

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **40162** _____

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

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

Sponsor **Zenith Goldline Pharmaceuticals, Inc.** _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 40162

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EA/FONSI				
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40162

APPROVAL LETTER

ANDA 40-162

JAN 20 1998

Zenith Goldline Pharmaceuticals, Inc.
Attention: Jason A. Gross
140 Legrand Avenue
Northvale, NJ 07647

Dear Sir:

This is in reference to your abbreviated new drug application dated August 28, 1995, 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 July 26, 1996, September 30 and December 1, 1997, and January 6, 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 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.

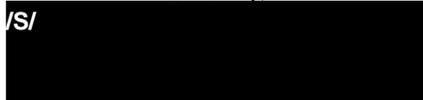
Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

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,

/s/

 1/19/98
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-162
Division File
FIELD COPY
HFD-600/Reading File
HFD-610/JPhillips
HFD-92
HFD-210/B.Poole
HFD-330/

Endorsements:

/s/ 
HFD-629/N.Nashed
HFD-629/P.Schwar
HFD-617/J.Buccin
HFD-613/L.Golson
HFD-613/J.Grace/
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1/8/98

APPROVAL

/s/

1/9/98

/s/

4/16/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40162

FINAL PRINTED LABELING

Zenith Goldline
 NDC 0172-3690-9

PROCHLORPERAZINE MALEATE TABLETS, USP

5 mg*

APPROVED

Store at controlled room temperature (59° - 86°F). Federal law prohibits dispensing without prescription. USUAL DOSAGE: 10 mg to 40 mg daily. See package insert. PHARMACIST: Dispense in a well-closed child-resistant container as defined in the USP. Use child-resistant closure when dispensing this product unless otherwise directed by the physician or requested by the purchaser. PROTECT FROM LIGHT

NDC 0172-3690-9
 Prochlorperazine maleate, USP equivalent to 5 mg prochlorperazine

Manufactured by:
 ZENITH GOLDLINE PHARMACEUTICALS, INC.
 MIAMI, FL 33137

1097K

LOT: 1172-3690-60 9
 EXP: JAN 20 1999

Zenith Goldline
 NDC 0172-3690-80

PROCHLORPERAZINE MALEATE TABLETS, USP

5 mg*

APPROVED

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NDC 0172-3690-80
 Prochlorperazine maleate, USP equivalent to 5 mg prochlorperazine

Manufactured by:
 ZENITH GOLDLINE PHARMACEUTICALS, INC.
 MIAMI, FL 33137

1097K

LOT: 0172-3690-60 9
 EXP: JAN 20 1998

Zenith Goldline
 NDC 0172-3690-70

PROCHLORPERAZINE MALEATE TABLETS, USP

5 mg*

APPROVED

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NDC 0172-3690-70
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Manufactured by:
 ZENITH GOLDLINE PHARMACEUTICALS, INC.
 MIAMI, FL 33137

1097K

LOT: 0172-3690-70 8
 EXP: JAN 20 1998

Zenith Goldline
 NDC 0172-3690-80

PROCHLORPERAZINE MALEATE TABLETS, USP

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 MIAMI, FL 33137

1097K

LOT: 0172-3690-80 7
 EXP: JAN 20 1998

Zenith Goldline

**PROCHLORPERAZINE
MALEATE
TABLETS, USP
5 mg***

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PROTECT FROM LIGHT
NDC 0172-3690-60
*Each Tablet Contains: Prochlorperazine maleate, USP equivalent to 5 mg prochlorperazine
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
MIAMI, FL 33137


N 3 0172-3690-60 9
LOT: JAN 20 1998
EXP:

Zenith Goldline

NDC 0172-3690-70

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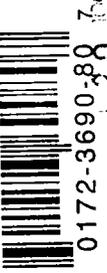

N 3 0172-3690-80 7
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Zenith Goldline

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Zenith Goldline
 NDC 0172-3690-60
PROCHLORPERAZINE MALEATE TABLETS, USP
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 N 3 0172-3690-60 9
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 Manufactured by: ZENITH GOLDLINE PHARMACEUTICALS, INC. MIAMI, FL 33137 1097K


 N 3 0172-3690-60 9
 LOT: JAN 20 1998
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Zenith Goldline
 NDC 0172-3690-70
PROCHLORPERAZINE MALEATE TABLETS, USP
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 Manufactured by: ZENITH GOLDLINE PHARMACEUTICALS, INC. MIAMI, FL 33137 1097K


