11552/SLR-112 enc.
NDA 11-552/SLR-112

GlaxoSmithKline
Attention: Thomas F. Kline
Assistant Director, U.S. Regulatory Affairs
1250 S. Collegeville Road
P.O.Box 5089
Collegeville, PA 19426

Dear Mr. Kline:

Please refer to your supplemental new drug application dated March 1, 2001, received March 5, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stelazine (trifluoperazine HCl) Tablets, Injection, and Concentrate.

We acknowledge receipt of your submission dated March 1, 2001. Your submission of March 1, 2001 constituted a complete response to our action letter of February 9, 2001.

This supplemental new drug application provides for labeling changes as requested in our letter of September 25, 2000, specifically modification of labeling text to more clearly state that these agents are indicated for the treatment of schizophrenia.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (package insert submitted March 1, 2001).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 11-120/SLR-086." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:
MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL
STELAZINE®
brand of
trifluoperazine hydrochloride
Antianxiety/Antipsychotic

DESCRIPTION
Tablets. Each round, blue, film-coated tablet contains trifluoperazine hydrochloride equivalent to trifluoperazine as follows; 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg. Each tablet contains trifluoperazine hydrochloride, lactose monohydrate, sodium starch glycolate, FD&C Blue No. 1, FD&C Yellow No. 6, FD&C Red No. 40, gelatin, iron oxide, lactose monohydrate, magnesium stearate, and titanium dioxide. The 1 mg tablets also contain FD&C Yellow No. 6. Amount per tablet: 1 mg trifluoperazine hydrochloride, 85 mg lactose monohydrate, 4 mg sodium starch glycolate, 1.5 mg FD&C Blue No. 1, 4 mg FD&C Yellow No. 6, 1.5 mg FD&C Red No. 40, 1.5 mg gelatin, 2 mg iron oxide, 1.5 mg lactose monohydrate, and 3 mg magnesium stearate.

INDICATIONS
For the management of the manifestations of certain psychotic disorders. Use has not been established for the management of schizophrenia. However, Stelazine should be administered at doses of more than 20 mg per day or for longer than 12 weeks. Because the use of Stelazine at higher doses of for longer intervals may cause persistent tardive dyskinesia that may prove irreversible (see WARNINGS).

The effectiveness of Stelazine as a treatment for non-psychotic anxiety is not established. However, Stelazine is not the first drug to be used in therapy for most patients with non-psychotic anxiety because certain risks associated with its use are not shared by common alternative treatments (i.e., benzodiazepines).

When used in the treatment of non-psychotic anxiety, Stelazine should be administered at doses of more than 20 mg per day or for longer than 12 weeks. Because the use of Stelazine at higher doses of for longer intervals may cause persistent tardive dyskinesia that may prove irreversible (see WARNINGS).
and weight linked to mental toxicity. These effects were not observed at half this dosage. No adverse effect on fetal development was observed in rabbits given 700 times the human dose or in monkeys given 25 times the human dose.

**Precautions**

**General**

Given the likelihood that some patients exposed chronically to antipsychotics may develop tardive dyskinesia, it is advisable for such patients in whom it is contemplated to 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.

Thrombocytopenia and anemia have been reported in patients receiving the drug. Agranulocytosis and pancytopenia have also been reported in rare instances. Patients should report the sudden appearance of fever, sore throat or other signs of infection. If white blood cell and differential counts indicate cellular depression, stop treatment and start antibiotic and other suitable therapy.

Jealousy of the chlorpromazine type of hepatitis or liver damage has been reported, if fever with chills or pain occurs, appropriate liver studies should be conducted. If jaundice is evident, an antagonist, stop treatment.

One result of tardive dyskinesia is an increase in mental and physical activity. For example, a few patients with Holton's disease have complained of increased pain while taking the drug. Therefore, any patient should be observed carefully and, if an unexplained response is noted, the drug should be withdrawn.

Because hypotension has occurred, large doses and parenteral administration should be avoided in patients with impaired cardiovascular systems. To minimize the occurrence of hypotension after injection, keep patient lying down and observe for at least 1/2 hour. If hypotension occurs from intramuscular or oral dosing, place patient in head-down position with legs raised. If a vasopressor is required, Levophed® and Neo-Synephrine® are available. Other pressor agents, including ephedrine, should not be used as they may cause a paradoxical further lowering of blood pressure.

Since certain phenothiazines have been reported to produce retinopathy, the drug should be discontinued if retinopathy on examination or visual field studies should demonstrate retinal changes.

