPROVAL LETTER

ANDA 40-268

Trigen Laboratories, Inc.
Attention: Rajan Embran
207 Kiley Drive
Salisbury, MD 21801

FEB 27 1998

Dear Sir:

This is in reference to your abbreviated new drug application dated August 5, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Prochlorperazine Maleate Tablets USP, 5 mg (base) and 10 mg (base).

Reference is also made to your amendments dated September 11, October 31, and November 7 and 24, 1997; and January 7 and 29, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Prochlorperazine Maleate Tablets USP, 5 mg (base) and 10 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Compazine Tablets, 5 mg (base) and 10 mg (base), respectively, 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,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40268

FINAL PRINTED LABELING

*Each tablet contains Prochlorperazine Maleate equivalent to 5 mg Prochlorperazine.

Usual Dosage:
10 to 40 mg daily.
See accompanying brochure for complete prescribing information.

Important: Use safety closure when dispensing this product unless otherwise directed by physician or requested by purchaser.

Dispense in tight, light resistant container.

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

NDC 59746-113-10

Prochlorperazine Maleate Tablets USP

5 mg*

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Trigen Laboratories, Inc.
Salisbury, MD 21801

3 59746-113-10 0

REV. 12/97

LOT:

EXP:

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NDC 59746-115-06

[redacted]

Prochlorperazine Maleate
Tablets USP
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Trigen Laboratories, Inc.
Salisbury, MD 21801

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FEB 27

N 3 59746-113-06 3

REV. 12/97

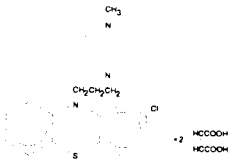
LOT:

EXP:

PROCHLORPERAZINE MALEATE TABLETS USP

DESCRIPTION

Prochlorperazine Maleate is classified as an anti-emetic and antipsychotic agent. Prochlorperazine Maleate is designated chemically as 2-chloro-10- [3-(4-methyl-1-piperazinyl) propyl] phenothiazine maleate (1:2). It has a molecular weight of 606.10 and the following structural formula:



$C_{20}H_{24}ClN_3S.\ 2C_4H_4O_4$

Prochlorperazine maleate is white or pale yellow, practically odorless, crystalline powder. It is insoluble in water and in alcohol; slightly soluble in warm chloroform.

Each tablet, for oral administration contains prochlorperazine maleate equivalent to 5 mg or 10 mg of prochlorperazine. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, pregelatinized starch, lactose monohydrate, stearic acid, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, polysorbate 80, FD & C yellow no.6 aluminum lake, FD & C blue no. 2 aluminum lake and D&C yellow no. 10 aluminum lake.

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

For control of severe nausea and vomiting.

For management of the manifestations of psychotic disorders.

Prochlorperazine is effective for the short term treatment of generalized nonpsychotic 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 nonpsychotic 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 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 syndrome 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 systems (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. If hypotension occurs after parental 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 1/3 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 patients 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.

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., chicken-pox, 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.

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MALEATE TABLET

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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; pill-rolling 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 antipsychotic 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 further lowering of blood pressure.

Limited experience indicates that phenothiazines are *not* dialyzable.

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 out patient 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 extra-pyramidal reactions, even on moderate doses. Therefore use lowest effective dosage. Tell parents not to exceed prescribed dosage, since the possibility for 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	2 ½ mg 1 or 2 times a day	7.5 mg per day
30 to 39 lbs	2 ½ mg 2 or 3 times a day	10 mg per day
40 to 85 lbs	2 ½ 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 in the following strengths and package sizes:

5 mg (Chartreuse, round, scored, film-coated, imprinted TL 113)
Bottles of 100 NDC 59746-113-06
Bottles of 1000 NDC 59746-113-10

10 mg (Chartreuse, round, scored, film-coated, imprinted TL 115)
Bottles of 100 NDC 59746-115-06
Bottles of 1000 NDC 59746-115-10

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

CAUTION: Federal law prohibits dispensing without prescription.

Trigen Laboratories, Inc.
Salisbury, MD 21801, USA
Revised December, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40268

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.2

2. ANDA # 40-268

3. NAME AND ADDRESS OF APPLICANT

Trigen Laboratories, Inc.
207 Kiley Drive
Salisbury, MD 21801

4. LEGAL BASIS FOR SUBMISSION

In the firm opinion and to the best of their knowledge there are no patents that claim the listed drug referred to in this application, and there is no marketing exclusivity in force covering this drug.