 N 3 0172-3690-70 8
 LOT: JAN 20 1998
 EXP:

Zenith Goldline
 NDC 0172-3690-80
PROCHLORPERAZINE MALEATE TABLETS, USP
5 mg*

APPROVED

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 Manufactured by: ZENITH GOLDLINE PHARMACEUTICALS, INC. MIAMI, FL 33137 1097K


 N 3 0172-3690-80 7
 LOT: JAN 20 1998
 EXP:

Zenith Goldline

NDC 0172-3691-60

**PROCHLORPERAZINE
MALEATE
TABLETS, USP**

10 mg*

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

CAUTION: Federal law prohibits
dispensing without prescription.

USUAL DOSAGE: 10 mg to 40 mg daily.

See package insert for complete prescribing information.
See package insert for complete pharmacology information.
See package insert for complete contraindications and warnings information.
See package insert for complete drug interactions information.
See package insert for complete adverse reactions information.
See package insert for complete clinical studies information.
See package insert for complete how to use information.
See package insert for complete patient counseling information.
See package insert for complete USP child-resistant container information.
See package insert for complete USP child-resistant closure information.
See package insert for complete USP child-resistant cap information.
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See package insert for complete USP child-resistant cap information.

PROTECT FROM LIGHT

*Each Tablet Contains Prochlorperazine maleate, USP equivalent to 10 mg prochlorperazine

NDC 0172-3691-60

Manufactured by ZENITH GOLDLINE PHARMACEUTICALS, INC. MIAMI, FL 33137



N 3 0172-3691-60 6

LOT: JAN 20

EXP:

Zenith Goldline

NDC 0172-3691-70

**PROCHLORPERAZINE
MALEATE
TABLETS, USP**

10 mg*

500 TABLETS (Gold)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: 10 mg to 40 mg daily. See package insert.

See package insert for complete prescribing information.
See package insert for complete pharmacology information.
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PROTECT FROM LIGHT

*Each Tablet Contains Prochlorperazine maleate, USP equivalent to 10 mg prochlorperazine

NDC 0172-3691-70

Manufactured by ZENITH GOLDLINE PHARMACEUTICALS, INC. MIAMI, FL 33137



1087K



N 3 0172-3691-70 5

LOT: JAN 20

EXP:

Zenith Goldline

NDC 0172-3691-80

**PROCHLORPERAZINE
MALEATE
TABLETS, USP**

10 mg*

1000 TABLETS (Gold)

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

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PROTECT FROM LIGHT

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NDC 0172-3691-80

Manufactured by ZENITH GOLDLINE PHARMACEUTICALS, INC. MIAMI, FL 33137



1097K



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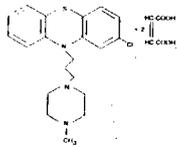
LOT: JAN 20

EXP:

PROCHLORPERAZINE MALEATE TABLETS, USP

DESCRIPTION

Prochlorperazine maleate is classified as an anti-emetic and antipsychotic agent. The chemical name of prochlorperazine maleate is 2-Chloro-10-[3-(4-methyl-1-piperazinyl)propyl] phenothiazine maleate (1:2) and it has the following structural formula:



C₂₀H₂₄ClN₃S·2C₄H₄O₄

M. W. 606.10

Prochlorperazine maleate is white or pale yellow, practically odorless, crystalline powder. It is practically 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 prochlorperazine. In addition, each tablet contains the following inactive ingredients: corn starch, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, stearic acid, talc, titanium dioxide, FD&C yellow #6 aluminum lake and D&C yellow #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 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 four-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 (anti-psychotic) 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 hyperreflexia 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 parenteral or oral dosing, place patient in head-low position with legs raised. If a vasoconstrictor is required, norepinephrine 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, gynecostasia 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 or 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.

Long-Term Therapy

Given the possibility that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that in 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, C.N.S. 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 for postprocedure.

ADVERSE REACTIONS

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

Cholestatic jaundice has occurred. If fever with gripe-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.

