CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40246

APPROVAL LETTER

ANDA 40-246

JUN 28 2000

Paddock Laboratories, Inc.
Attention: Carol Anding
3940 Quebec Avenue North
Minneapolis, MN 55427

Dear Madam:

This is in reference to your abbreviated new drug application dated February 6, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Compro™ (Prochlorperazine Suppositories USP, 25 mg).

Reference is also made to your amendments dated December 23, 1997; May 12, 1998; and March 1, May 17, and June 6, 2000.

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 Compro™ Suppositories (Prochlorperazine Suppositories USP, 25 mg) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Compazine® Suppositories, 25 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 section 506A of the Act, 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 and 314.98. 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 that 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

for 6/28/00

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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DRAFT FINAL PRINTED LABELING

PRESCRIBING INFORMATION

COMPRO™
PROCHLORPERAZINE SUPPOSITORIES USP, 25mg

Rx only

ANTIEMETIC - TRANQUILIZER

1241140

JUN 28 2000

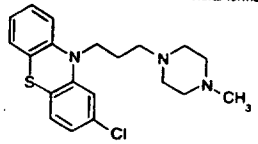
APPROVED

DESCRIPTION

Prochlorperazine is a clear, pale yellow, viscous liquid. It is sensitive to light, very slightly soluble in water, freely soluble in alcohol, in chloroform, and in ether.

Each suppository, for rectal administration, contains 25 mg of prochlorperazine; with glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated coconut oil fatty acids and hydrogenated palm kernel oil fatty acids.

Prochlorperazine has the molecular formula $C_{20}H_{24}ClN_3S$. Its molecular weight is 373.95. The chemical name for prochlorperazine is 2-Chloro-10-[3-(4-methyl-1-piperazinyl)propyl] phenothiazine. The structural formula is:



CLINICAL PHARMACOLOGY

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

INDICATIONS AND USAGE

Prochlorperazine 25 mg suppositories are indicated in the control of severe nausea and vomiting in adults.

CONTRAINDICATIONS

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

Do not use in pediatric surgery.

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

WARNINGS

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

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

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process.

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

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

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

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

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

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

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

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

General: 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 judgement 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 parenteral or oral dosing, place patient in head-low position with legs raised. If a vasoconstrictor is required, norepinephrine bitartrate and phenylephrine hydrochloride are suitable. Other pressor agents, including epinephrine, should not be used because they may cause a paradoxical further lowering of blood pressure.

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

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

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

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

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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 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.

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

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

There is no known effective treatment for tardive dyskinesia; anti-parkinsonism agents do not alleviate the symptoms of this syndrome. It is suggested that all 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 the 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. See prescribing information for these products. Care should be taken to avoid increasing respiratory depression.

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

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

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

Limited experience indicates that phenothiazines are *not* dialyzable.

DOSAGE AND ADMINISTRATION

Adults: 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.

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

Rectal Dosage: 25 mg twice daily.

HOW SUPPLIED

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.

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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 the 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. See prescribing information for these products. Care should be taken to avoid increasing respiratory depression.

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

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

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

Limited experience indicates that phenothiazines are *not* dialyzable.

DOSAGE AND ADMINISTRATION

Adults: 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.

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

Rectal Dosage: 25 mg twice daily.

HOW SUPPLIED

Compro™ Prochlorperazine Suppositories USP, 25 mg (for adults) are easy to open, and available in boxes of 12.

12's - NDC 0574-7226-12

Store between 15°and 30°C (59° and 86°F).

Do not remove from wrapper until ready to use.

Manufactured by:

Paddock Laboratories, Inc.
Minneapolis, MN 55427

Paddock Laboratories, Inc.

124140 (06-99)

COMPRO™
Prochlorperazine Suppository USP, 25 mg
Paddock Laboratories, Inc.
Minneapolis, MN 55427
NOT FOR CHILDREN

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COMPRO™

APPROVED JUN 28 2000

RC 28/06/99 Commessa 1561 Ordine C99158
Pantone 320C

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RC 28/06/99 Commessa 1561 Ordine C99158
Pantone 320C

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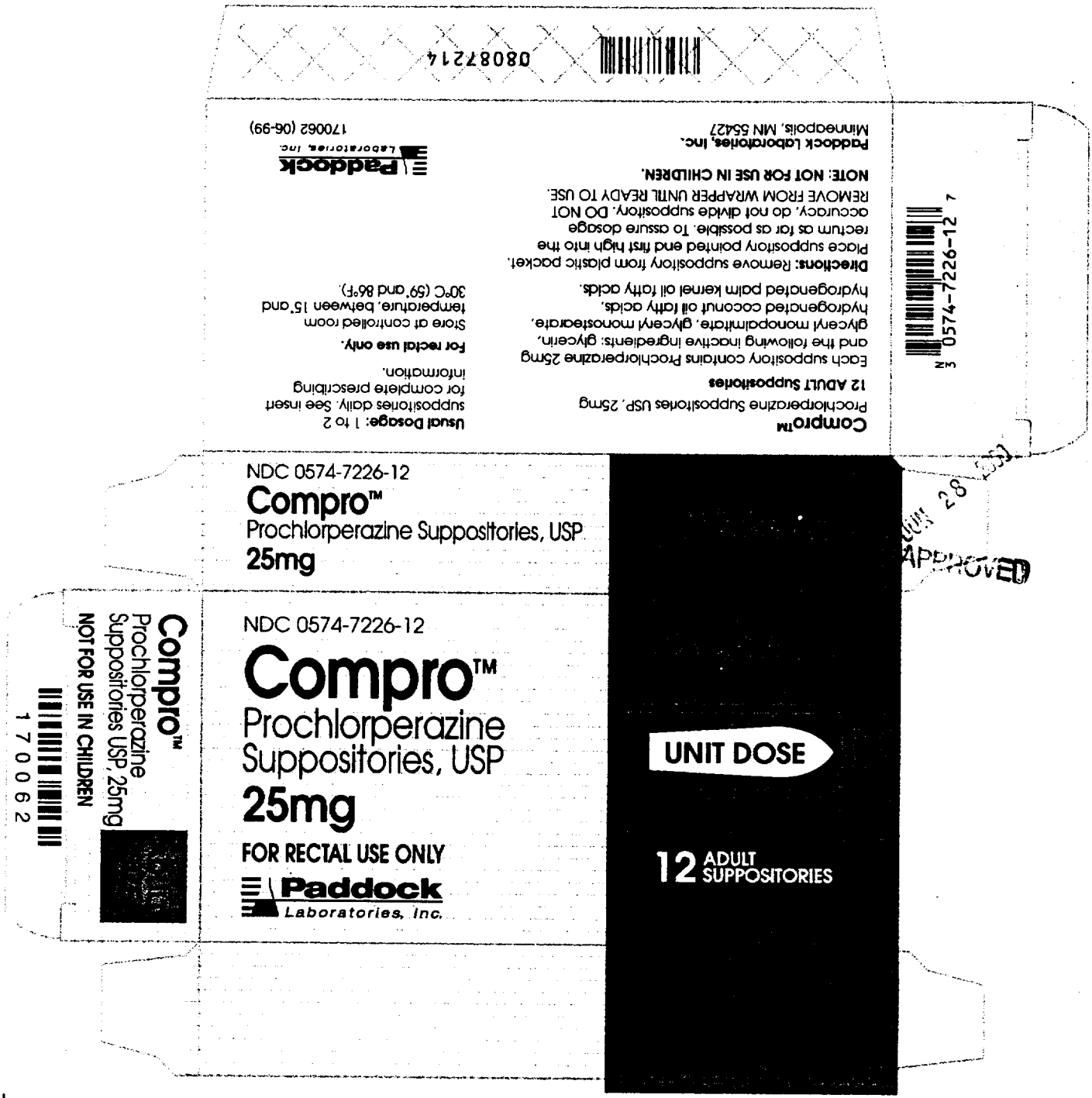
170062(06-99).80872 Paddock Proof A 6/23/99 BO
Proof C 7/15/99.G
Black Pms 320



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40246

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 40-246

DRUG PRODUCT: Prochlorperazine Suppositories, USP 25 mg

FIRM: Paddock Laboratories, Inc.

DOSAGE FORM: Suppositories **STRENGTH:** 25 mg

CGMP: Statement/EIR Update Status:

The EER is acceptable (OC recommendation, 6/21/00).

BIO: The bioequivalence study was evaluated to be acceptable by the Division of Bioequivalence, Office of Generic Drugs (5/21/98, Bio reviewer: P. Sathe).

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
The drug substance and the drug product are included in the USP monographs. Method validation is not required.

STABILITY: (Are containers used in study identical to those in container section?)
The laminated suppository film used in the stability study is identical to one described in the container section.

LABELING:

Container, carton and insert labeling have been found satisfactory (Labeling approval summary 6/16/00, reviewed by Debra M Catterson)

STERILIZATION VALIDATION (IF APPLICABLE):

Sterilization validation is not required.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Executed batch sizes:
kg units)
DMF Prochlorperazine USP drug substance was found to be adequate (reviewed by Liang-Lii Huang, Ph.D. 4/13/00).

SIZE OF STABILITY BATCHES- (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The exhibit batches were the stability batches.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

Proposed production batch sizes:
kg of the Prochlorperazine Suppositories, USP 25 mg

The manufacturing process will be the same as was used for the exhibit batch.

CHEMIST: Liang-Lii Huang, Ph.D /S/ 6/22/00 **DATE**: June 21, 2000
SUPERVISOR: Paul Schwartz, Ph.D. For, GK 6/22/00 **DATE**: June 21, 2000

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER

4 (four)

2. ANDA NUMBER

40-246

3. NAME AND ADDRESS OF APPLICANT

Paddock Laboratories, Inc.
Attention: Carol Anding
3940 Quebec Avenue North
Minneapolis, MN 55427

4. LEGAL BASIS for ANDA SUBMISSION

The applicant has certified that the list drug products referred to in the application are not covered by any patents and exclusivity provisions. The reference listed drug is Compazine® manufactured by SmithKline Beecham Pharmaceuticals.

5. SUPPLEMENT(s)

None.

6. NAME OF DRUG

None.

7. NONPROPRIETARY NAME

Prochlorperazine Suppositories

8. SUPPLEMENT(s) PROVIDE(s) FOR

None.