5. SUPPLEMENT(s)

Original 8/5/97

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Prochlorperazine Maleate

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 9/11/97
Amendment 10/31/97
Telephone Amendment 1/7/98
Amendment 1/29/98

10. PHARMACOLOGICAL CATEGORY

Antipsychotic Disorders

11. Rx or OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

14. POTENCY

Tablets 5mg and 10 mg

15. CHEMICAL NAME AND STRUCTURE

2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl] phenothiazine

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E, Nashed, Ph.D. 2/17/98

Supervisor: Paul Schwartz, Ph.D.

cc: ANDA 40-268
Division File
Field Copy

Endorsements:
HFD-627/N.Nashed, Ph.D./2-17-98
HFD-627/P.Schwartz, Ph.D./2-18-98
X:\NEW\FIRMSNZ\TRIGEN\LTRS&REV\40268.2
F/T by: bc/2-19-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40268

BIOEQUIVALENCE REVIEW(S)

Prochlorperazine Maleate Tablets	Trigen
5 mg and 10 mg Tablets	Salisbury, MD
ANDA #40-268	Submission Date:
Reviewer: Moo Park	8/5/97; 11/7/97; 11/24/97
Filename: 40268sdw.897	

Review of an In Vivo Bioequivalence Study, Dissolution Data and a Waiver Request

I. Objectives

Review of:

- Two-way crossover *in vivo* bioequivalence study comparing Trigen's Prochlorperazine Maleate Tablets, 10 mg strength, to SmithKline Beecham's Compazine® (prochlorperazine maleate) Tablets, 10 mg strength, following administration of a 20 mg dose under fasting conditions.
- Dissolution data for 5 mg and 10 mg tablets.
- A waiver request for 5 mg tablets.

II. Background

Prochlorperazine is a propylpiperazine derivative of phenothiazine, used for the control of severe nausea and vomiting of various etiologies, and for the symptomatic management of psychotic disorders. For adults, the usual daily dose is one 5 mg or 10 mg tablet 3 or 4 times daily.

Following oral administration of prochlorperazine maleate in a tablet formulation, the drug has an onset of action of approximately 30-40 minutes and a duration of action of 3-4 hours. Isah et al (Isah AO, Rawlins MD, Bateman DN. Clinical

pharmacology of prochlorperazine in healthy young males. Br J Clin Pharmac: 1991;32:677-684.) reported that the plasma pharmacokinetic parameters obtained after administration of a single oral 50 mg dose of prochlorperazine were: Cmax of 4 ng/mL , tmax of 5.4 hours and terminal half-life of 8 hours. The oral bioavailability found in the study was 12.5%.

Adverse reactions of prochlorperazine include drowsiness, dizziness, amenorrhea, blurred vision, skin reactions, hypotension and neuromuscular (extrapyramidal) reactions.

Prochlorperazine Maleate is available commercially as oral extended-release capsules, Compazine^{R}, 10 mg, 15 mg and 30 mg, and oral film-coated tablets, Compazine^{R}, 5 mg, 10 mg and 25 mg, manufactured by Smith-Kline Beecham. According to PDR, the formulations of the 5 mg and 10 mg strengths of the reference product were modified and are different from the 25 mg strength in inactive ingredients.

III. Study Details

Protocol No.	
Applicant	Trigen, Salisbury, MD
Study sites	
Investigators	

Study dates	Period 1: 4/5-8/97 Period 2: 4/19-22/97
Study design	A randomized, single-dose, two-way crossover study under fasting conditions.
Subjects	Thirty-six healthy male subjects participated in the study and 35 subjects completed the study. Subject #1 dropped out prior to Period 2 for personal reasons.

