11552/SLR-112 enc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

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PRESCRIBING INFORMATION

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 imprinted SKF and S03; 2 mg imprinted SKF and S04; 5 mg imprinted SKF and S06; 10 mg imprinted SKF and S07. Inactive ingredients consist of cellulose, croscarmellose sodium, FD&C Blue No. 2, FD&C Yellow No. 6, FD&C Red No. 40, gelatin, iron oxide, lactose, magnesium stearate, talc, titanium dioxide and trace amounts of other inactive ingredients.

Multi-Dose Vials, 10 mL (2 mg/mL)—Each mL contains, in aqueous solution, trifluoperazine, 2 mg, as the hydrochloride; sodium tartrate, 4.75 mg; sodium biphosphate, 11.6 mg; sodium saccharin, 0.3 mg; benzyl alcohol, 0.75%, as preservative.

Concentrate—Each mL of clear, yellow, banana-vanilla-flavored liquid contains 10 mg of trifluoperazine as the hydrochloride. Inactive ingredients consist of D&C Yellow No. 10, FD&C Yellow No. 6, flavor, sodium benzoate, sodium bisulfite, sucrose and water.

N.B.: The Concentrate is for use in severe neuropsychiatric conditions when oral medication is preferred and other oral forms are considered impractical.

schizophrenia

INDICATIONS

For the management of the manifestations of psychotic disorders

: schizophrenia.

Stelazine (trifluoperazine HCl) is effective for the short-term treatment of generalized non-psychotic anxiety. 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 not be administered at doses of more than 6 mg per day or for longer than 12 weeks because the use of *Stelazine* at higher doses or 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 was established in a 4-week clinical multicenter study of outpatients with generalized anxiety disorder (DSM-III). This evidence does not predict that *Stelazine* will be useful in patients with other non-psychotic conditions in which anxiety, or signs that mimic anxiety, are found (i.e., physical illness, organic mental conditions, agitated depression, character pathologies, etc.).

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Stelazine (trifluoperazine HCl) has not been shown effective in the management of behavioral complications in patients with mental retardation.

CONTRAINDICATIONS
A known hypersensitivity to phenothiazines, comatose or greatly depressed states due to central nervous system depressants and, in cases of existing blood dyscrasias, bone marrow depression and pre-existing liver damage.

WARNINGS
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 neuroleptic 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 sta-

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tus 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.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus [illegible] In some instances, the syndrome was followed by irreversible brain damage. Because of a possible causal relationship between these events and the concomitant administration of lithium and [illegible] patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome (NMS).

Patients who have demonstrated a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) with a phenothiazine should not be re-exposed to any phenothiazine, including Stelazine (trifluoperazine HCl), unless in the judgment of the physician the potential benefits of treatment outweigh the possible hazard.

Stelazine Concentrate contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Stelazine (trifluoperazine HCl) 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).

If agents such as sedatives, narcotics, anesthetics, tranquilizers or alcohol are used either simultaneously or successively with the drug, the possibility of an undesirable additive depressant effect should be considered.

Usage in Pregnancy: Safety for the use of *Stelazine* during pregnancy has not been established. Therefore, it is not recommended that the drug be given to pregnant patients except when, in the judgment of the physician, it is essential. The potential benefits should clearly outweigh possible hazards. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

Reproductive studies in rats given over 600 times the human dose showed an increased incidence of malformations above controls and reduced litter size and weight linked to maternal 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 nor in monkeys given 25 times the human dose.

Nursing Mothers: There is evidence that phenothiazines are excreted in the breast milk of nursing mothers. Because of the potential for serious adverse reactions in nursing infants from trifluoperazine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PRECAUTIONS

General

Given the likelihood that some patients exposed chronically to [illegible] 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.

Thrombocytopenia and anemia have been reported in patients receiving the drug. Agranulocytosis and pancytopenia have also been reported—warn patients to report the sudden appearance of 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.