9. AMENDMENTS AND OTHER DATES

02/06/97	Original submission
02/13/98	Major amendment
12/04/98	Major amendment
03/01/00	Minor amendment
05/17/00	Amendment (withdrawal of Trade name)
06/06/00	Correspondence (reinstate Trade name "Compro")

10. PHARMACOLOGICAL CATEGORY

Anti-emetic, antipsychotic

11. HOW DISPENSED

Prescription (℞)

12. RELATED DMF(s)

Product	Holder	DMF (type)	LOA letter
Prochlorperazine USP			v1.2, p90
Laminated film			v1.2, p315

13. DOSAGE FORM

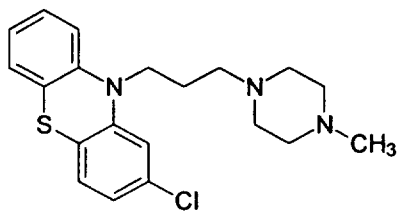
Suppositories

14. POTENCY

25 mg

15. CHEMICAL NAME AND STRUCTURE

Prochlorperazine. 10*H*-Phenothiazine, 2-Chloro-10-[3-(4-methyl-1-piperazinyl)-propyl]-. $C_{20}H_{24}ClN_3S$. 373.95. 58-38-8. USP 23, page 1301.



16. RECORDS AND REPORTS

None.

17. COMMENTS

The application is approvable.

May 17, 2000 Paddock Labs' amendment was to request for the withdrawal of the trade name.

June 6, 2000 Paddock Labs sent OGD a new correspondence to reinstate the trade name "Compro".

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER AND DATE COMPLETED

Liang-Lii Huang, Ph.D. June 20, 2000

Endorsed by Paul Schwartz, Ph.D. June 20, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40246

BIOEQUIVALENCY REVIEW(S)

JUN 25 1997

Prochlorperazine
25 mg Suppository
ANDA 40-246
Reviewer: Pradeep M. Sathe, Ph.D.
WP #40246SD.297

Paddock Laboratories Inc.
Minneapolis, MN-55427
Submission Date:
February 6, 1997

REVIEW OF A BIO-STUDY AND DISSOLUTION

I.INTRODUCTION : Prochlorperazine, chemical name 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10H-phenothiazine, molecular formula $C_{20}H_{24}ClN_3S$, molecular weight 373.94, obtained as minute crystals, is slightly soluble in water, methanol or ethanol. Though a phenothiazine, it has questionable utility as an antipsychotic agent with frequent occurrences of acute extrapyramidal reactions. It is therefore indicated primarily in the control of severe nausea and vomiting as opposed to the management of the manifestations of psychotic disorders. Phenothiazines are highly bound in the blood, metabolized by the liver and eliminated primarily by the renal route.

II.CURRENT SUBMISSION : The current application consists of a single dose bio-equivalency study comparing 25 mg test (Paddock) and 25 mg reference (SmithKline Beecham's Compazine^R) suppository formulations, and dissolution testing methodology and data comparing the test and the reference formulations.

The orange book lists SmithKline Beecham's Compazine^R as the reference product for Prochorperazine rectal suppository formulation. Besides the innovator, there is a generic formulation on the market, implying if approved this will not be the first generic formulation.

III.TEST FORMULATION : The test formulation composition is given in Table 1. Prochlorperazine is the active ingredient which is dispersed in the hydrogenated vegetable oil and glycerine base. The average suppository size is approximately 2 grams. The production batch size will be around kgs, corresponding to approximately units/batch.

Table 1

Ingredients	% W/W	Amount/Batch	mg/dose
Glycerine, USP	0.5	1.5 kg	10.0 mg
Prochlorperazine, USP*		kg	mg
Hydrogenated Vegetable Oil,		kg	mg
Hydrogenated Vegetable Oil,		kg	mg

* represents a 3% overage.

IV.BIO-STUDY NUMBER 167-01-10293, BIOEQUIVALENCE STUDY:

A. TITLE : Bioavailability of Prochlorperazine suppositories, 25 mg.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY :

1. Principal Investigator:

2. Bio-Study Site:

3. Project Director:

4. Clinical Study Dates: Group 1 (subject 1-16), Period I, August 2-5, 1996
Gruop 1 (subject 1-16), Period II, August 16-19, 1996

Group 2 (subject 17-30), Period I, August 13-16, 1996
Gruop 2 (subject 17-30), Period II, August 27-30, 1996

Group 3 (subject 31-42), Period I, August 27-30, 1996
Gruop 3 (subject 31-42), Period II, September 10-13, 1996

C. STUDY OBJECTIVE: To compare the bioavailability of paddocks's prochlorperazine suppository formulation, 25 mg, to that of a marketed reference formulation, prochlorperazine suppository, 25 mg (Compazine^{R}), manufactured by SmithKline Beecham pharmaceuticals.

D. STUDY DESIGN AND NUMBER OF SUBJECTS: This was a two treatment, crossover design in forty-two healthy male subjects. The subjects were dosed in three groups. There was a two-week washout period between the two dosing occasions. Forty-two subjects entered the study. Thirty-five subjects completed the study, however there was sufficient data for pharmacokinetic and statistical analysis for only thirty-two subjects. Out of the forty-two, seven subjects failed to complete the study. Three subjects, (#6, #30 and #41) failed to return to the clinical facility for period II for personal reasons. Two subjects (subject #5 and #11) failed to return because of adverse events experienced after completing period I. One subject, (Subject #1), withdrew after period II dosing for personal reasons. One person (Subject #39) was withdrawn after period II dosing because he had a bowel movement within nine hours of dosing.

E. SUBJECT SELECTION CRITERIA: Volunteers were selected for the study, if they met the following:

1. Male, healthy 18-50 years of age.
2. No more than $\pm$ 15% from ideal weight for his height as defined by the Metropolitan life insurance company statistical bulletin 1983.
3. Without a history of perirectal disease or proctitis, glaucoma, urinary retention, seizures, neurological diseases, asthma, serious cardiovascular, hepatic, renal, hematopoietic or gastrointestinal or ongoing infectious diseases, alcohol or drug abuse, as evidenced by a medical history and physical examination within 30 days prior to the start of the study. The physical exam included a (visual) rectal examination for evidence of hemorrhoids, rectal fissures, tears or other pathology. Deviations were acceptable if deemed not clinically significant by the investigator.
4. Blood chemistry (including alkaline phosphatase, glucose, AST, ALT, LDH, BUN, GGT, creatinine, bilirubin), hematology (including hematocrit, hemoglobin, red blood cell count, white blood cell count, differential, platelet count) and urinalysis values within clinically acceptable limits upon evaluation by the investigator. The above tests were performed within 30 days prior to the start of the study.
5. No known allergy to prochlorperazine, neuroleptics, or to benztropine mesylate.
6. No recent experience of flu-like symptoms.
7. No prescription drugs within 14 days, or OTC medications (excluding aspirin, acetaminophen, ibuprofen, vitamins, medicated lozenges, dietary supplements, and non-ingested medications) within 7 days of the first drug administration.

8. No alcohol consumption for at least 48 hours prior to drug administration each period.
9. Subjects with a minimum screening and/or check-in blood pressure of at least 100/60 mm Hg.
10. Acceptable electrocardiogram: sinus rhythm with no evidence of AV heart block within 30 days of study start date.
11. No caffeine for at least 12 hours prior to drug administration, each period.
12. Negative HIV 1, hepatitis B surface antigen, and urine screen for drugs of abuse within 30 days prior to the start of the study.

F. SUBJECT RESTRICTIONS: The firm has reported the restrictions under the title 'subject control'. The restrictions were as follows:

1. Subjects were housed at least 12 hours before until 48 hours after drug administration each period.
2. No smoking from 1 hour prior until 4 hours after dosing.
3. Fasting from at least 10 hours prior to until 6 hours after drug administration.
4. Only xanthine-free (including caffeine-free) foods and beverages were provided.

G. STUDY SCHEDULES:

1. **Methods**: One 25 mg prochlorperazine suppository was administered rectally to each participating subject, according to the randomization schedule. The dosing occurred at two minute intervals and began at 0800 hours for groups 1 and 2 and at 0828 for group 3. The subjects were required to drink 240 ml of hot water 10 hours and 2 hours prior to dosing. They were then required to attempt a bowel movement. Following insertion of suppository, subjects remained lying on their left side for three hours. Any subject defecating within nine hours following dosing was withdrawn from the study. The subjects were not permitted to smoke for 1 hour before dosing until 4 hours following drug administration, or within 1 hour prior to any blood pressure measurement. Subjects fasted for no fewer than 10 hours prior to dosing and 6 hours after administration of study drug. A standardized menu was served to all study subjects for both study periods. Water was allowed ad lib except from 2 hours before until 4 hours after drug administration.

2. **Randomization Schedule**:

Treatment		
Phase I	Phase II	Volunteer Number
A	B	1, 3, 5, 8, 10, 11, 13, 16, 17, 20, 21, 23, 25, 28, 29, 32, 34, 36, 38, 40, 41
B	A	2, 4, 6, 7, 9, 12, 14, 15, 18, 19, 22, 24, 26, 27, 30, 31, 33, 35, 37, 39, 42

3. **Blood Sample Scheme**: Venous blood samples (2*7ml) were collected in Vacutainers containing EDTA anticoagulant at 0 (pre-dose) and at 0.5, 1.5, 2.5, 3.5, 4.5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 36, 48 and 60 hours post-dose. A total of 18 samples were collected. Plasma samples were separated and stored at -20 C until analysis. An extra 7 ml blood was obtained before dosing each period for screening.

H. DRUG TREATMENTS:

1. TEST PRODUCT, TREATMENT A : Prochlorperazine suppository, 25mg (Paddock Labs.), Lot #6C935, Assay Potency= %, Batch Size= units, Expiry date: 2/98

2. REFERENCE PRODUCT, TREATMENT B : Prochlorperazine (Compazine^{R}) suppository, 25mg (SmithKline Beecham), Lot #4259, Assay Potency=Not Seen, Expiry date: 9/97

I. ASSAY METHODOLOGY :

4.**Analytical Validation** : For the analytical validation following details were observed:

J. PHARMACOKINETICS AND STATISTICS: The following pharmacokinetic parameters were calculated: AUCt, area under the curve until the last detectable sample point, AUCinf, area under the curve until the infinite time, Cmax, maximum observed plasma concentration, Tmax, time of the maximum observed concentration, $T_{1/2}$ or half-life of elimination and Kel rate of elimination. Additionally the firm has also reported

the parameter (Cmax/AUCinf). The calculated pharmacokinetic parameters were analyzed using analysis of variance (ANOVA). The ANOVA was conducted on the untransformed and log transformed parameters. Bioequivalence was assessed using the two one sided tests criterion. As mentioned in the 'STUDY DESIGN AND NUMBER OF SUBJECTS' section, thirty-five subjects completed the clinical portion of the study. All plasma samples from the subjects who completed the study were analyzed. Three subjects were excluded from the data due to excessive number of missing values-any subject with three adjacent missing values were excluded. The data from thirty-two subjects were included in the statistical analysis of prochlorperazine. Regarding the missing sample values the firm has stated the following "There were numerous (43 in a matrics of 1260 data points: 3.4%) missing values in the plasma concentration versus time data set. A relatively large volume of plasma was required for prochlorperazine assay (2 ml), and for many samples that required reanalysis, sufficient sample volume was not available. Thus no analytical valid results were obtained for these samples. This was more common for groups one and two. When group three was dosed, the phlebotomists were made more aware of the need to recover as much plasma as possible from the blood samples. Absence of multiple samples from the plasma concentration time profile for several of the subjects resulted in incomplete pharmacokinetic profiles for reliable estimation of AUC and Cmax parameters. To obtain reliable estimates of AUC and Cmax parameters, data from any subject with at least three sequential missing concentration values was excluded from the pharmacokinetic and statistical analysis. There were three subjects (#18, #19 and #25) that were excluded using this criterion. Thirty-two subjects were included in the statistical analysis."