Drug products	1. Test product- Trigen's Prochlorperazine Maleate Tablets, 10 mg, Lot #TB-024, Mfg date: 3/97. 2. Reference product- SmithKline Beecham's Compazine^{R} Tablets, 10 mg, Lot #X836C67J, Exp. Date: 3/98.
Dosing	Subjects received a single, oral 20 mg dose (2 tablets) with 240 mL of water after an overnight fast.
Food and fluid	Subjects were required to fast overnight before dosing and for 4 hours thereafter. Water was not permitted for 1 hour before and 2 hours after the dose. At 2 hours post-dose, all subjects consumed 240 mL of water. Four hours after the dose, water was allowed ad lib. Standard meals were provided at 4 and approximately 10 hours after drug administration. During housing, meal plans were identical for both periods.
Housing	From 10 hours before dosing until after the 24-hour blood draw.
Washout	Two weeks.
Blood samples	Ten mL blood samples were collected in Vacutainers with EDTA at the following times: predose, 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours after dosing.
IRB	Institutional Review Board.
Informed consent	Written consent was obtained from each subject prior to entering the study.
Assay method for blood samples	
Analytes	Prochlorperazine in human plasma.
PK analysis	AUCT, AUCI, CMAX, TMAX, KE, and THALF were calculated.

Statistical analysis SAS-GLM procedures were used on AUCT, AUCI, CMAX, TMAX, KE, and THALF. The 90% confidence intervals (CI) were calculated for log-transformed AUCT, AUCI, and CMAX.

IV. Validation of Assay Method for Plasma Samples

V. In Vivo Results with Statistical Analysis

Subjects:

Thirty-six healthy male subjects participated in the study and 35 subjects completed the study. Subject #1 dropped out prior to Period 2 for personal reasons.

Protocol Deviations:

No significant protocol deviations were reported except minor sampling time deviations.

Adverse events:

Twenty subjects reported 43 adverse events, most of these were considered unrelated to the study drugs. Only two events for two subjects (dizziness and dyspepsia) were considered probably or possibly related to the study drugs.

Bioanalytical problem:

No bioanalytical problems were encountered.

Statistical Analyses:

All PK parameters were recalculated by this reviewer except the KE (elimination rate constant).

Mean plasma levels:

The mean plasma prochlorperazine profiles for the test and reference products are comparable as shown in Table V-1 and Fig P-1. Peak mean plasma levels were 1181 pg/mL at 5 hours for the test product and 1279 pg/mL at 5 hours for the reference product, respectively.

Table V-1. MEAN PLASMA PROCHLORPERAZINE LEVELS FOR TEST AND REFERENCE PRODUCTS
Unit: pg/mL; N=35
MEAN1=TEST MEAN; MEAN2=REF MEAN; RMEAN12=T/R RATIO
Test (Trigen), 10 mg, #TB-024; Reference (SKB), 10 mg, #X836C67J

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	363.14	445.86	296.53	255.92	1.22
2	658.60	549.79	609.37	487.82	1.08
3	903.43	548.80	927.60	618.67	0.97
3.5	1001.83	576.21	1007.56	605.95	0.99
4	1001.71	581.15	1043.46	619.09	0.96
4.5	1133.29	766.70	1159.91	771.46	0.98
5	1180.94	746.77	1278.94	950.36	0.92
5.5	1178.26	816.03	1245.00	844.53	0.95
6	1111.83	702.19	1186.14	783.55	0.94
6.5	1067.29	716.27	1121.69	730.48	0.95
7	999.86	698.65	1041.91	665.10	0.96
8	856.57	568.68	884.31	517.51	0.97
10	630.00	397.20	660.17	395.67	0.95
12	489.49	326.83	508.17	314.59	0.96
16	308.85	219.17	308.63	208.30	1.00
24	209.87	145.70	206.24	126.71	1.02
36	89.21	74.84	104.31	82.39	0.86
48	51.03	61.22	51.08	56.96	1.00
60	22.97	42.35	22.94	41.16	1.00
72	12.63	28.94	11.03	25.08	1.14

Pharmacokinetic parameters:

The test/reference ratios (RMEAN12) were within 0.97-1.0 range for the non-transformed and log-transformed AUCT, AUCI and CMAX as shown in Table V-2. The 90% confidence intervals for log-transformed AUCT, AUCI and CMAX are all within 80-125% range as shown in Table V-3.

There was no significant sequence or treatment effect for the log-transformed AUCT, AUCI and CMAX.