Jaundice of the cholestatic type of hepatitis or liver damage has been reported. If fever with grippe-like symptoms occurs, appropriate liver studies should be conducted. If tests indicate an abnormality, stop treatment.

One result of therapy may be an increase in mental and physical activity. For example, a few patients with angina pectoris have complained of increased pain while taking the drug. Therefore, angina patients should be observed carefully and, if an unfavorable 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 ½ hour. If hypotension occurs from parenteral or oral dosing, place patient in head-low position with legs raised. If a vasoconstrictor is required, Levophed® and Neo-Synephrine® are suitable. Other pressor agents, including epinephrine, 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 ophthalmoscopic examination or visual field studies should demonstrate retinal changes.

An antiemetic 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 intestinal obstruction, brain tumor and Reye's syndrome.

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

[illegible] drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately ½ 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,

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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.

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

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

Phenothiazines may diminish the effect of oral anticoagulants.

Phenothiazines can produce alpha-adrenergic blockade.

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

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

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

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 Dilantin®‡ and thus precipitate *Dilantin* toxicity.

Drugs which lower the seizure threshold, including phenothiazine derivatives, should not be used with Amipaque®§. As with other phenothiazine derivatives, *Stelazine* 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 or postprocedure with *Amipaque*.

The presence of phenothiazines may produce false-positive phenylketonuria (PKU) 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 Stelazine trifluoperazine HCl and/or other neuroleptics 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, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision and neuromuscular (extrapyramidal) reactions.

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 Benadryl®§ 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.

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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 this phase becomes too troublesome, the symptoms can usually be controlled by a reduction of dosage or change of drug. Treatment with antiparkinsonian 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. Also, intravenous caffeine with sodium benzoate seems to be effective. *In children*, reassurance and barbiturates will usually control symptoms. (Or, injectable *Benadryl* may be useful.) Note: See *Benadryl* prescribing information for appropriate children's dosage. If appropriate treatment with anti-parkinsonism agents or *Benadryl* fails to reverse the signs and symptoms, the diagnosis should be reevaluated.

Pseudo-parkinsonism: Symptoms may include: mask-like facies; drooling; tremors; pill-rolling motion; cogwheel rigidity; and shuffling gait. Reassurance and sedation are important. In most cases these symptoms are readily controlled when an anti-parkinsonism agent is administered concomitantly. Anti-parkinsonism agents should be used only when required. Generally, therapy of a few weeks to 2 to 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 Stelazine (trifluoperazine HCl) 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. If clinically feasible, 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 Stelazine (trifluoperazine HCl) or Other Phenothiazine Derivatives: Adverse effects 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 effects 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.

Neuroleptic 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 (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) some of which have lasted months and even years–particularly in elderly patients with previous brain damage; grand mal and petit mal convulsions, particularly in patients with EEG abnormalities or history of such disorders; altered cerebrospinal fluid proteins; cerebral edema; intensification and prolongation of the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol), atropine, heat, organophosphorus insecticides; autonomic reactions (dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis); reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia, hemolytic anemia, aplastic anemia); liver damage (jaundice, biliary stasis); endocrine disturbances (hyperglycemia, hypoglycemia, glycosuria, lactation, galactorrhea, gynecomastia, menstrual irregularities, false-positive pregnancy tests); skin disorders (photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes–particularly nonspecific, usually reversible Q and T wave distortions–have been observed in some patients receiving phenothiazine tranquilizers. Although phenothiazines cause neither psychic nor physical dependance, 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.

DOSAGE AND ADMINISTRATION—ADULTS

Dosage should be adjusted to the needs of the individual. The lowest effective dosage should always be used. Dosage should be increased more gradually in debilitated or emaciated patients. When maximum response is achieved, dosage may be reduced gradually to a maintenance level. Because of the inherent long action of the drug, patients may be controlled on convenient b.i.d. administration; some

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patients may be maintained on once-a-day administration.

