

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

**APPLICATION NUMBER: 10-775/S-031
11-213/S-024**

APPROVAL LETTER



NDA 10-775 / S-031
NDA 11-213 / S-024

Schering Corporation
Attention: Mary Jane Nehring
Sr. Director, Marketed Products Support
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Nehring:

Please refer to your supplemental new drug applications of September 28, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trilafon (perphenazine) Tablets and Injection.

We acknowledge receipt of your submission dated April 19, 2002, which constituted a complete response to our October 18, 2001 action letter.

These supplemental new drug applications provide for revisions to the OVERDOSAGE section of the labeling. The revisions update the description of signs, symptoms, and laboratory findings of acute overdosage and general principles of treatment. (We note that these submissions also provide final printed labeling (FPL), relevant to geriatric use, which was approved in our letter of October 18, 2001, to NDA 10-775 / S-030 and NDA 11-213 / S-022. A separate letter will acknowledge and retain the FPL to these supplements.)

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted April 19, 2002 - copy attached). Accordingly, these supplemental applications are approved effective on the date of this letter.

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.

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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

attachment

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

**APPLICATION NUMBER: 10-775/S-031
11-213/S-024**

APPROVABLE LETTER



NDA 10-775/SLR-031
NDA 11-213/SLR-024

Schering Corporaton
Attention: Mary Jane Nehring
Senior Director, Marketed Products
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Nehring:

Please refer to your supplemental new drug applications dated September 28, 2001, received October 1, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trilafon (perphenazine) Tablets and Injection.

These supplemental applications provide for changes to the OVERDOSAGE section of labeling. The revisions update the description of signs, symptoms, and laboratory findings of acute overdosage and general principles of treatment.

We have completed the review of these applications, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as follows (the following changes have been effected in the attached labeling):

The second sentence under the "Treatment" subsection _____
_____ should be replaced with the following language to more explicitly discourage the induction of emesis and to specifically suggest the use of activated charcoal and gastric lavage --

"Induction of emesis is not recommended because of the possibility of a seizure, CNS depression, or dystonic reaction of the head or neck and subsequent aspiration. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered."

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) 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 (to each application), ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

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NDA 11-213/SLR-024
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If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

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**APPLICATION NUMBER: 10-775/S-031
11-213/S-024**

FINAL PRINTED LABELING

1 **TRILAFON®**

2 **brand of perphenazine, USP**

3 **Tablets,**

4 **Injection**

5

6 **DESCRIPTION** TRILAFON products contain perphenazine, USP (4-[3-(2-
7 chlorophenothiazin-10-yl)propyl]-1-piperazineethanol), a piperazinyl phenothiazine
8 having the chemical formula, C₂₁H₂₆ClN₃OS. They are available as **Tablets**, 2, 4,
9 8, and 16 mg; and **Injection**, perphenazine 5 mg per 1 mL.

10 The inactive ingredients for TRILAFON **Tablets**, 2, 4, 8, and 16 mg, include:
11 acacia, black iron oxide, butylparaben, calcium phosphate, calcium sulfate,
12 carnauba wax, corn starch, lactose, magnesium stearate, sugar, titanium dioxide,
13 and white wax. The inactive ingredients for TRILAFON **Injection** include: citric
14 acid, sodium bisulfite, sodium hydroxide, and water.

15 **ACTIONS** Perphenazine has actions at all levels of the central nervous system,
16 particularly the hypothalamus. However, the site and mechanism of action of
17 therapeutic effect are not known.

18 **CLINICAL PHARMACOLOGY Pharmacokinetics:** Following oral administration
19 of TRILAFON® **Tablets**, mean peak plasma perphenazine concentrations were
20 observed between 1 to 3 hours. The plasma elimination half-life of perphenazine
21 was independent of dose and ranged between 9 and 12 hours. In a study in which
22 normal volunteers (n=12) received TRILAFON 4 mg q8h for 5 days, steady-state
23 concentrations of perphenazine were reached within 72 hours. Mean (%CV) C_{max}
24 and C_{min} values for perphenazine and 7-hydroxyperphenazine at steady-state are
25 listed below:

26	Parameter	Perphenazine	7-Hydroxyperphenazine
27	C _{max} (pg/mL)	984 (43)	509 (25)
28	C _{min} (pg/mL)	442 (76)	350 (56)

29 Peak 7-hydroxyperphenazine concentrations were observed between 2 to 4 hours
30 with a terminal phase half-life ranging between 9.9 to 18.8 hours. Perphenazine is
31 extensively metabolized in the liver to a number of metabolites by sulfoxidation,
32 hydroxylation, dealkylation, and glucuronidation. The pharmacokinetics of
33 perphenazine covary with the hydroxylation of debrisoquine which is mediated by
34 cytochrome P450 2D6 (CYP 2D6) and thus is subject to genetic polymorphism—
35 ie, 7%-10% of Caucasians and a low percentage of Asians have little or no activity
36 and are called “poor metabolizers.” Poor metabolizers of CYP 2D6 will metabolize
37 perphenazine more slowly and will experience higher concentrations compared
38 with normal or “extensive” metabolizers.

39 **INDICATIONS** Perphenazine is indicated for use in the treatment of schizophrenia;
40 and for the control of severe nausea and vomiting in adults.

41 TRILAFON has not been shown effective for the management of behavioral
42 complications in patients with mental retardation.