Table V-2. ARITHMETIC AND GEOMETRIC MEANS AND TEST/REFERENCE RATIOS
UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
MEAN1=TEST; MEAN2=REF; RMEAN12=T/R RATIO
Test (Trigen), 10 mg, #TB-024; Reference (SKB), 10 mg, #X836C67J

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	17848.22	10820.63	17906.10	10288.37	1.00
AUCT	16139.88	10561.11	16385.82	10146.34	0.98
CMAX	1343.71	875.69	1390.31	988.55	0.97
KE	0.05	0.01	0.05	0.01	0.98
LAUCI	15089.77	0.59	15406.20	0.56	0.98
LAUCT	13252.83	0.64	13716.84	0.62	0.97
LCMAX	1128.21	0.59	1144.87	0.62	0.99
THALF	15.13	4.71	14.66	3.54	1.03
TMAX	4.70	1.09	4.89	1.02	0.96

Table V-3. 90% CONFIDENCE INTERVALS
UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR
LSM1=TEST LSMEAN; LSM2=REF LSMEAN; RLSM12=TEST/REF RATIO
LOWCI12=LOWER 90% CI; UPPCI12=UPPER 90% CI
Test (Trigen), 10 mg, #TB-024; Reference (SKB), 10 mg, #X836C67J

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	15117.60	15384.67	0.98	90.87	106.26
LAUCT	13278.68	13695.94	0.97	88.87	105.77
LCMAX	1130.93	1143.80	0.99	89.44	109.31

Test/Reference ratios for individual subjects:

The test/reference ratios for PK parameters were calculated for individual subjects and its statistics are shown Table V-4:

TABLE V-4. STATISTICS ON THE TEST/REFERENCE RATIOS

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	35	1.01	0.27	0.25	1.72
RAUCI12	35	1.01	0.25	0.29	1.63
RCMAX12	35	1.04	0.31	0.19	1.87
RTMAX12	35	0.98	0.23	0.55	1.67
RKE12	35	0.99	0.19	0.52	1.45
RTHALF12	35	1.04	0.22	0.69	1.92

AUCT/AUCI ratios:

The AUCT/AUCI ratios for the test and reference products were calculated for individual subjects and its statistics were summarized in Table V-5:

Table V-5. Statistics on AUCT/AUCI Ratios

	N	Mean	Std Dev	Minimum	Maximum
TRT=1	35	0.88	0.07	0.67	0.96

	N	Mean	Std Dev	Minimum	Maximum
TRT=2	35	0.89	0.05	0.76	0.97

VI. Product Information

1. Formulation

Test formulations for the 5 mg and 10 mg tablets are shown in Table VI-1. Two test formulations are proportional in active and inactive ingredients. Inactive ingredients of the reference product consist of cellulose, lactose, magnesium stearate, sodium croscarmellose, starch, stearic acid, and other inactive ingredients.

Table VI-1. Test Formulations

Ingredient	5 mg Strength mg/tablet	10 mg Strength mg/tablet
Prochlorperazine Maleate	8.25	16.5
Magnesium Stearate NF		
Stearic Acid NF		
Lactose Monohydrate NF		
Microcrystalline Cellulose NF		
Pregelatinized Starch NF		
Opadry		
Total		

2. Assay and content uniformity

Table VI-2 summarizes assay and content uniformity data for the test and reference products.

Table VI-2. Assay and Content Uniformity

Product	Assay, %	Content Uniformity (%CV)
Test (Trigen), 5 mg, #TB-026	100.5	100.1 (1.9)
Reference (SKB), 5 mg, #H125C66J Exp. Date:8/1997	99.9	100.1 (1.0)
Test (Trigen), 10 mg, #TB-024	100.9	99.1 (1.2)
Reference (SKB), 10 mg, #X836C67J Exp. Date: 3/1998	98.6	98.7 (2.5)

3. Dissolution

Test and reference products met USP dissolution specifications as shown in Table VI-3. USP dissolution specifications are shown below:

Medium and Volume	0.1N HC1; 500 mL
Apparatus and rpm	2 (paddle); 75 rpm
Time	60 min
Tolerances	NLT 75% (Q)

4. Waiver Request

The applicant requested a waiver for the 5 mg tablets. Based on the acceptable *in vivo* and *in vitro* data and proportionality of formulations, the waiver for the 5 mg tablets is granted.