PROCHLORPERAZINE MALEATE TABLETS, USP



0196-01



PROCHLORPERAZINE MALEATE TABLETS, USP

0196-01

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 discontinued, it should be at a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should be stopped and not reinstated. In most cases barbiturates by suitable route of administration will suffice. (Or, injectable diphenhydramine may be useful.) In more severe cases, the administration of an antiparkinsonism 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 antiparkinsonian agents, benzodiazepines or propranolol may be helpful.

Dystonia

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 may be useful. Note: See diphenhydramine prescribing information for appropriate children's dosage.) If appropriate treatment with anti-parkinsonism agents or diphenhydramine fails to reverse the signs and symptoms, the diagnosis should be reevaluated.

Pseudo-parkinsonism

Symptoms may include: mask-like faces; 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 two or three 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 one 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, arthralgias, ejaculatory disorders, impotence, priapism, atrophic vaginitis, urinary retention, miosis and mydriasis; reactivation of coexistent processes: catarrh of the stomach; 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, gynecostasia, 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

Primary 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 antiparkinsonism drugs, barbiturates, or diphenhydramine. 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.

DOSEAGE 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. 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 two, longer treatment is usually required before maximal improvement is seen.

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 mg 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.

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 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 two 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.

More than one day's therapy is seldom necessary.

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

2. In Psychotic Children

For children 2 to 12 years, starting dosage is 2 1/2 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 gold-colored, round, film-coated, unscored tablets, debossed "3690" on one side, and "5" on the other side containing prochlorperazine maleate equivalent to 5 mg prochlorperazine packaged in bottles of 100, 500 and 1000 tablets. Prochlorperazine Maleate Tablets, USP are available as gold-colored, round, film-coated, unscored tablets, debossed "3691" on one side, and "10" on the other side containing prochlorperazine maleate equivalent to 10 mg prochlorperazine packaged in bottles of 100, 500 and 1000 tablets.

PHARMACIST: Dispense in a well-closed container as defined in the USP. Use child-resistant closure when dispensing this product unless otherwise directed by the physician or requested by the purchaser.

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

PROTECT FROM LIGHT

CAUTION: Federal law prohibits dispensing without prescription.

MANUFACTURED BY
ZENITH GOLDLINE PHARMACEUTICALS, INC.
MIAMI, FL 33137

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PROCHLORPERAZINE MALEATE TABLETS, USP



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40162

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-162

3. NAME AND ADDRESS OF APPLICANT

Zenith Laboratories, Inc.
140 Legrand Ave.
Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION

Zenith Laboratories, Inc. certifies that to the best of its knowledge the patent 2,902,484 has been expired on September 1976 and no exclusivity has been granted under the new drug provisions for the listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Prochlorperazine Maleate

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

N/A

9. AMENDMENTS AND OTHER DATES:

Original 8/28/95
Amendment 9/12/95
Amendment 9/30/97
Amendment 1/6/98

10. PHARMACOLOGICAL CATEGORY

For control of severe nausea and vomiting; for management of the manifestations of psychotic disorders.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

(b)(4)(CC)

13. DOSAGE FORM

Tablets

14. POTENCY

5, and 10 mg

15. CHEMICAL NAME AND STRUCTURE

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

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER:

DATE COMPLETED:

Nashed E. Nashed, Ph.D.

Supervisor: Paul Schwartz, Ph.D.

12/18/97

cc: ANDA 40-162
Division File
Field Copy

Endorsements:

HFD-627/NNashed

HFD-627/PSchwar

X:\NEWFIRMS\NZENITH\LTRS&REV\40-162.2

F/t by:

[Redacted]

12/18/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40162

BIOEQUIVALENCE REVIEW(S)

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # 40-162

SPONSOR : Zenith Goldline

DRUG & DOSAGE FORM : Prochlorperazine Maleate Tablets

STRENGTH (s) : 5 mg & 10 mg

TYPE OF STUDY: A single-dose, fasting BE study, Dissolution testings & a Waiver Request

CINICAL STUDY &

STATISTICAL ANALYSIS SITE: (b)(4)(CC)

ANALYTICAL SITE : (b)(4)(CC)

STUDY SUMMARY (excluding subject #28):

Parameter	test LS Means	reference (n=33)	ratio (T/R)	90% CI (%)
LNCmax (ng/ml)	1678.7	1814.5	0.92	84.3-101.5
LNAUC(0-T) ngxhr/ml	24644.2	26024.3	0.95	86.9-103.4
LNAUC(0-Inf) ngxhr/ml	26595.6	27999.0	0.95	87.6-102.9
Tmax hr	5.58	5.08	1.10	
Half-life hr	13.21	13.05	1.01	