When Stelazine (trifluoperazine HCl) 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 phenothiazine drugs should avoid direct contact.

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.

Schizophrenia

Non-psychotic Anxiety
Usual dosage is 1 or 2 mg twice daily. Do not administer at doses of more than 6 mg per day or for longer than 12 weeks.

Psychotic Disorders
Oral: Usual starting 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 or 3 weeks.

When the Concentrate dosage form is to be used, it should be added to 60 mL (2 fl oz) or more of diluent *just prior to administration* to insure palatability and stability. Vehicles suggested for dilution are: tomato or fruit juice, milk, simple syrup, orange syrup, carbonated beverages, coffee, tea or water. Semisolid foods (soup, puddings, etc.) may also be used.

Intramuscular (for prompt control of severe symptoms): Usual dosage is 1 mg to 2 mg (½ to 1 mL) by deep intramuscular injection q4 to 6h, p.r.n. More than 6 mg within 24 hours is rarely necessary.

Only in very exceptional cases should intramuscular dosage exceed 10 mg within 24 hours. Injections should not be given at intervals of less than 4 hours because of a possible cumulative effect.

Note: Stelazine (trifluoperazine HCl) Injection has been usually well tolerated and there is little, if any, pain and irritation at the site of injection.

This solution should be protected from light. This is a clear, colorless to pale yellow solution; a slight yellowish discoloration will not alter potency. If markedly discolored, solution should be discarded.

SCHIZOPHRENIA IN CHILDREN

DOSAGE AND ADMINISTRATION—PSYCHOTIC CHILDREN
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.

Oral: The starting dosage is 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.

While it is usually not necessary to exceed dosages of 15 mg daily, some older children with severe symptoms may require higher dosages.

Intramuscular: There has been little experience with the use of Stelazine (trifluoperazine HCl) injection in children. However, if it is necessary to achieve rapid control of severe symptoms, 1 mg (½ mL) of the drug may be administered intramuscularly once or twice a day.

OVERDOSAGE
(See also under 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 *Benadryl*. 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, *Levophed* and *Neo-Synephrine* 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.

HOW SUPPLIED
Tablets, 1 mg, 2 mg, 5 mg and 10 mg in bottles of 100.

1 mg 100's: NDC 0108-4903-20
2 mg 100's: NDC 0108-4904-20
5 mg 100's: NDC 0108-4906-20
10 mg 100's: NDC 0108-4907-20

Multi-Dose Vials, 10 mL (2 mg/mL), in 1's: NDC 0108-4902-01

Concentrate (for institutional use), 10 mg/mL, in 2 fl oz bottles and in cartons of 12 bottles.

The Concentrate form is light-sensitive. For this reason, it should be protected from light and dispensed in amber bottles. *Refrigeration is not required.*

10 mg/mL 2 fl oz (carton of 12): NDC 0108-4901-42

Store all Stelazine (trifluoperazine HCl) formulations between 15° and 30°C (59° and 86°F).

* norepinephrine bitartrate, Sanofi Winthrop Pharmaceuticals.

† phenylephrine hydrochloride, Sanofi Winthrop Pharmaceuticals.

‡ phenytoin, Parke-Davis.

§ metrizamide, Sanofi Winthrop Pharmaceuticals.

¶ diphenhydramine hydrochloride, Parke-Davis.

DATE OF ISSUANCE APR. 1988

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

S2-L71 Printed in U.S.A.

/s/

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
Correspondence Date:	December 15, 2000
Date Received:	December 18, 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 in 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

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

/s/

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

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

cc: NDA #11-552
HFD-120 (Div. Files)
HFD-120/GDubitsky
/TLaughren
/SHardeman

/s/

Greg Dubitsky
3/26/01 04:49:14 PM
MEDICAL OFFICER

Thomas Laughren
3/27/01 12:25:30 PM
MEDICAL OFFICER
I agree that this supplement may be approved.--TPL