VII. Comments

1. Thirty-six healthy male subjects participated in the 2-way crossover single dose (2 x 10 mg tablets) study under fasting conditions and 35 subjects completed the study. Subject #1 dropped out prior to Period 2 for personal reasons. Data from the 35 subjects were used in the PK and statistical analyses.

2. The mean plasma prochlorperazine profiles for the test and reference products are comparable.

3. The test/reference ratios (RMEAN12) were within 0.97-1.0 range for the non-transformed and log-transformed AUCT, AUCI and CMAX. The 90% confidence intervals for log-transformed AUCT, AUCI and CMAX are all within 80-125% range.

4. Assay method validation: Pre-study and within-study validations are acceptable.

5. Test products (5 mg and 10 mg strengths) met the USP dissolution specifications.

6. Formulations: Two test formulations, 5 mg and 10 mg tablets, are proportional in active and inactive ingredients.

7. There was no severe medical event which required a clinical action.

8. The batch size of the bio-batch was tablets.

9. Waiver is granted for the 5 mg tablets.

VIII. Deficiency

None.

IX. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Trigen on its Prochlorperazine Maleate Tablets, 10 mg strength, lot #TB-024, comparing it to SmithKline Beecham's Compazine® Tablets, 10 mg strength, lot #X836C67J, has been found acceptable. The study demonstrates that Trigen's Prochlorperazine Maleate Tablets, 10 mg strength, is bioequivalent to the reference product, Compazine® Tablets, 10 mg strength.

2. The USP dissolution testing conducted by Trigen on its Prochlorperazine Maleate Tablets, 10 mg strength, lot #TB-024, and 5 mg strength, lot #TB-026, is acceptable. The formulation for the 5 mg strength tablets is proportionally similar to the 10 mg strength tablets of the test product which underwent an acceptable bioequivalence study (submission date: 8/5/97). The waiver of *in vivo* bioequivalence study requirements for the 5 mg strength tablets of the test product is granted. The 5 mg strength tablets of the test product are therefore deemed bioequivalent to SmithKline Beecham's Compazine®, 5 mg strength tablets.

3. The USP 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 hydrochloric acid at 37°C using USP 23 Apparatus 2 (Paddle) at 75 rpm. The test product should meet the following

specifications:

Not less than 75% of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED MMAKARY
FT INITIALED MMAKARY

Concur: _____ Date: 1/8/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

File History: Draft (1/6/98)

Table VI-3. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Prochlorperazine Maleate Tablets					
Strength	5 mg and 10 mg Tablets					
ANDA Number	40-268					
Applicant	Trigen					
Reference Drug Product	SKB's Compazine®, 5 mg and 10 mg Tablets					
II. USP Method for Dissolution Testing						
Medium and Volume	0.1N HCl; 500 mL					
Apparatus and rpm	2 (paddle); 75 rpm					
Time	60 min					
Tolerances	NLT 75% (Q)					
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No:TB-026 Strength:5 mg No of Units:12			Reference Product Lot No:H125C66J Strength:5 mg No of Units:12		
Min	Mean	Range	%CV	Mean	Range	%CV
10	105		4.1	90		10.3
20	107		3.7	99		7.5
30	107		2.4	102		5.3
45	108		2.2	104		4.1
60	107		2.2	105		3.4

Time	Test Product Lot No:TB-024 Strength:10 mg No of Units:12			Reference Product Lot No:X836C67J Strength:10 mg No of Units:12		
Min	Mean	Range	%CV	Mean	Range	%CV
10	53		27.8	66		10.3
20	99		1.8	77		6.7
30	101		1.5	81		5.8
45	101		1.4	85		6.9
60	102		1.4	90		7.5