DISSOLUTION :

Conditions: Paddle, 75 RPM, 500 mL of 0.1N HCl

Time (min)	Test Mean(range)		Ref. Mean(range)	
	5 mg	10 mg	5 mg	10 mg
10	87.4 (b)(4)(CC)	77.2 (b)(4)(CC)	76.7 (b)(4)(CC)	72.4 (b)(4)(CC)
20	95.2 (b)(4)(CC)	97.7 (b)(4)(CC)	88.3 (b)(4)(CC)	84.4 (b)(4)(CC)
30	96.5 (b)(4)(CC)	100.1 (b)(4)(CC)	93.7 (b)(4)(CC)	91.0 (b)(4)(CC)
45	97.3 (b)(4)(CC)	101.6 (b)(4)(CC)	95.2 (b)(4)(CC)	93.4 (b)(4)(CC)
60	97.6 (b)(4)(CC)	102.0 (b)(4)(CC)	95.6 (b)(4)(CC)	93.6 (b)(4)(CC)

Q = USP 23, NLT 75%(Q) in 60 min..

PRIMARY REVIEWER : Lin-Whei Chuang

BRANCH : I

INITIAL : /S/

DATE : 1/6/98

BRANCH CHIEF : Yih-Chain Huang, Ph.D.

BRANCH : I

INITIAL : /S/

DATE : 1/6/98

DIRECTOR

DIVISION OF BIOEQUIVALENCE : Dale Conner, Pharm.D.

INITIAL : /S/

DATE : 1/6/98

ANDA 40-162

2.1

7-26-96

Zenith Goldline Pharmaceuticals
Attention: Joan Janulis, R.A.C.
140 Legrand Avenue
Northvale NJ 07676
|||||

JAN 10 1997

Dear Madam:

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

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,

/s/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN - 7 1997

Prochlorperazine Maleate
Tablets, 5 mg & 10 mg
ANDA 40-162
Reviewer: L. Chuang

Zenith Goldline Pharmaceuticals
Northvale, NJ
Submission Date:
July 26, 1996

Review of an Amendment to a Bioequivalence Study, Dissolution Data and Waiver Request

Background:

The original ANDA submitted on 08/28/96 included results of a bioequivalence study, dissolution data and waiver request. Two deficiencies were found in the review completed on 02/12/96. This amendment is in response to those deficiencies.

Review:

1. *The firm did not explain why the plasma sample of subject #28 at hour 3 during treatment B (period 1) was not received at the analytical site.*

Firm's Response: The firm has a policy of separating each plasma sample into 2 aliquots and transporting them in 2 shipment to the analytical site.

However, due to technical oversight, both aliquots of sample 28-3.0-1 were transported in the first shipment which encountered analytical difficulties and resulted in assay failure.

Although the second shipment was analyzed successfully, the samples analyzed did not contain sample #28-3.0-1. Therefore the plasma sample of subject #28 at 3-hour during period 1 (treatment B) was listed as "not received at the clinical site".

Comment: The T_{max} of subject #28 during period 1 (treatment B) was 4.0 hours, which was adjacent to the missing time point (3 hours). Therefore, the estimated C_{max} may not be as accurate as other subjects'. Analysis of Variance is performed by the reviewer without the data of subject #28 from both periods. The results are presented below:

Statistical Results Excluding Subject #28				
Parameter	LS Means (Test)	LS Means (Ref.)	T/R	90% Conf. Int.
AUC _{0-t}	36023.6	37475.7	0.96	(0.889; 1.034)
AUC _{0-inf}	38106.7	39548.5	0.96	(0.895; 1.032)
C _{max}	2115.5	2333.1	0.91	(0.806; 1.007)

LNAUC _{0-t}	10.11311 (24664.2) ^a	10.16679 (26024.3) ^a	0.95 ^b	(0.869; 1.034)
LNAUC _{0-inf}	10.18850 (26595.6) ^a	10.23992 (27999.0) ^a	0.95 ^b	(0.876; 1.029)
LNC _{max}	7.42578 (1678.7) ^a	7.50357 (1814.5) ^a	0.92 ^b	(0.843; 1.015)
a = LS Geometric mean, b = ratio of LS geometric means				

The confidence intervals of AUC_{0-t}, AUC_{0-inf}, and C_{max}, both non-transformed and log-transformed, calculated without the data from subject #28 are all within the 80-125% range.