K. RESULTS OF THE BIOEQUIVALENCE STUDY: Table BS 1.1 gives the mean plasma concentration time data for both the test and the reference formulations. Table BS 1.2 lists the relevant mean pharmacokinetic parameters and the 90% confidence intervals of the mean parameter differences. Figure 1 gives the mean plasma concentration time profiles of the two treatments. In the tables, the plasma concentrations including maximum observed concentration Cmax, are expressed as ng/ml, area under the curve AUC as ng/ml*hr, time of maximum concentration Tmax and half-life $T_{1/2}$ as hours.

Table BS1.1: Mean plasma prochlorperazine levels, ng/ml, with (Standard Deviations) of the treatments

Time (hour)	#Sub	Test (Paddock)	Reference (SmithKline Beecham)	Test/Ref. Ratio
0.0	30	0.00	0.00	---------
0.5	31	0.00 (0.00)	0.00 (0.00)	---------
1.5	32	0.075 (0.16)	0.106 (0.18)	0.70
2.5	32	0.308 (0.38)	0.259 (0.31)	1.19
3.5	32	0.941 (0.84)	0.869 (0.85)	1.08
4.5	32	1.469 (1.26)	1.489 (1.34)	0.99
6.0	32	2.000 (1.72)	2.032 (1.82)	0.98
7.0	32	2.570 (1.91)	2.614 (2.08)	0.98
8.0	32	2.870 (2.06)	2.686 (2.13)	1.07
9.0	31	2.928 (2.06)	2.932 (2.25)	1.00
10.0	32	3.118 (2.15)	3.033 (2.28)	1.03
11.0	32	3.115 (2.08)	3.182 (2.35)	0.98
12.0	32	2.983 (2.15)	2.978 (2.28)	1.00
16.0	32	2.184 (1.65)	2.305 (1.92)	0.95
24.0	31	1.675 (1.45)	1.688 (1.52)	0.99
36.0	32	0.737 (0.71)	0.757 (0.72)	0.97
48.0	31	0.400 (0.42)	0.435 (0.46)	0.92
60.0	28	0.188 (0.27)	0.196 (0.26)	0.96

Table BS 1.2: LSMEAN pharmacokinetic parameters with standard errors in parentheses and the relevant statistics, N=32, units: AUC, ng/ml*hr, Cmax, ng/ml, Tmax, hr

Parameter	Test (Paddock)	Reference (SmithKline Beecham)	Test/Reference Ratio	90% Confidence Interval
$AUC_{(0-t)}$	70.51 (4.59)	72.79 (4.59)	0.97	0.82-1.12
Ln $AUC_{(0-t)}$, Geometric*	3.95 (0.07), 51.82*	3.90 (0.07), 49.32*	1.05*	0.89-1.24
$AUC_{(0-inf)}$	77.72 (4.87)	80.82 (4.87)	0.96	0.82-1.11
Ln $AUC_{(0-inf)}$, Geometric*	4.099 (0.06), 60.34*	4.092 (0.06), 59.85*	1.01*	0.87-1.17
Cmax	3.483 (0.16)	3.452 (0.16)	1.01	0.90-1.12
LnCmax, Geometric*	1.047 (0.054), 2.849*	0.978 (0.054), 2.659*	1.07*	0.94-1.22
Tmax	9.86 (0.315)	9.897 (0.315)	1.00	----------
Half-Life	12.81 (0.52)	13.18 (0.52)	0.97	----------

L. ADVERSE EFFECTS : 16 subjects reported 32 adverse events. 22 were mild in severity, 8 moderate and 2 severe. The most frequently reported events were agitation (6 subjects, 6 events) and restlessness (6 subjects, 7 events). Two events (subjects #5 and #11) were serious and resulted in hospitalization and subsequent withdrawal from the study. Subject #5 was hospitalized for feeling of depression, 4 days after discharge from Period 1 of the study. Subject #11 was hospitalized 5 days after discharge from Period 1 of the study with complaints for chest pain. The subject was diagnosed with acute inferior myocardial infarction with positive isozyme and electrocardiogram changes.

M. COMMENTS:

1. From tables BS 1.1 and BS 1.2, it could be seen that the mean plasma levels, and their standard deviations as well as mean pharmacokinetic parameters and their standard errors are comparable across the two formulations. The 90% confidence intervals of the mean parameters differences are within the regulatory limits of 80-125%, suggesting the possibility of bioequivalence of the two formulations. The mean AUCt's are more than

90% of the mean AUCinf, indicating adequacy of the blood sample scheme. The mean Cmax and half-lives are comparable.

2. It is not clear why a mean of only 30 subjects was reported for the zero hour draw.

3. The arithmetic means are substantially different than the geometric means.

4. The plasma level coefficients of variations are rather high (invariably more than %), suggesting a rather high inter-subject variability. The reported intra-subject variability is also substantial, more than % for the extent of absorption.

5. The firm has not reported the long term analytical assay stability data.

V.DISSOLUTION METHODOLOGY : USP 23 does not recommend dissolution testing under the Prochlorperazine suppositories monograph. The firm has conducted the comparative dissolution of the test and reference formulations. The firm has not stated the dissolution testing method for the comparative dissolution testing. The dissolution testing method used for the stability studies is as follows:

Apparatus: USP 23 Apparatus II (paddle)
Speed: 50 rpm
Medium: 0.1 N HCl
Volume: 900 ml

Firm's proposed dissolution specifications are,

'Q': Not less than % dissolved in 60 minutes.

A. RESULTS OF THE DISSOLUTION TESTING : The mean dissolution testing data and results are given in table D1.

B. COMMENTS ABOUT THE DISSOLUTION TESTING :

1. Based on the firm's proposed dissolution method and reported mean data, the two formulations appear to release more than % drug in 60 minutes. The mean data however indicates that the Paddock formulation release in slower than the innovator formulation after 15 minutes. The test formulation release also appears to be relatively incomplete (mean release %) in 60 minutes compared to the innovator (Mean release %).

2. The dissolution has not been conducted using FDA recommended method. The FDA recommended method is outlined in the 'DEFICIENCIES' section.

VI. DEFICIENCIES:

1. The firm had used its own proposed dissolution method and even using that method it had not provided the individual unit dissolution data for the test formulation. The comparative dissolution data for the test and the reference formulations should be provided using the following FDA recommended dissolution method. The dissolution data should be reported for at least 12 units. The data should be reported as the mean, dissolution range (minimum-maximum) and %CV with respect to each sample point.

Apparatus: USP 23 apparatus II (paddle)
Rotation Speed: 50 rpm
Medium: 900 mL Deaerated Water
Recommended 'Q': Not less than % dissolved in 45 minutes.

2. A diskette in ASCII format containing pharmacokinetic data and the model codes used in statistical analyses should be submitted. For each study, two separate files should be configured as follows:

(a) subj seq trt per AUC_{0-t} AUC_{inf} (Where applicable) C_{max} T_{max} K_{el} and $t_{1/2}$;...

(b) subj seq per trt C_1 C_2 C_3.....C_n,

where C is the concentration at various sampling times. Fields should be delimited by one blank space and each missing value should be denoted by a period (.).

3. The assay potencies of both the test as well as reference formulations should be provided.

4. The firm needs to document the long term stability of the study samples for a duration of at least 60 days to cover the study, shipping and analysis. In future, the freeze thaw cycle stability should be studied after 3 freeze thaw cycles as against only 2 cycles as has been done for the study. From the data it appears that QC sample concentrations are ng/ml, ng/ml, ng/ml and ng/ml. Please clarify why they are not consistent for all tests e.g. stability tests (2 freeze-thaw, 24 hr and autosampler).

5. It is not clear why the mean of only 30 subjects was reported for the zero hour draw. It is unclear why plasma samples may not be sufficient for the zero hour screen. Please clarify. The arithmetic and geometric means of the treatments are considerably different. Please comment on the cause.

6. The protocol should state the 'Exclusion Criteria' used in the conduct of the study. Also, the 'Subject Control' section of the protocol does not mention, non-consumption of alcohol or alcoholic beverages during the study. Were these allowed? Please explain.

7. On page 32, the protocol says that Group 2 comprised of study subjects 17-20. The actual statistical analysis shows Group II comprising of subjects 17-30. Please clarify.

VII.RECOMMENDATIONS:

1. The bioequivalence study conducted by Paddock laboratories on its Prochlorperazine, 25 mg suppository, lot #6C935 comparing it to SmithKline Beecham's Compazine, 25 mg suppository, lot #4259 has been found incomplete by the Division of Bioequivalence. The firm should submit additional information as outlined in Deficiencies 1-7.

2. The dissolution testing conducted by Paddock laboratories on its Prochlorperazine 25 mg suppository, lot #6C935, is not acceptable. The firm is advised to conduct dissolution testing on 12 individual dosage units of the test and reference product employing the FDA recommended dissolution method which is outlined in Deficiency 1.

3. Deficiencies 1-7 should be forwarded to the firm.

/S/

6/17/97

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG /S/ 6/20/97
FT INITIALED BY YCHUANG

Concur: /S/ Date: 6/25/97
for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 40-246 (original, duplicate), HFD-650 (Director), HFD-652 (Huang, Sathe), Division File, Drug File.