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-268 APPLICANT: Trigen

DRUG PRODUCT: Prochlorperazine Maleate Tablets, U.S.P. 5 mg and 10 mg

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

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

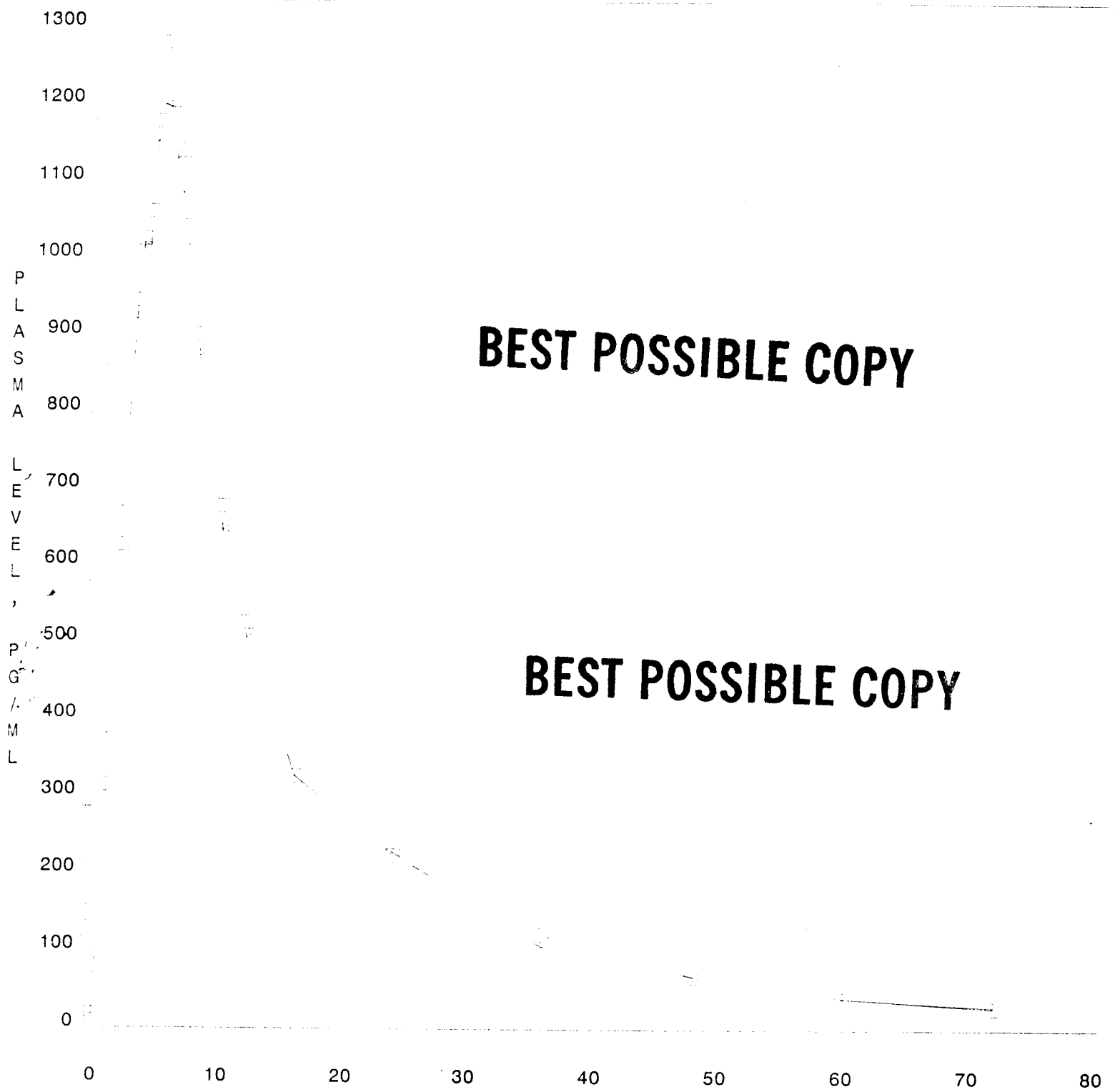
Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FIG P-1. PLASMA PROCHLORPERAZINE LEVELS

PROCHLORPERAZINE MALEATE TABLETS, 10 MG, ANDA #40-268
UNDER FASTING CONDITIONS
DOSE=2 X 10 MG



BEST POSSIBLE COPY

1=TEST(TRIGEN) 2=REF(SKB)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40268

ADMINISTRATIVE DOCUMENTS

D W

APPROVAL PACKAGE SUMMARY FOR 40-268

ANDA: 40-268

FIRM: Trigen Laboratories, Inc.

DRUG: Prochlorperazine Maleate

DOSAGE: Tablets

STRENGTH: 5 mg and 10 mg

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 1/6/98.

BIO STUDY/BIOEQUIVALENCE STATUS: Bioequivalence is satisfactory 1/8/98.

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has submitted satisfactory 3 months accelerated stability data at 40°C/75%RH and 3 months room temperature for all packaging sizes and for the bulk container.