- The storage period for the study samples (b)(4)(CC) exceeded the documented period of frozen stability (b)(4)(CC)

The firm addressed this concern with an amended report. The revised method validation provided data to support the long term stability of 2 levels of QC samples for a period of (b)(4)(CC) days (b)(4)(CC)

Comment: The reported stability of (b)(4)(CC) for QC samples of (b)(4)(CC) and (b)(4)(CC) respectively, are acceptable.

Recommendation:

- The bioequivalence study conducted by Zenith Goldline Pharmaceuticals Inc. on its Prochlorperazine Maleate 10 mg tablet, Lot #ND-239, comparing it to Compazine[®] 10 mg tablet, lot #843C67J, manufactured by SmithKline Beecham, in fasting volunteers, has been found acceptable by the Division of Bioequivalence. The study demonstrated that Zenith's prochlorperazine maleate 10 mg tablet is bioequivalent to the reference listed drug, Compazine[®] 10 mg tablet manufactured by SmithKline Beecham Pharmaceuticals when administered under fasting condition.
- The dissolution tests conducted by Zenith Goldline Pharmaceuticals on its 5 mg and 10 mg tablets, lot #ND-3690-2A and #ND3691-2A (ND-247 and ND-239) respectively, have been found acceptable. 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 0.1N HCl at 37° C using USP 23 apparatus 2 (paddle) at 75 rpm. The test products should meet the following USP 23 specification:

Not less than 75% of the labeled amount of prochlorperazine maleate in the dosage form is dissolved in 60 minutes.
- The formulation information submitted by the firm indicated that Zenith's prochlorperazine maleate 5 mg and 10 mg tablets are proportionally identical in their active and inactive

ingredients. The waivers of in vivo bioequivalence study requirement for Zenith's prochlorperazine maleate 5 mg tablet is granted per 21 CFR Section 320.22(d)(2). The firm's prochlorperazine maleate 5 mg tablet is therefore deemed bioequivalent to Compazine^R 5 mg tablet manufactured by SmithKline Beecham Pharmaceuticals.

/s/ [REDACTED]

1/6/97

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

/s/ [REDACTED]

1/6/97

Concur: [REDACTED]

/s/ [REDACTED]

1/7/97

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

cc: ANDA 40-162 (original, duplicate), Chuang HFD-652 (Huang), Drug File,
Division File.

First Draft, LWC, 01/03/97, c:\wpfiles\40-162a.796
Final Pink, LWC, 01/06/97, x:\new\firmnsz\lrs&rev\40-162a.796

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40162

ADMINISTRATIVE DOCUMENTS

APPROVAL PACKAGE SUMMARY FOR 40-162

ANDA: 40-162

FIRM: Zenith Laboratories, Inc.

DRUG: Prochlorperazine Maleate

DOSAGE: Tablets

STRENGTH: 5 mg and 10 mg

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 4/30/97
^

BIO STUDY/BIOEQUIVALENCE STATUS: Bioequivalence is satisfactory 1/6/97

METHODS VALIDATION: The method validation is satisfactory 10/7/96

STABILITY: The firm has provided three months accelerated stability data at 40 °C/75RH and 6 months room temperature data (25-30°C) for lots ND-239 and ND-247.

LABELING REVIEW STATUS: Labeling is satisfactory 12/11/97

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has submitted copies of executed batch records for prochlorperazine maleate tablets USP, 5 mg; Batch #ND 247 (b)(4)(CC) tablet batch size) and Batch #ND 239 (b)(4)(CC) tablet batch size)for 10 mg.

The firm has provided copies of the master formula for maximum intended batch size. The firm will be using same drug substance manufacture (b)(4)(CC) same manufacturing procedure and equipment.

COMMENTS: The Application is Approvable.

REVIEWER: Nashed E. Nashed, Ph.D. /S/

12/18/97
DATE: 12/18/97

SUPERVISOR: Paul Schwartz, Ph.D. /S/ 12/18/97
X:\NEWFIRMS\NZZENITH\LTRS&REV\40-162.SUM