Table D1. In-Vitro Dissolution Testing

Drug (Generic Name): Prochlorperazine Suppository
Dose Strength: 25 mg
ANDA Number: 40-246
Firm: Paddock Laboratories
Submission Date: 2/6/97

I. Conditions for Dissolution Testing: Not reported for comparative testing

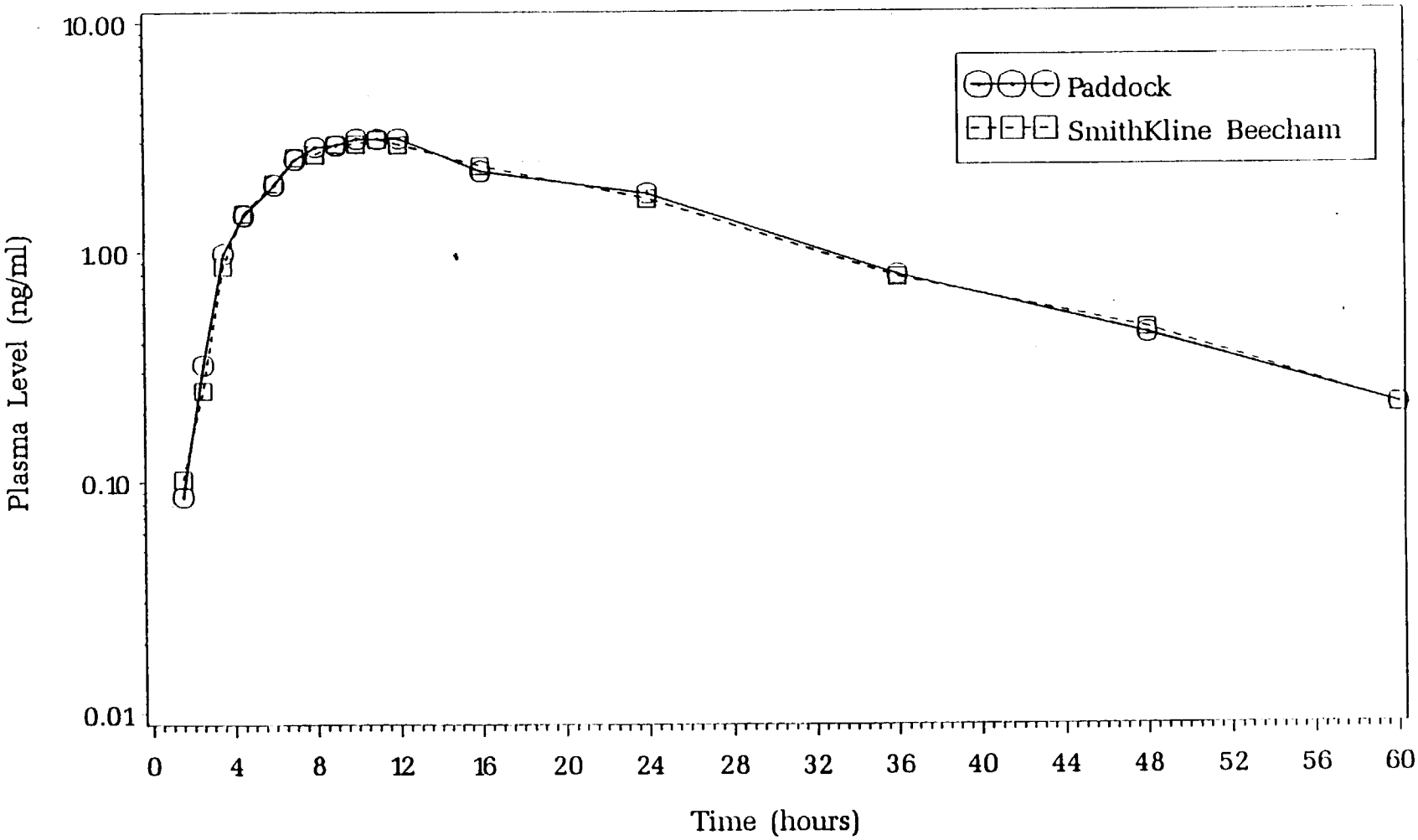
II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Prochlorperazine suppository, Lot # 6C935 Strength (25 mg)			Reference Product: Compazine suppository, Lot # 4259 Strength (25 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
0	0		------	0		------
15	36.3		------	35.8		13.3
30	58.5		-------	70.1		6.5
45	73.2		------	86.6		4.8
60	84.5		------	96.7		4.2

Figure 2: Mean Prochlorperazir. lasma Levels (Semi–log Scale)

#167–01–10293

N = 35



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-246 APPLICANT:Paddock Laboratories Inc.

DRUG PRODUCT:Prochlorperazine Suppository, 25 mg

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

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

> The dissolution testing should be conducted in 900 mL of ,0.1N HCl, using USP Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

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,

/S/

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 40-246 SPONSOR : Paddock Labs
DRUG & DOSAGE FORM : Prochloperazine Suppository
STRENGTH (s) : 25 mg
TYPE OF STUDY: SD XX Dissolution XX
STUDY SITE: CLINICAL : PharmaKinetics Labs, Baltimore, MD
ANALYTICAL : PharmaKinetics Labs, Baltimore, MD

SUMMARY :

Bio-study results are acceptable. Dissolution is acceptable. Application is acceptable.

PRIMARY REVIEWER :Pradeep M. Sathe, Ph.D. BRANCH : I

INITIAL : _____ DATE : 5/15/98

Team Leader : Yi-Chain Huang, Ph.D. BRANCH : I

INITIAL : _____ DATE : 5/15/98

DIRECTOR : Dale Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL : _____ DATE : 5/21/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

Prochlorperazine
25 mg Suppository
ANDA 40-246
Reviewer: Pradeep M. Sathe, Ph.D.
WP #40246SD.D97

Paddock Laboratories Inc.
Minneapolis, MN-55427
Submission Date:
December 23, 1997

REVIEW OF AN AMENDMENT

I.INTRODUCTION: Prochlorperazine, chemical name 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10H-phenothiazine, molecular formula $C_{20}H_{24}ClN_3S$, molecular weight 373.94, obtained as minute crystals, is slightly soluble in water, methanol or ethanol. Though a phenothiazine, it has questionable utility as an antipsychotic agent with frequent occurrences of acute extrapyramidal reactions. It is therefore indicated primarily in the control of severe nausea and vomiting as opposed to the management of the manifestations of psychotic disorders. Phenothiazines are highly bound in the blood, metabolized by the liver and eliminated primarily by the renal route.

II.BACKGROUND: The firm had submitted an application on February 6, 1997. The application consisted of a single dose bioequivalence and dissolution testing studies on the 25 mg test and reference (SmithKline Beecham's Compazine^R) formulations. The application was reviewed by the Division on June 25, 1997 and was found deficient. In a letter dated June 30, 1997, the firm was appraised of the deficiencies.

III.THE AMENDMENT: The current application consists of the firm's response to the Division cited deficiencies. The review is formatted in the order of Deficiency, Firm's Response and Division Comment.

Deficiency 1:

The firm had used its own proposed dissolution method and even using that method it had not provided the individual unit dissolution data for the test formulation. The comparative dissolution data for the test and the reference formulations should be provided using the following FDA recommended dissolution method. The dissolution data should be reported for at least 12 units. The data should be reported as the mean, dissolution range (minimum-maximum) and %CV with respect to each sample point.

Apparatus: USP 23 apparatus II (paddle)
Rotation Speed: 50 rpm
Medium: 900 mL Deaerated Water
Recommended 'Q': Not less than % dissolved in 45 minutes.

Firm's Response:

The firm has mentioned that the dissolution results using water as the dissolution medium are poor. The firm therefore plans to stay with its previously recommended dissolution method and specifications which uses 0.1N HCl as the medium instead of water. The proposed specifications are NLT % dissolved in 60 minutes. The comparative dissolution results for the test and the reference products are given in Table I.

Division Comment:

The firm's argument for using the 0.1N HCl medium and the comparative dissolution test results are acceptable based on the supportive data.

Deficiency 2:

A diskette in ASCII format containing pharmacokinetic data and the model codes used in statistical analyses should be submitted. For each study, two separate files should be configured as follows:

(a) subj seq trt per AUC_{0-t} AUC_{inf} (Where applicable) C_{max} T_{max} K_{el} and $t_{1/2}$;...

(b) subj seq per trt C_1 C_2 C_3.....C_n,

where C is the concentration at various sampling times. Fields should be delimited by one blank space and each missing value should be denoted by a period (.).

Firm's Response:

The diskette has been formatted as described above and is provided.

Division Comment:

Using the provided data diskette, the reviewer performed regular statistical analysis of variance. The results are given in Tables 1, 2 and 3. The firm has not provided the mean plasma levels for n=35 subjects. The 90% confidence intervals of the log transformed Cmax and AUCt parameters (n=35) (Table 3), were outside the regulatory bioequivalence acceptance limit of 80-125%. The 90% confidence intervals of the log transformed Cmax and AUC parameters (n=32)(Table 2), however were within the

regulatory bioequivalence acceptance limit of 80-125%, suggesting bioequivalence of the test and the reference formulations.

Note: Regarding the fasting study and the number of subjects, the firm on February 6, 1997, had provided the following information: This was a two treatment, crossover design in forty-two (42) healthy male subjects. The subjects were dosed in three groups. There was a two-week washout period between the two dosing occasions. Forty-two subjects entered the study. **Thirty-five (35) subjects completed the study, however there was sufficient data for pharmacokinetic and statistical analysis for only thirty-two (32) subjects.**

Regarding the three (#18, #19 and #25) subject data which could not be used in the statistical evaluation, the firm has stated the following: "To obtain reliable estimates of the AUC and Cmax parameters, data from any subject with at least three sequential missing concentration values were excluded from the pharmacokinetic and statistical analysis".