LABELING REVIEW STATUS: Labeling is satisfactory 1/16/98.

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the master formulas for the commercial batches . The maximum will be tablets for the 5 mg and ablets for the 10 mg. Also, submitted copies of the exhibit batch lot #TB-026 for tablets for the 5 mg strength and lot #TB-024 for ablets for 10 mg strength. The firm will be using the same drug substance manufacture
The DMF is satisfactory, and same equipment and manufacturing procedure.

COMMENTS: The Application is Approvable.

2/18/98

Reviewer: Nashed E. Nashed, Ph.D. Date: 2/17/98

Supervisor: Paul Schwartz, Ph.D.

2/19/98

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APPROVAL SUMMARY

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

ANDA Number: 40-268 Date of Submission: January 7, 1998

Applicant's Name: Trigen Laboratories, Inc.

Established Name: Prochlorperazine Maleate Tablets USP, 5 mg and 10 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (100s and 1000s)
Satisfactory as of January 7, 1998 submission

Professional Package Insert Labeling:
Satisfactory as of January 7, 1998 submission

Revisions needed post-approval:

DOSAGE AND ADMINISTRATION - ADULTS (Elderly Patients)

Revise the combine the second and third sentences as follows: ...neuromuscular reactions, such patients...

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Compazine®

NDA Number: 10-571

NDA Drug Name: Prochlorperazine Maleate Tablets

NDA Firm: SmithKline Beecham

Date of Approval of NDA Insert and supplement: June 28, 1993

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: NDA 10-571

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			

Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	x		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. The USP recommends that this product be stored in tight, light-resistant containers. Are the proposed containers light resistant?

2. Trigen was telephone to clarify the process used to imprint their tablets. Apparently, the tablets are "debossed".

FOR THE RECORD:

1. Labeling review based on the insert stamped June 28, 1993 (rev. 11/92) in the folder for SmithKline Beecham's Compazine®. The insert is combined for tablet, extended-release capsules, injection, syrup, and suppositories. The last permitted date in the MIS system for this drug product is 9/30/92. Although there appears to be more current and somewhat different labeling in the marketplace, OGD based its revisions on the currently approved labeling.

   It was noted that reference to the injectable product contained in the third paragraph of the PRECAUTIONS section and the penultimate sentence of the D&A-Children (Severe N/V in Children) subsection of the innovator labeling has been retained in the labeling for the tablets. This decision was based on the approved labeling for ANDA 40-185 (Mylan) and ANDA 40-120 (Copley), containing this information. It was also included in the insert labeling for Roxane's suppository.

2. Packaging
   The RLD packages its 5 mg and 10 mg tablets in bottles of 100 and single unit packages of 100 (for institutional use only).

   The applicant is proposing to market its product in HDPE bottles of 100 and 1000. The bottles of 100 will have CRCs.

   This product is light sensitive, therefore, the chemist has been asked to verify that the proposed containers are light resistant.

3. Labeling
   The firm revised their labels so that the established name and strength does appear as the most prominent information.

Firm has differentiated their products such that the strength of the 5 mg tablet label is blocked in purple and that of the 10 mg tablet is blocked in red.

Trigen did revise to describe the scoring configuration of its products in the HOW SUPPLIED section of their insert labeling.

Trigen was telephoned for clarification on the process used to imprint its tablets. Mr. Rajan Embran indicated that the tablets are "debossed".

The labeling for the RLD does not contain a CLINICAL PHARMACOLOGY section. However, Trigen had incorporated the one used by OGD into its. It appears that in a 1983 guidance, more descriptive language was used for this section, but in 1994, it somehow was changed to the 2 sentence version included in this labeling. It is not clear whether this change was intended just for the suppositories or for all products as is currently the case.

4. USP Issues
USP - Preserve in well closed containers protected from light.
NDA - Dispense in a tight, light-resistant container.
ANDA - Dispense in a tight, light-resistant container.
Store at CRT.

5. Bioequivalence Issues - Waiver granted January 8, 1998

6. Patent/Exclusivity Issues - None

Date of Review: January 14, 1998

Date of Submission: January 7, 1998

Primary Reviewer: Date:

Team Leader: Date:

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cc: ANDA: 40-268
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
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Review