An anesthetic action of Stelazine (trifluoperazine HCl) may mask the signs and symptoms of toxicity or overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as inhaled anesthesia, brain tumor and Reyes's syndrome.

With prolonged administration at high dosages, the possibility of cumulative effects, with evident onset of severe central nervous system or vascular symptoms, should be kept in mind.

**Antipsychotics**

Drugs elevate protective levels; the elevation persists during chronic administration. Tissue culture studies indicate that approximately 1/2 of human breast cancer is preclinical depend on these, a factor of potential importance if the prescribing of these drugs is considered in patients with a previously detected breast cancer. Although disturbances such as gynecomastia, amenorrhea, galactorrhea, 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 antipsychotic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumors or breast cancer; 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 antipsychotics. Because of the risk of chromosomal abnormalities in sperm, antipsychotics may cause fetal harm when administered to pregnant women. Antipsychotics may diminish the effect of oral anti-conceptional agents.

Phenothiazines can produce alpha-adrenergic blockade. Concomitant administration of propranolol with phenothiazines results in increased plasma levels of both drugs.

Antihypersecretive effects of promazine and related compounds may be counteracted when phenothiazines are used concurrently.

The incidence of postural hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Participant sleep disorders can occur in the elderly both spontaneously and during treatment with phenothiazines or other antipsychotics.

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

The presence of phenothiazines may produce false-positive phenylthiourea (PTU) test results.

Long-Term Therapy: To lessen the likelihood of adverse reactions related to cumulative drug effect, patients with a history of long-term therapy with phenothiazine derivatives, H2 receptor antagonists, and/or other antipsychotics should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

ADVERSE REACTIONS

Drowsiness, dizziness, skin reactions, rash, dry mouth, incontinence, anorexia, fatigue, muscular weakness, anorexia, lactation, blurred vision and neuromuscular antipsychomimetic reactions.

Neanoeurotoxic (Neurotoxicity) Reactions

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

Depending on the severity of symptoms, dosage should be reduced or discontinued. If therapy is maintained, it should be at a lower dosage. Should these symptoms occur in children or pregnant women, the drug should be stopped and not reconstituted. In most cases responsiveness to suitable dosage adjustment will suffice. The injectable long-acting may be useful in more severe cases, the administration of an anti-parkinsonian agent, except levodopa (L-dopa) 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 irritability and sometimes insomnia. These symptoms often appear spontaneously. At times these symptoms may be similar to the original neu- rotic or psychotic symptoms. Dosage should not be increased until these side effects have subsided. If this phase becomes too troublesome, the symp- toms can usually be controlled by a reduction of dosage or change of drug. Treatment with anti- parkinsonian agents, benztropine mesylate or propanolol may be helpful.

Dyskinesias: Symptoms may include scanty or absent movements, or, occasionally, flexion or extension, or other movements. These movements may be severe enough to produce conspicuous movements, such as writhing of the tongue, or tremulousness of the face. These movements may be severe enough to produce uncontrolled movements of the body, including the head and neck. The movements may be so severe that they are difficult to control with antipsychotic drugs. In some cases, these movements may be controlled with antipsychotic drugs.

Nausea: Nausea may be severe enough to cause vomiting. This symptom may be controlled with antipsychotic drugs.

Tremor: Tremor may be severe enough to cause loss of balance. This symptom may be controlled with antipsychotic drugs.

Adverse Reactions Reported with Biperiden (Trihexyphenidyl Hydrochloride) or Other Phenothiazine Derivatives: Adverse effects with different phenothiazines may vary in type, frequency, and mechanism of occurrence. In general, adverse effects are more likely to occur at higher doses or in patients with higher body weight. The following side effects have been reported with biperiden: nausea, vomiting, dizziness, orthostatic hypotension, tachycardia, and drowsiness. In some cases, these side effects may be controlled with antipsychotic drugs.

Neuropsychiatric Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. (See WARNINGS.)

Not all of the following adverse reactions have been observed with every phenothiazine derivative, but they have been reported with one or more and should be borne in mind when drugs of this class are administered. Extrapyramidal symptoms (iron- tharamine, dyskinesias, Parkinsonism, akathisia, akinesia, akathisia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, akinesia, 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patients may be maintained on once-a-day administration.

When Stelazine (trifluoperazine) HCI is administered by intramuscular injection, equivalent oral dosage may be substituted once symptoms have been controlled.