Table 1: Mean plasma prochlorperazine levels, ng/ml, with (SD) of the treatments

Time (hour)	N	Test (Paddock)	Reference (SmithKline Beecham)	Test/Ref. Ratio
0.0	30	0.00	0.00	---------
0.5	31	0.00 (0.00)	0.00 (0.00)	---------
1.5	32	0.075 (0.16)	0.106 (0.18)	0.70
2.5	32	0.308 (0.38)	0.259 (0.31)	1.19
3.5	32	0.941 (0.84)	0.869 (0.85)	1.08
4.5	32	1.469 (1.26)	1.489 (1.34)	0.99
6.0	32	2.000 (1.72)	2.032 (1.82)	0.98
7.0	32	2.570 (1.91)	2.614 (2.08)	0.98
8.0	32	2.870 (2.06)	2.686 (2.13)	1.07
9.0	31	2.928 (2.06)	2.932 (2.25)	1.00
10.0	32	3.118 (2.15)	3.033 (2.28)	1.03
11.0	32	3.115 (2.08)	3.182 (2.35)	0.98
12.0	32	2.983 (2.15)	2.978 (2.28)	1.00
16.0	32	2.184 (1.65)	2.305 (1.92)	0.95
24.0	31	1.675 (1.45)	1.688 (1.52)	0.99
36.0	32	0.737 (0.71)	0.757 (0.72)	0.97
48.0	31	0.400 (0.42)	0.435 (0.46)	0.92
60.0	28	0.188 (0.27)	0.196 (0.26)	0.96

Table 2: LSMEAN pharmacokinetic parameters with standard errors in parentheses and the relevant statistics, N=32, units: AUC, ng/ml*hr, Cmax, ng/ml, Tmax, hr

Parameter	Test (Paddock)	Reference (SmithKline Beecham)	Test/Reference Ratio	90% Confidence Interval
$AUC_{(0-t)}$	70.51 (4.59)	72.79 (4.59)	0.97	0.82-1.12
Ln $AUC_{(0-t)}$, Geometric*	3.95 (0.07), 51.82*	3.90 (0.07), 49.32*	1.05*	0.89-1.24
$AUC_{(0-inf)}$	77.72 (4.87)	80.82 (4.87)	0.96	0.82-1.11
Ln $AUC_{(0-inf)}$, Geometric*	4.099 (0.06), 60.34*	4.092 (0.06), 59.85*	1.01*	0.87-1.17
Cmax	3.483 (0.16)	3.452 (0.16)	1.01	0.90-1.12
LnCmax, Geometric*	1.047 (0.054), 2.849*	0.978 (0.054), 2.659*	1.07*	0.94-1.22
Tmax	9.86 (0.315)	9.897 (0.315)	1.00	----------
Half-Life	12.81 (0.52)	13.18 (0.52)	0.97	----------

Table 3: LSMEAN pharmacokinetic parameters with standard errors in parentheses and the relevant statistics, N=35, units: AUC, ng/ml*hr, Cmax, ng/ml, Tmax, hr

Parameter	Test (Paddock)	Reference (SmithKline Beecham)	Test/Reference Ratio	90% Confidence Interval
$AUC_{(0-t)}$	72.88 (4.38)	71.82 (4.37)	1.02	86.9-116.1
Ln $AUC_{(0-t)}$, Geometric*	3.93 (0.07), 50.91*	3.82 (0.07), 45.60*	1.12*	**94.6-131.2**
$AUC_{(0-inf)}$	80.39 (4.73)	79.92 (4.86)	1.005	86.2-115
Ln $AUC_{(0-inf)}$, Geometric*	4.088 (0.06), 59.62*	4.035 (0.06), 56.54*	1.054*	90.8-122.4
Cmax	3.53 (0.15)	3.35 (0.15)	1.05	94.4-115.8
LnCmax, Geometric*	1.03 (0.050), 2.80*	0.92 (0.050), 2.51*	1.16*	**98.6-125.1**

Deficiency 3:

The assay potencies of both the test as well as reference formulations should be provided.

Firm's Response:

The firm has provided the following assay potencies for the test and the reference lots:
% for the test and % for the reference product.

Division Comment:

Firm's response is acceptable. It indicates that the bio-equivalency lot assay potencies were within % of each other.

Deficiency 4:

The firm needs to document the long term stability of the study samples for a duration of at least 60 days to cover the study, shipping and analysis. In future, the freeze thaw cycle stability should be studied after 3 freeze thaw cycles as against only 2 cycles as has been done for the study. From the data it appears that QC sample concentrations are ng/ml. ng/ml, ng/ml and ng/ml. Please clarify why they are not consistent for all tests e.g. stability tests (2 freeze-thaw, 24 hr and auto-sampler).

Firm's Response:

Though the firm has not responded directly to the question of QC samples of different concentrations. Regarding the long term stability, the firm has stated that the long term stability was studied after storage of samples at -20^{0}C for 89 days, which is equal to the clinical and analytical portions of the study.

Division Comment:

The firm in the original application did not provide any table for the long term stability. On page 5 22, of the Feb.6, 1997 application, the firm states the long term stock solution stability as % after 69 days. There was no mention of the 89 day stability. Subsequent to a telephone enquiry, in a fax dated may 5, 1998, the firm provided information on the long term stability. After a storage of 89 days at -20^{0}C, the long

term stability percent relative error was less than % and %, for the ng/ml and ng/ml theoretical concentrations. The long term stability data are acceptable.

Deficiency 5:

It is not clear why the mean of only 30 subjects was reported for the zero hour draw. It is unclear why plasma samples may not be sufficient for the zero hour screen. Please clarify. The arithmetic and geometric means of the treatments are considerably different. Please comment on the cause.

Firm's Response:

For only the 30 subjects zero hour draw the firm has stated the following:

"The method requires two milliliters of sample for analysis. The pre-dose sample is analyzed two times on each run (requiring 4 ml of sample), once without internal standard and once with internal standard to test for the selectivity of the assay. In case, where the original analytical run was not acceptable, there may have been insufficient volume to re-assay the pre-dose sample. The selectivity of the analytical run is confirmed prior to analysis of each subjects sample set. For two of the subjects in each treatment, pre-dose samples were exhausted in during this pre-run validation and sufficient sample volumes were not available for the assay of drug levels in pre-dose samples. The lack of sample volume for repeated assay of these samples may be attributed to the high sample volume required for each assay".

The firm has attributed the substantially large differences in the arithmetic and geometric means of the pharmacokinetic parameters to the increased variance or skewness in distribution and sample distribution pattern.

Division Comment:

Since the study has already been conducted, the firm's response is deemed acceptable.

Deficiency 6:

The protocol should state the 'Exclusion Criteria' used in the conduct of the study. Also, the 'Subject Control' section of the protocol does not mention, non-consumption of alcohol or alcoholic beverages during the study. Were these allowed? Please explain.

Firm's Response:

The firm has stated that the alcohol was prohibited for at least 48 hours prior to the drug administration. It is further stated that "subjects were questioned regarding their alcohol consumption and none of the subjects dosed reported alcohol use within 48 hours of entry to the facility".

Division Comment:

This was a general comment regarding future study protocols. Due to the nature of formulation and the route of administration, alcohol may not be of a great significance in this particular situation. However, since this drug formulation has a large intra-subject variability, all factors which may potentially contribute to the high variability should be controlled. The firm's response is acceptable.

Deficiency 7:

On page 32, the protocol says that Group 2 comprised of study subjects 17-20. The actual statistical analysis shows Group II comprising of subjects 17-30. Please clarify.

Firm's Response:

The firm has stated that on page 32, it "incorrectly" stated that group 2 was comprised of subject #17-20 and in fact Group 2 consisted of subjects 17-30.

Division Comment:

The response is acceptable.

Note:

Since the recommendations are based on the acceptability of the 32 subject data due to deletion of 3 subject data based on the three consecutive missing samples, it is suggested that the analytical portion of the study should be audited by the Division of Scientific Investigations (HFD-340), to confirm that the missing values and therefore the three subject data can be omitted based on the firms criterion.

V.RECOMMENDATIONS:

1. The bioequivalence study conducted by Paddock laboratories on its Prochlorperazine, 25 mg suppository, lot #6C935 comparing it to SmithKline Beecham's Compazine, 25 mg suppository, lot #4259 has been found acceptable by the Division of Bioequivalence. The firm's Prochlorperazine, 25 mg suppository is deemed bioequivalent to SmithKline Beecham's Compazine, 25 mg suppository.

2. The dissolution testing conducted by Paddock laboratories on its Prochlorperazine 25 mg suppository, lot #6C935, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing, controls and stability program. The dissolution should be conducted in 900 ml 0.1N HCl, Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

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

3. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalency and in-vitro dissolution testing and the application is acceptable.

/S/

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG
FT INITIALED BY YCHUANG 5/12/98

/S/

Concur: Date: 5/15/98

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

cc: ANDA 40-246 (original, duplicate), HFD-650 (Director), HFD-652 (Sathe), Division File, Drug File.

Table I. *In-Vitro* Dissolution Testing

Drug (Generic Name): Prochlorperazine Suppository
Dose Strength: 25 mg
ANDA Number: 40-246
Firm: Paddock Laboratories
Submission Date: 12/23/97

I. Dissolution Conditions: 900 ml, 0.1N HCl, Apparatus 2 (paddle), 50 rpm.

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Prochlorperazine suppository, Lot # 6C935 Strength (25 mg)			Reference Product: Compazine suppository, Lot # 4259 Strength (25 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	36.3		27.9	35.8		13.3
30	58.5		13.4	70.1		6.5
45	73.2		9.1	86.6		4.8
60	84.5		3.4	96.7		4.2

CC: ANDA 40-246
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer (P.Sathe)

X:\NEW\FIRMSNZ\PADDOCK\LTRS&REV\40246SD.D97
Printed in final on 05/08/98

Endorsements: (Final with Dates)
HFD-652/ Reviewer (P.Sathe) 05/08/98
HFD-655/ Bio team Leader (YCHuang) 5/15/98
HFD-650/ D. Conner 5/15/98

BIOEQUIVALENCY - ACCEPTABLE

submission dates: Feb.6, 1997
December 23, 1997

1. **FASTING STUDY** (STF)
Clinical:
Analytical:

Strengths: 25 mg
Outcome: AC

2. **DISSOLUTION DATA** (DIS)

Strength: 25 mg
Outcome: **AC**

3. **STUDY AMENDMENT** (STA)

Strengths: 25 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments: Bio-study and dissolution acceptable

Prochlorperazine
25 mg Suppository
ANDA 40-246
Reviewer: Pradeep M. Sathe, Ph.D.
WP #40246O.598

Paddock Laboratories Inc.
Minneapolis, MN-55427
Submission Date:
May 12, 1998

REVIEW OF AN AMENDMENT

The amendment consists of a hard copy of the long term (89 days) stability data and corresponding statistics. The same information was faxed to the Agency on May 5, 1998, and was reviewed. Since the information is already reviewed, no further review is necessary at this time.

/S/ 5/19/98
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG
FT INITIALED BY YCHUANG 5/14/98

Concur: 5/21/98 Date: 5/21/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA 40-246 (original, duplicate), HFD-650 (Director), HFD-652 (Sathe), Division File, Drug File.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40246

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 40-246 Date of Submission: February 13, 1998 (Amendment)

Applicant's Name: Paddock Laboratories, Inc.

Established Name: Prochlorperazine Suppositories USP, 25 mg

Proposed Proprietary Name: Proctazine™

Labeling Deficiencies:

1. GENERAL COMMENT:

   Our review has revealed names which sound like your proposed proprietary name, Proctazine: Proctocream (an anorectal preparation - Reed & Carnrick), Pramoxine (a topical local anesthetic - Ferndale), promazine HCl (a neuroleptic, ataraxic, anticholinergic - USP 23). Although these products are different dosage forms, we believe they are sufficiently close in pronunciation to cause confusion. We believe that the proposed name is misleading as defined in 21 CFR 201.10(c)(5).

   Also, the use of the root "proct", inplies that this product has some use in treating conditions of the anorectal area, as exemplified in the names of products such as Proctocream, Proctofoam, etc. Although the route of administration of this product is per rectum or rectally, the desired effect of the active ingredient is systemic and not localized in the anorectal region. Therefore, we believe the name is misleading as defined in 21 CFR 201.10(c)(3).

   Revise all labels and labeling accordingly.

2. CONTAINER (Unit dose)

   a. See GENERAL COMMENT.

   b. Replace the statement with the symbol "Rx only" or "℞ only". We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site,

http://www.fda.gov/cder/guidance/index.htm for guidance.

3. CARTON (12s)

   a. See GENERAL COMMENT.

   b. See CONTAINER comment (b).

4. INSERT

   See GENERAL COMMENT.

Please revise your labels and labeling, as instructed above, and submit in draft. We will not request final print pending the findings of the Labeling and Nomenclature Committee regarding your proposed proprietary name.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40246

CORRESPONDENCE

ANDA 40-246

JUN 30 1997

Paddock Laboratories Inc.
Attention: Carol Anding
3940 Quebec Avenue North
Minneapolis, MN 55427

Dear Madam:

Reference is made to the Abbreviated New Drug Application, submitted February 6, 1997, for Prochlorperazine Suppository, 25mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Comparative dissolution data for both the test and the reference formulations should be provided using the following FDA recommended dissolution method. The dissolution data should be reported for at least 12 units. The individual data should be reported as well as the mean, dissolution range (minimum-maximum) and %CV with respect to each sample point.

Apparatus	:	USP 23 apparatus II (paddle)
Rotation Speed	:	50 rpm
Medium	:	900 mL Deaerated Water
Recommended (Q)	:	Not less than % dissolved in 45 minutes.

The proposed dissolution method used failed to provide the individual unit dissolution data for the test formulation.

2. A diskette in ASCII format containing pharmacokinetic data and the model codes used in statistical analyses should be submitted. For each study, two separate files should be configured as follows:

(a) subj seq trt per AUC_{0-t} AUC_{inf} (Where applicable) C_{max} T_{max} K_{el} and $t_{1/2}$;...

(b) subj seq trt per C_1 C_2 C_3.....C_n,

where C is the concentration at various sampling times. Fields should be delimited by one blank space and each missing value should be denoted by a period (.).

3. The assay potencies of both the test as well as reference formulations should be provided. The two products should assay within %.

4. Document the long term stability of the study samples for a period of at least 60 days to cover the study, shipping and analysis. In the future, the freeze thaw cycle stability should be studied after 3 freeze thaw cycles instead of only 2 cycles as was done for the study. From the data, it appears that QC sample concentrations are ng/mL, ng/mL, ng/mL and ng/mL. Please clarify why they are not consistent for all stability tests (2 freeze-thaw, 24 hr and autosampler).

5. It is not clear why the mean of only 30 subjects was reported for the zero hour draw. It is also unclear why plasma samples may not be sufficient for the zero hour screen. Please clarify. The arithmetic and geometric means of the treatments are considerably different. Please comment on the cause.

6. The protocol should state the 'Exclusion Criteria' used in the conduct of the study. Also, the 'Subject Control' section of the protocol does not mention, non-consumption of alcohol or alcoholic beverages during the study. Were these permitted? Please explain.

7. On page 32, the protocol states that Group 2 was comprised of study subjects 17-20. The actual statistical analysis shows Group II being comprised of subjects 17-30. Please clarify.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

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

Paddock
Laboratories, Inc.

Pharmaceuticals for Medicine, Pharmacy and Science

June 6, 2000

Elaine Hu, Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**Re: New Correspondence – Reinstate Tradename "Compro"
for ANDA 40-246 for Prochlorperazine Suppositories USP, 25 mg**

Dear Ms. Hu:

Please accept this new correspondence in regard to a May 17, 2000, gratuitous amendment to Paddock Laboratories' Abbreviated New Drug Application for Prochlorperazine Suppositories USP 25 mg, ANDA 40-246.

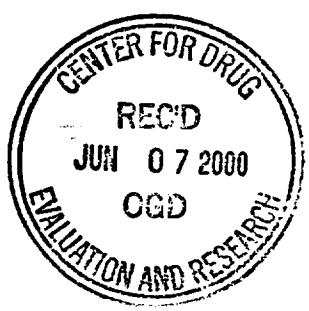
In the May 17, 2000, amendment, we asked that the proposed tradename be withdrawn in the interest of expediting the approval process. On June 2, 2000, we received a telephone communication from Debbie Catterson, FDA, OGD, Labeling Reviewer for this application. Ms. Catterson informed us that the Office of Post-Marketing Drug Risk Assessment had documented in a May 22, 2000, correspondence that they had no objections to the proposed tradename "Compro". In light of this new information, we do indeed wish to maintain the tradename and not to withdraw it. We ask that you reinstate the tradename and continue review of our application.

This communication is being sent via facsimile (301-594-0180). Archival and review copies of this correspondence are being provided via overnight express. Please let me know if you have any questions or need further information. I can be reached at 763-546-4676 (direct dial) and 763-546-4842 (fax). In addition, we wish to thank Ms. Catterson and the agency for informing us of this matter so ultimately we were able to take advantage of the use of a tradename. This is very important to us.

Sincerely,

Carol Anding

Carol Anding
Regulatory Affairs Manager



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Paddock
Laboratories, Inc.

3.1

Pharmaceuticals for Medicine, Pharmacy and Science

NEW CORRESP
NC

May 17, 2000

Elaine Hu, Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Gratuitous Amendment – Withdrawal of Tradename to ANDA 40-246 for Prochlorperazine Suppositories USP, 25 mg

Dear Ms. Hu:

Please accept this gratuitous amendment to Paddock Laboratories' Abbreviated New Drug Application for Prochlorperazine Suppositories USP 25 mg, ANDA 40-246.

At this time, we are withdrawing the proposed tradename in the interest of expediting the approval process for this application.

Archival and review copies are provided. Please let me know if you have any questions or need further information. I can be reached at 763-546-4676 (direct dial) and 763-546-4842 (fax).

Sincerely,

Carol Anding

Carol Anding
Regulatory Affairs Manager

CENTER FOR DRUG
RECD
MAY 16 2000
CDD
EVALUATION AND RESEARCH

3940 Quebec Avenue North, Minneapolis, MN 55427 • 612.546.4676 • FAX: 612.546.4842 • 800.328.5113

Paddock
Laboratories, Inc.

Pharmaceuticals for Medicine, Pharmacy and Science

March 1, 2000

NDA ORIG AMENDMENT
N / Am

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855-2773

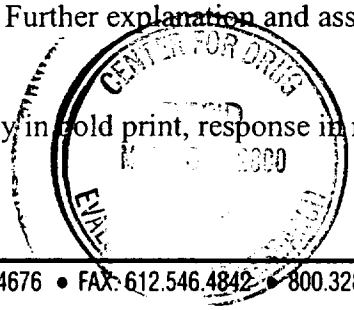
Re: Minor Amendment to ANDA 40-246
and Response to Deficiency Letter dated May 12, 1999, for
Prochlorperazine Suppositories USP, 25 mg

Dear Staff:

Please accept this minor amendment and response to the Agency's deficiency letter of May 12, 1999, regarding Paddock Laboratories' abbreviated new drug application dated February 6, 1997, and our amendments dated February 13, 1998 and December 4, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Prochlorperazine Suppositories USP 25 mg, ANDA 40-246.

In addition to providing our response to the May 12, 1999 deficiency letter, this amendment includes data from a demonstration batch of prochlorperazine suppositories manufactured with the revised formulation removing 3% excess prochlorperazine. (In our major amendment dated December 4, 1998, we had committed to manufacturing a batch with the revised formulation.) Samples from the batch (Lot No. 8M6354) were put on 90-day accelerated stability to demonstrate the acceptability of 24-month expiration dating. A copy of the executed batch record for Lot No. 8M6354 is provided in Attachment 2. Finished dosage form test results for the batch are provided in Attachment 4. Accelerated stability data and shelf stability data through the 12-month time point are provided in Attachment 5.

Finally, we are replacing the method for USP Identification B with an alternative method. Identification B is a finished dosage form test performed to distinguish suppositories containing chlorpromazine versus prochlorperazine. We will perform an identification test, which is more specific and more accurate than the USP method. Further explanation and associated documentation are provided in Attachment 4.



We respond to the May 12, 1999 deficiencies (deficiency in bold print, response in non-bold print) as follows:

3940 Quebec Avenue North, Minneapolis, MN 55427 • 612.546.4676 • FAX: 612.546.4842 • 800.328.5113

NDA 40-246
3-1-00

Chemistry Deficiencies

A. Deficiencies

1. **Please provide the stability testing results of melting point and impurities at the 24 month station since your stability protocol was revised to add the testing for melting point and impurities in the major amendment dated February 13, 1998.**

   We have provided a revised stability report for the bioequivalence batch (Lot No. 6C935) at the 24-month time point in Attachment 5. The revised report includes data on melting point and impurities.

2. **The DMF is not currently acceptable. The DMF holder has been notified.**

   The supplier and DMF holder for the has addressed the DMF deficiencies. A copy of the letter from informing us that the DMF has been updated is provided in Attachment 3.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. **A satisfactory compliance evaluation of the facilities listed for drug product manufacturing and quality control in the applications is necessary at the time of the approval of the applications.**

   Acknowledged.

2. **Please clarify what the role of is since you state that you will be doing the finished product and stability testing.**

   At one time we anticipated functioning as an alternate testing facility for finished product and stability testing of the prochlorperazine suppositories. Because this is no longer the case, we withdraw our proposal to have act as an alternative testing facility for finished product and stability testing. All such testing will be performed by Paddock Laboratories.

Labeling Deficiencies

1. **General Comment:**

   Our review has revealed names which sound like your proposed proprietary name, Proclor: Procort (a topical corticosteriod - Roberts), Pochlorin (an anti-hypercholesteremic agent), Potachlor (a potassium supplement - Rosemont). These names are sufficiently close in pronunciation to the proposed name to be misleading as defined in 21 CFR 201.10 (c) (5).

Delete or propose another name.

We propose to use the proprietary name, Compro™. (This name was proposed as our preferred alternate choice in our major amendment dated December 4, 1998.)

2. **CONTAINER (Unit dose)**
   See GENERAL COMMENT.

   We propose to use the proprietary name, Compro™.

3. **CARTON (12s)**
   See GENERAL COMMENT.