Note: Although there is little likelihood of contact dermatitis due to the drug, persons with known sensitivity to phenothiazines drugs should avoid direct contact.

Elderly Patients: In general, dosages in the lower range are more efficient 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 initiated at the individual, response carefully monitored, and dosage adjusted accordingly. Dosage should be increased more gradually in elderly patients.

Neonates and Neonates: Usual dosage is 1 mg twice daily. Do not administer more than 6 mg per day or for longer than 12 weeks.

Revised January-February

Drug-Novel parenteral dosage is 2 mg to 5 mg b.i.d. (Small or emaciated patients should always be started on the lower dosage.)

Most patients will show optimum response on 15 mg or 20 mg daily, although a few may require 40 mg a day or more. Optimum therapeutic dosage levels should be reached within 2 to 3 weeks.

When the Concentrate dosage form is to be used, it should be added to 60 ml of 5% dextrose or 5% dextrose in saline solution or 5% dextrose in water. It should be given in divided doses at intervals of at least 4 hours because of a possible cumulative effect.

SCIENTIFIC RESEARCH—

Note: Stelazine (trifluoperazine) HCI Injection has been extensively and there is little, if any, pain or irritation at the site of injection. This solution should be protected from light. This is a stable, clear, pale yellow solution; a slight yellow discoloration will not alter potency. If markedly discolored, solution should be discarded.

DOSE AND ADMINISTRATION—

Dosage should be adjusted to the weight of the child and severity of the symptoms. These dosages are for children, ages 6 to 12, who are hospitalized or under close supervision.

Once a day, nonoral dosages are 1 mg administered once a day or b.i.d. Dosage may be increased gradually until symptoms are controlled or until side effects become troublesome.

Intramuscular: There has been little experience with the use of Stelazine (trifluoperazine) HCI injection in children. However, if it is necessary to achieve rapid control of severe symptoms, 1 mg (1 ml) of the drug may be administered intramuscularly once or twice a day.

OVERDOSE (See also under ADVERSE REACTIONS.) SYMPTOMS—Primary involvement of the extrapyramidal mechanism producing some of the dystonic reactions described above. Symptoms of central nervous system depression to the point of somnolence or coma. Agranulocytosis and restlessness may also occur. Other possible manifestations include convulsions. EEG changes and cardiac arrhythmias, fever and autonomic reactions such as hypotension, dry mouth, and fever.

TREATMENT—It is important to determine other medications taken by the patient since multiple dose therapy is common in overdose 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 overdose. 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 anticholinergic drugs, barbiturates or Benadryl. See prescribing information for these products. Care should be taken to avoid increasing respiratory depression. If administration of a stimulant is desirable, amphetamine, desoxynormazine or caffeine with sodium benzoate is recommended. Stimulants that may cause convulsions (e.g., procaine or phenyltoluenesulfonate) should be avoided.

If hypotension occurs, the standard measures for managing circulatory shock should be instituted. If it is desirable to administer a vasopressor, Leovas and Neo-Synephrine are most suitable. Other pressor agents, including epinephrine, are not recommended because of the potential for producing dystonic reactions.

Special formulation for institutional use, 10 mg/ml, in 2 oz bottles and in cartons of 12 bottles.

This Concentrate is a light-sensitive. For this reason, it should be protected from light and dispensed in amber bottles. Refrigeration in not recommended. Store at room temperature 10 mg/ml, 2 oz or 10 to 12 oz bottles 10 mg/ml.

Storage of Stelazine (trifluoperazine) HCI formulations between 15° and 30° C. (59° and 86° F.)

* norpinephrine bitartrate, Sanofi Winthrop Pharmaceuticals.

** phenylalanine hydrochloride, Sanofi Winthrop Pharmaceuticals.

† caffeine, Parke-Davis.

‡ verapamil hydrochloride, Sanofi Winthrop Pharmaceuticals.

† diphendyline hydrochloride, Parke-Davis.

DATE OF ISSUE: 1/1/1991

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Printed in U.S.A.

Philadelphia, PA 19101

8 9
/s/
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Russell Katz
4/3/01 10:28:58 AM

APPEARS THIS WAY ON ORIGINAL
Review and Evaluation of Clinical Data
NDA #11-552

Sponsor: SmithKline Beecham
Drug: Stelazine Tablets, Injection, and Concentrate
Indication: Schizophrenia
Material Submitted: SLR-112: Response to Request for Labeling Change
Date Received: December 15, 2000

On 9-25-00, the Division issued a letter to all holders of NDA's for antipsychotic drug products that requested modification of labeling language to more clearly indicate that these agents are indicated for the treatment of schizophrenia. This submission contains the response from SmithKline Beecham with respect to Stelazine.