   We propose to use the proprietary name, Compro™.

4. **INSERT**

   a. DESCRIPTION

      Revise the third paragraph to read, "molecular formula" rather than

      The third paragraph has been revised to read "molecular formula" rather than

   b. **HOW SUPPLIED**

      Relocate "Rx Only" to appear directly below the title.

      The "Rx Only" statement has been relocated to directly below the title.

   c. **See GENERAL COMMENTS.**

      We propose to use the proprietary name, Compro™.

Please revise your labels and labeling, as instructed above, and submit in final print or draft, if you prefer.

Revised labels and labeling are being submitted in final printed form. Twelve final printed copies of each level of labeling: insert, unit dose container (printed suppository film) and carton are provided in Attachment 1.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Acknowledged.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A side-by-side comparison of the current proposed labeling with the previously submitted (December 4, 1998) proposed labeling is provided in Attachment 1. All differences are annotated and explained in the same attachment.

Review and archival copies are included in this submission. A third copy has been sent to the Minneapolis District Office (field copy). Paddock Laboratories, Inc., does hereby certify that the submitted field copy is a true copy of the technical section of this application [21 CFR 314.94(d)(5)].

Please call if you have any questions or need further information.

Sincerely,

Carol Anding

Carol Anding
Regulatory Affairs Manager

Attachments

Paddock
Laboratories, Inc.

NDA 40-246 AMENDMENT
M/B

Pharmaceuticals for Medicine, Pharmacy and Science

May 12, 1998

RECEIVED
MAY 13 1998
GENERIC DRUGS

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Re: May 5, 1998, **Bioequivalence Telephone Amendment** to ANDA 40-246
in Response to April 22, 1998, Bioequivalence Deficiency Telephone Notification,
for Prochlorperazine Suppositories USP, 25 mg

Dear Staff:

Please accept this follow-up hard copy of the May 5, 1998, Bioequivalence Telephone Amendment in response to the Agency's bioequivalence deficiency telephone notification of April 22, 1998, regarding our abbreviated new drug application dated February 6, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Prochlorperazine Suppositories USP, 25 mg, ANDA 40-246. The attached information was sent via fax communication on May 5, 1998, from
on behalf of Paddock Laboratories. is the contract research organization who performed the bioequivalence trial and bioequivalence-related analytical testing for this study and was best able to answer the questions posed in this deficiency.)

We were contacted on April 22, 1998, by Ms. Lizzie Sanchez, Pharm D., on behalf of the bioequivalence reviewer who was looking for further data to support the stability of the study samples. After reviewing the submission documentation, I contacted Ms. Sanchez on April 30, 1998, for additional clarification. On or about May 1, 1998, Dr. Wilkinson spoke with Ms. Sanchez and the reviewer to obtain further clarification. On May 5, 1998, Dr. Wilkinson faxed tables for stock solution and frozen storage stability as requested by the reviewer. The hard copy of the faxed tables are provided in Attachment 1 of this amendment.

Review and archival copies are included in this submission. A third copy has been sent to the Minneapolis District Office (field copy).

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Paddock Laboratories, Inc., does hereby certify that the submitted field copy is a true copy of the technical section of this application [21 CFR 314.94(d)(5)].

Please call if you have any questions or need further information.

Sincerely,

Carol Anding

Carol Anding
Regulatory Affairs Manager

Paddock Laboratories, Inc.

Pharmaceuticals for Medicine, Pharmacy and Science

February 13, 1998

NDA ORIG AMENDMENT

N/AC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Major Amendment to ANDA 40-246
in Response to Deficiency Letter dated July 31, 1997, for
Prochlorperazine Suppositories USP, 25 mg

Dear Staff:

Please accept this Major Amendment in response to the Agency's deficiency letter of July 31, 1997, regarding Paddock Laboratories' abbreviated new drug application dated February 6, 1997, for Prochlorperazine Suppositories, USP 25 mg, ANDA 40-246. In addition to the deficiency letter response, we are making the following amendments.

1. We propose to bring assay, content uniformity, and dissolution testing in-house. (Assay and dissolution testing for the bio batch were performed by Paddock Laboratories' methods and method validation information for these tests are provided in Attachment 6.

2. On incoming raw material testing of the drug substance, we propose to change from performing USP tests for *Ordinary Impurities <466>* and *Assay* to performing a more specific impurities test and the above mentioned assay developed by Paddock Laboratories. Further discussion and supporting documentation for this change are provided in Attachment 2, page 057.

3. We propose to add an additional supplier of the inactive ingredient, glycerin USP. Information supporting this change is provided in the response to deficiency 2. and in Attachment 2, page 072.

4. We have added the tradename "Proctazine™" to our labeling (Attachment 1).

RECEIVED

FEB 17 1998

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GENERIC DRUGS

We respond to the specific deficiencies (deficiency in bold print, response in non-bold print) as follows:

Chemistry Deficiencies

A. Deficiencies

1. **Please justify the necessity to have % excess of Prochlorperazine in the drug product manufacturing processes, since the finished product assay is mg/g % of label claim).**

   We have observed some decrease in prochlorperazine assay during long term stability (Attachment 7, page 242). We would like to continue to manufacture with a % overage of prochlorperazine base to assure product potency throughout the expiration period.

2. **Full monograph testing on the inactive ingredients should be performed unless the suppliers' certificates of analysis were validated.**

   Glycerin, USP is the only inactive ingredient with a monograph. The suppliers' certificates of analysis are being validated.

   In addition, we propose to add an additional supplier of glycerin, USP. The additional supplier is Paddock Laboratories' revised Chemical Component Specification, adding and certificates of analysis are provided in Attachment 2, page 072. certificates of analysis are also being validated.

   Certificates of analysis for the nonmonograph inactives, and (hydrogenated vegetable oils), will be validated against the manufacturers' specifications.

3. **The drug substance, Prochlorperazine, should be retested annually. Please revise its retest schedule.**

   The drug substance will be retested annually. The retest schedule, documented in Paddock Laboratories SOP 07A-0013, "Reapproval of Chemical Components for Release to Production", has been revised to reflect this accordingly. See section 5.1.2 of the revised SOP provided in Attachment 2, page 077.

4. **Please incorporate the compounding and filling yield calculations (page 260 and 274, respectively) into your production batch record and establish the tolerance ranges.**

   Compounding and filling yields are part of the batch record but were not included in the Master Batch Record section. Blank versions of the yield calculations are provided in Attachment 4.

   The established tolerance ranges are provided on the Finished Product Analysis. The tolerance range for the filling yield is % and is stated on the Finished Product Analysis specification. The tolerance range for the compounding yield is % and has been added to the Finished Product Analysis specification. The revised Finished Product Analysis specification is provided in Attachment 5, page 088.

5. **Since Prochlorperazine is a light-sensitive drug, please demonstrate that the proposed packaging system can protect the drug product from light properly.**

   A light transmission study was performed to evaluate the ability of the purposed packaging system to properly protect the drug product from light. The study is provided in Addendum 1 of Validation File Prochlorperazine Stability Indicating Assay" provided in Attachment 6, page 177.

6. **Please add a test and specifications for individual impurity and total impurities in finished product release and stability specifications.**

   Analytical Method "Prochlorperazine Suppository Impurity Profile", will be performed to determine individual and total impurities for finished product release and stability testing. The specification is NMT % for individual impurities and NMT % for total impurities.

   Analytical Method is provided in Attachment 5, page 104. A revised finished product analysis is provided in Attachment 5, page 088. A revised stability protocol is provided in Attachment 7, page 238.

7. **The content uniformity commitment on page 341 is not acceptable. A prior approval supplement is required before the content uniformity test is suspended.**

   Content uniformity will be performed for each lot and will not be suspended until such time as a prior approval supplement is submitted and approved.

8. Please submit a validation study for Dissolution Method

We propose to perform the dissolution on all future batches of prochlorperazine suppositories in-house using Paddock Laboratories Analytical Procedure "Prochlorperazine Suppository Dissolution". The validation study and method are included in Attachment 6, page 112.

9. The system suitability parameters such as tailing factor and number of theoretical plates should be incorporated into your dissolution and assay methods.

analytical methods for determination of prochlorperazine in prochlorperazine suppositories and determination of dissolution of prochlorperazine suppositories have been revised to include system suitability parameters such as tailing factors and number of theoretical plates. The revised methods are provided in Attachment 8, pages 243 and 248 respectively.

In addition, Paddock Laboratories Analytical Procedures "Prochlorperazine Stability Indicating Assay" and "Prochlorperazine Suppository Dissolution" include the appropriate system suitability parameters. These methods are included in Attachment 5, pages 098 and 090 respectively.

10. Please submit detailed information for preparing Prochlorperazine reference standard used in the dissolution method, since it is not currently available from USP.

crossed-over a lot of prochlorperazine base to a USP prochlorperazine maleate standard prior to its use as the standard for dissolution testing. The lot of prochlorperazine base was manufactured by , the drug substance manufacturer listed in this application. standard operating procedure for creating cross-over reference standards is provided in Attachment 8, page 250.

The USP reference standard, prochlorperazine maleate, will be used as the reference standard for all future dissolution testing and is specified in the relevant Paddock Laboratories' Analytical Procedures.

11. The following crucial conditions: flow rate, detection, injection volume, and running time are not specified in the assay method
Please clarify.

analytical method has been revised to include flow rate, detection, injection volume, and running time. The revised method is provided in Attachment 8, page 243.

In addition, Paddock Laboratories Analytical Procedure "Prochlorperazine Stability Indicating Assay" includes flow rate, detection, injection volume, and running time. This method is included in Attachment 5, page 098.

12. In the assay method, the placebo may interfere with the measurement of Prochlorperazine since the placebo retention times were about minutes (page 431-432) and the Prochlorperazine retention times were from minutes.
Please clarify.

During accuracy/linearity studies, noted the placebo chromatogram exhibited a peak at minutes. They believe that this particular peak was not from components of the placebo but due to contamination of a syringe with prochlorperazine. (The placebo injection had been made after the injection of the highest concentration of prochlorperazine solution during linearity studies.) To confirm this premise, conducted additional studies with a small quantity of the placebo material. The resulting chromatograms confirm the premise; showing no peaks to be present. The chromatograms are provided in Attachment 8, page 253 through 256.

13. In the assay method validation report, large variations of the Prochlorperazine retention times from minutes in the accuracy & linearity studies to minutes in the ruggedness study were observed. Please explain.

Retention time of the peak is directly related to its flow rate. During ruggedness studies, a different column was used to establish robustness of the method. This column showed high pressure at mL/minute. The flow was reduced to mL/minute to accommodate a workable column pressure. This resulted in the change in retention time from about minutes.

14. **assay method is different from the validated assay method because the reference standard changed to Prochlorperazine Maleate and the final concentration of reference standard reduced to µg/mL (equivalent to µg/mLof Prochlorperazine). Therefore, a cross validation should be performed.**

Linearity studies have been completed for both assay and dissolution. For assay purposes, a linearity study was conducted by using method , with the range varying from µg/ml of prochlorperazine. The correlation coefficient was found to be

For dissolution purposes, a linearity study was conducted by using method with the range varying from µg/ml of prochlorperazine. The correlation coefficient was found to be

Linearity curves and chromatograms are provided for both studies in Attachment 8, starting on page 253.

15. **Since the peak of Prochlorperazine can appear around minutes, the peaks eluted between minutes in the forced degradation studies may be the peaks of Prochlorperazine not the degradation products as stated on page 444. Please clarify.**

During forced degradation studies, retention time for the prochlorperazine peak was around minutes. These studies were conducted on an system where system suitability, precision, accuracy, and linearity studies were conducted.

Ruggedness of the method was studied on a second system. In these studies, retention for the prochlorperazine peak was observed to be minutes. As explained in the response to deficiency 13., states that the change in retention time is a result of reduced flow rate used to accommodate a workable column pressure.

believes there is no possibility the peaks eluted at around minutes in the forced degradation studies (performed in the first system) are prochlorperazine. It is believed these peaks are some unknown molecule.

16. **In method, the sample preparation procedure and calculation are illustrated for an assay sample only. Please add a appropriate procedure and calculation for a content uniformity sample.**

method has been revised to accommodate the appropriate calculations for content uniformity samples. See Attachment 8, page 243.

Appropriate calculations have also been incorporated into Paddock Laboratories' analytical method for content uniformity.

17. **Please submit the currently available long-term stability results for the bio batch (Lot 6C935).**

Currently available long-term stability results for the bio batch (Lot 6C935) are provided in Attachment 7, page 242.

18. **Please revise the stability specifications to include a softness test such as melting point.**

Stability specifications have been revised to include Analytical Procedure , "Melting Point Test for Suppositories". The specification is 33 to 37°C. This is the same method as provided in the February 6, 1997, original application and used in finished product testing. The test will be performed by Paddock Laboratories.

A revised stability protocol including melting point testing is provided in Attachment 7, page 238.

B. **In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:**

1. **Please respond to the bioequivalency comments communicated to you on June 30, 1997.**

Paddock Laboratories responded to the agency's June 30, 1997, bioequivalency comments in an amendment dated December 23, 1997. A photocopy of the amendment cover letter is provided in Attachment 9.

2. **Your analytical methodology is not identical to the US Pharmacopeial methods for the finished drug product. Please be advised that the USP methods are the regulatory methods and will prevail in the event of any dispute.**

Acknowledged.

Labeling Deficiencies

All labeling deficiencies are addressed in Attachment 1.

1. **Container (Unit Dose)**

   a. **Revise to use the established name of the product, Prochlorperazine Suppositories USP, 25 mg.**

   b. **Revise to enhance the prominence of "NOT FOR CHILDREN".**

      Acknowledged and addressed in Attachment X containing side-by-side comparison of labeling.

2. **CARTON (12s)**

   a. **Revise to use include the following statement on the front and back panels;**

      12 ADULT Suppositories

      Acknowledged and addressed.

   b. **Revise to include on the front panel,**

      FOR RECTAL USE ONLY

      Acknowledged and addressed.

   c. **Revise to add the following statement in prominent type,**

      DO NOT REMOVE FROM WRAPPER UNTIL READY TO USE

      Acknowledged and addressed.

   d. **Revise the following to read,**
      "Caution: Federal law...without prescription."

      Acknowledged and addressed.

   e. **Revise the storage temperature range to include**
      "Store at controlled room temperature, 15° C...".

      Acknowledged and addressed.

f. Revise to delete the sentence that reads, See package insert for indications...

Acknowledged and addressed.

g. Include the following on the end flaps:

NOT FOR USE IN CHILDREN
25 mg
Adult Size

We were able to add the above information to one of the end flaps. The other end flap contains a barcode and there was not room to add the information. We decided to remove all statements from this end flap rather than include partial information.

h. Revise to delete the 3 bullets appearing on the side of the carton.

Acknowledged and addressed.

i. You indicate that your suppositories are "color coded". Please elaborate on the meaning of this statement.

We have chosen to delete this statement.

3. INSERT

a. GENERAL COMMENT

The most current permitted date for SmithKline Beecham's Compazine® insert labeling is September 30, 1992; revised November 1992. Please revise your insert labeling, as follows, to be in accord with the most currently permitted labeling.

Acknowledged and addressed.

b. TITLE

You are encouraged to include the designation "USP" with the established name of your drug product.

Acknowledged and addressed.

c. DESCRIPTION

i. **Revise to make the following the first paragraph:**

Prochlorperazine is a clear, pale yellow, viscous liquid. It is sensitive to light, very slightly soluble in water, freely soluble in alcohol, in chloroform, and in ether.

ii. **Revise so that the following is the second paragraph:**

Each suppository, for rectal administration, contains...

iii. **Revise to include the product's molecular weight, chemical name, structural and molecular formulas.**

Acknowledged and addressed items i. through iii. above.

d. **Include the following section to appear immediately after the DESCRIPTION section:**

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.

Acknowledged and addressed.

e. INDICATIONS

i. **Revise the section heading to read,**
INDICATIONS AND USAGE

ii. **Revise this section to read,**
"Prochlorperazine 25 mg suppositories are indicated in the control of severe nausea and vomiting in adults." Delete the remainder of the section.

Acknowledged and addressed items i. and ii. above.

f. CONTRAINDICATIONS

i. **Revise to delete the first sentence. The first contraindication now begins with**

ii. **Revise the make the following the second contraindication,**

-

iii. **Revise to make the following the third contraindication: "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."**

Acknowledged and addressed items i. through iii. above.

g. WARNINGS

i. **Neuroleptic Malignant Syndrome (NMS)**

Revise to delete the fifth paragraph which begins,

ii. **Revise to make the sixth paragraph which begins,**
a new subsection entitled "General:".

iii. **Nursing Mothers**

Revise to delete the second sentence.

Acknowledged and addressed items i. through iii. above.

h. PRECAUTIONS

i. **Revise to delete the second sentence of the third paragraph.**

ii. **Revise the penultimate sentence of the third paragraph to read, . . . norepinephrine bitartrate and phenylephrine hydrochloride are suitable.**

iii. **In the 15th paragraph, replace with "phenytoin" in two places.**

iv. **Revise to make the following the 3rd paragraph of the "Long Term Therapy" subsection using bold print:**

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.

v. **In the ultimate paragraph, replace with "metrizamide" in two places.**

Acknowledged and addressed items i. through v. above.

i. **ADVERSE REACTIONS**

i. **Revise to delete the second sentence of the first paragraph.**

ii. **Neuromuscular (Extrapyramidal) Reactions**

A) **Revise the third sentence of the second paragraph to read, . . . occur in children or pregnant. . .**

B) **Revise to replace with "diphenhydramine" in the second paragraph**

iii. **Dystonias**

A) **Revise to make the following the fourth sentence of the third paragraph: *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.)**

B) **Revise to replace with "diphenhydramine" in the last sentence of the ultimate paragraph.**

Acknowledged and addressed items i. through iii. above.

j. **OVERDOSAGE**

i. **Move this section, revise to follow the ADVERSE REACTIONS section.**

ii. **Revise to replace "Levophed", and with "diphenhydramine", "norepinephrine bitartrate", and "phenylephrine hydrochloride", respectively.**

Acknowledged and addressed items i. and ii. above.

k. DOSAGE AND ADMINISTRATION

Revise to add a subsection heading "Adults" to the first paragraph.

Acknowledged and addressed.

l. HOW SUPPLIED

i. **Revise to use the established name.**

ii. **Revise to include the storage temperature range and the statement "Do not remove from wrapper until ready to use."**

iii. **You are encouraged to include the "CAUTION: Federal law. . . " statement.**

iv. **Revise to delete the footnotes and corresponding established names which appear at the end of this section.**

Acknowledged and addressed items i. through iv. above.

Please revise your labels and labeling, as instructed above, and submit in final print, or draft if you prefer.

Revised labels and labeling are being submitted in draft form. Four copies are provided in Attachment 1.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Acknowledged.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A side-by-side comparison of the current proposed labeling with the previously submitted (February 6, 1997) proposed labeling is provided in Attachment 1, page 018. All differences are also annotated and explained in the same attachment.

Review and archival copies are included in this submission. A third copy has been sent to the Minneapolis District Office (field copy). Paddock Laboratories, Inc., does hereby certify that the submitted field copy is a true copy of the technical section of this application [21 CFR 314.94(d)(5)].

Please call if you have any questions or need further information.

Sincerely,

Carol Anding

Carol Anding
Regulatory Affairs Manager

Enclosures:
Review Copy (red)
Archival Copy (blue)

Paddock Laboratories, Inc.

505(j)(2)(a)(ok)
Anne Marie H. Weibel
2/25/97

Pharmaceuticals for Medicine, Pharmacy and Science

February 6, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Original Submission, Abbreviated New Drug Application for Paddock Laboratories Prochlorperazine Suppositories 25 mg

Dear Staff:

Paddock Laboratories, Inc. (Paddock Laboratories) is submitting this original abbreviated new drug application (ANDA) seeking approval to market Paddock Laboratories Prochlorperazine Suppositories 25 mg. The prochlorperazine rectal suppository is bioequivalent to the listed drug, Compazine® Prochlorperazine Suppositories 25 mg, manufactured by SmithKline Beecham Pharmaceuticals, Inc. pursuant to NDA #11-127.

This ANDA consists of five volumes. Paddock Laboratories is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in a red folder) which contains all the information in the archival copy with the exception of the Bioequivalence section (Section VI.). A separate copy of the Bioequivalence section is provided in orange folders.

This also certifies that, concurrently with filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the Form FDA 3439 and a certification that the contents are a true copy of those filed with Office of Generic Drugs) was sent to our local district office. This "field copy" was contained in a red folder.

Please direct any written communications regarding this ANDA to me at the address below. If you need to call or fax me, my phone numbers are 612-546-4676 (direct dial) and 612-546-1081 (fax). Thank you.

Sincerely,
Paddock Laboratories, Inc.

Carol Anding

Carol Anding
Regulatory Affairs Manager

RECEIVED
FEB 10 1997
GENERIC DRUGS

3940 Quebec Avenue North, Minneapolis, MN 55427 • 612.546.4676 • FAX: 612.546.4842 • 800.328.5113