Amended labeling was reviewed and most of the requested changes have been incorporated into draft labeling. However, in four places in labeling (under DESCRIPTION, INDICATIONS, and in two locations under DOSAGE AND ADMINISTRATION), the sponsor proposes to retain language which suggests that Stelazine is indicated for psychosis, such as or including schizophrenia. They contend that a restriction of the indication to schizophrenia may be misleading to prescribers and would unnecessarily restrict its use since Stelazine is commonly used to treat psychotic disorders of all etiologies.

The purpose of this labeling initiative is to discontinue the currently misleading use of "psychosis" as the indication for these drugs, which were approved on the basis of antipsychotic efficacy in patients with schizophrenia. The fact that off-label use of a drug is common cannot justify the continuance of labeling which suggests efficacy in conditions other than those for which the drug is approved. Hence, the sponsor's objection to these changes is not defensible.
It is recommended that the sponsor be notified that approval of this supplement is contingent on implementation of all requested changes to clearly state that Stelazine is indicated for the treatment of schizophrenia as opposed to the more general indication of psychotic disorders.

Gregory M. Dubitsky, M.D.
January 26, 2001

CC:   NDA #11-552
      HFD-120 (Div. File)
      HFD-120/GDubitsky
      /TLaughren
      /SHardeman
Greg Dubitsky
1/26/01 10:03:35 AM
MEDICAL OFFICER

Thomas Laughren
1/26/01 01:02:17 PM
MEDICAL OFFICER
I agree that this supplement is not approvable.--TPL

APPEARS THIS WAY ON ORIGINAL
NDA 11-552/SLR-112

SmithKline Beecham
Attention: Thomas F. Kline
Assistant Director, U.S. Regulatory Affairs
1250 S. Collegeville Road
P.O.Box 5089
Collegeville, PA 19426

Dear Mr. Kline:

Please refer to your supplemental new drug applications dated December 15, 2000, received December 18, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stelazine (trifluoperazine HCl) Tablets, Injection, and Concentrate.

These supplements were submitted in response to the Agency letter of September 25, 2000, addressed to all holders of NDA's for antipsychotic drugs whose products are labeled as indicated for "the management of the manifestations of psychotic disorders."

We have completed our review and note that most of the changes requested in our letter have been incorporated. However, you assert that a restriction of the indication to schizophrenia may be misleading to prescribers and would unnecessarily restrict its use since Stelazine is commonly used to treat psychotic disorders of all etiologies. Thus, changes under DESCRIPTION, INDICATIONS, and DOSAGE AND ADMINISTRATION are not completely in compliance with our request.

We find the information presented is inadequate, and the supplemental applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

The purpose of this labeling initiative is to abate the currently misleading use of "psychosis" as the indication for these drugs, which were approved on the basis of antipsychotic efficacy in patients with schizophrenia. The fact that off-label use of a drug is common cannot justify the continuance of labeling which suggests efficacy in conditions for which the drug is not approved. Hence, your objection to these changes is not tenable.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.
These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
/s/

Russell Katz
2/2/01 11:24:40 AM

APPEARS THIS WAY ON ORIGINAL
Review and Evaluation of Clinical Data
NDA #11-552

Sponsor: GlaxoSmithKline
Drug: Stelazine
Indication: Schizophrenia
Material Submitted: SLR-112(AL): Response to Request for Labeling Change
Correspondence Date: March 1, 2001
Date Received: March 5, 2001

On 9-25-00, the Division issued a letter to all holders of NDA’s for antipsychotic drug products that requested modification of labeling language to more clearly indicate that these agents are indicated for the treatment of schizophrenia. This submission contains the response from GlaxoSmithKline with respect to Stelazine.

Labeling changes are indicated in Attachment 1 to this submission. These changes were reviewed and are in compliance with our request.

It is recommended that this supplement be approved.

Gregory M. Dubitsky, M.D.
March 26, 2001

APPEARS THIS WAY ON ORIGINAL

cc: NDA #11-552
HFD-120 (Div. Files)
HFD-120/GDubitsky
/TLaughren
/SHardeman
APPEARS THIS WAY
ON ORIGINAL