43 **CONTRAINDICATIONS** TRILAFON products are contraindicated in comatose or
44 greatly obtunded patients and in patients receiving large doses of central nervous
45 system depressants (barbiturates, alcohol, narcotics, analgesics, or anti-
46 histamines); in the presence of existing blood dyscrasias, bone marrow
47 depression, or liver damage; and in patients who have shown hypersensitivity to
48 TRILAFON products, their components, or related compounds.

49 TRILAFON products are also contraindicated in patients with suspected or
50 established subcortical brain damage, with or without hypothalamic damage, since
51 a hyperthermic reaction with temperatures in excess of 104°F may occur in such
52 patients, sometimes not until 14 to 16 hours after drug administration. Total body
53 ice-packing is recommended for such a reaction; antipyretics may also be useful.

54 **WARNINGS** Tardive dyskinesia, a syndrome consisting of potentially irreversible,
55 involuntary, dyskinetic movements, may develop in patients treated with
56 antipsychotic drugs. Older patients are at increased risk for development of tardive
57 dyskinesia. Although the prevalence of the syndrome appears to be highest among

58 the elderly, especially elderly women, it is impossible to rely upon prevalence
59 estimates to predict, at the inception of antipsychotic treatment, which patients are
60 likely to develop the syndrome. Whether antipsychotic drug products differ in their
61 potential to cause tardive dyskinesia is unknown.

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

67 There is no known treatment for established cases of tardive dyskinesia,
68 although the syndrome may remit, partially or completely, if antipsychotic treatment
69 is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially
70 suppress) the signs and symptoms of the syndrome, and thereby may possibly
71 mask the underlying disease process. The effect that symptomatic suppression
72 has upon the long-term course of the syndrome is unknown.

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

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

85 (For further information about the description of tardive dyskinesia and its
86 clinical detection, please refer to **Information for Patients** and **ADVERSE**
87 **REACTIONS**.)

88 TRILAFON **Injection** contains sodium bisulfite, a sulfite that may cause
89 allergic-type reactions including anaphylactic symptoms and life-threatening or less
90 severe asthmatic episodes in certain susceptible people. The overall prevalence of
91 sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

92 **NEUROLEPTIC MALIGNANT SYNDROME (NMS)**

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

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

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

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

114 If hypotension develops, epinephrine should not be administered since its
115 action is blocked and partially reversed by perphenazine. If a vasopressor is
116 needed, norepinephrine may be used. Severe, acute hypotension has occurred
117 with the use of phenothiazines and is particularly likely to occur in patients with

118 mitral insufficiency or pheochromocytoma. Rebound hypertension may occur in
119 pheochromocytoma patients.

120 TRILAFON products can lower the convulsive threshold in susceptible
121 individuals; they should be used with caution in alcohol withdrawal and in patients
122 with convulsive disorders. If the patient is being treated with an anticonvulsant
123 agent, increased dosage of that agent may be required when TRILAFON products
124 are used concomitantly.

125 TRILAFON products should be used with caution in patients with psychic
126 depression.

127 Perphenazine may impair the mental and/or physical abilities required for the
128 performance of hazardous tasks such as driving a car or operating machinery;
129 therefore, the patient should be warned accordingly.

130 TRILAFON products are not recommended for pediatric patients under 12
131 years of age.

132 Usage in Pregnancy: Safe use of TRILAFON during pregnancy and lactation has
133 not been established; therefore, in administering the drug to pregnant patients,
134 nursing mothers, or women who may become pregnant, the possible benefits must
135 be weighed against the possible hazards to mother and child.

136 **PRECAUTIONS** The possibility of suicide in depressed patients remains during
137 treatment and until significant remission occurs. This type of patient should not
138 have access to large quantities of this drug.

139 As with all phenothiazine compounds, perphenazine should not be used
140 indiscriminately. Caution should be observed in giving it to patients who have
141 previously exhibited severe adverse reactions to other phenothiazines. Some of
142 the untoward actions of perphenazine tend to appear more frequently when high
143 doses are used. However, as with other phenothiazine compounds, patients
144 receiving TRILAFON products in any dosage should be kept under close
145 supervision.

146 Antipsychotic drugs elevate prolactin levels; the elevation persists during
147 chronic administration. Tissue culture experiments indicate that approximately one-

148 third of human breast cancers are prolactin dependent *in vitro*, a factor of potential
149 importance if the prescription of these drugs is contemplated in a patient with a
150 previously detected breast cancer. Although disturbances such as galactorrhea,
151 amenorrhea, gynecomastia, and impotence have been reported, the clinical
152 significance of elevated serum prolactin levels is unknown for most patients. An
153 increase in mammary neoplasms has been found in rodents after chronic
154 administration of antipsychotic drugs. Neither clinical studies nor epidemiologic
155 studies conducted to date, however, have shown an association between chronic
156 administration of these drugs and mammary tumorigenesis; the available evidence
157 is considered too limited to be conclusive at this time.

158 The antiemetic effect of perphenazine may obscure signs of toxicity due to
159 overdosage of other drugs, or render more difficult the diagnosis of disorders such
160 as brain tumors or intestinal obstruction.

161 A significant, not otherwise explained, rise in body temperature may suggest
162 individual intolerance to perphenazine, in which case it should be discontinued.

163 Patients on large doses of a phenothiazine drug who are undergoing surgery
164 should be watched carefully for possible hypotensive phenomena. Moreover,
165 reduced amounts of anesthetics or central nervous system depressants may be
166 necessary.

167 Since phenothiazines and central nervous system depressants (opiates,
168 analgesics, antihistamines, barbiturates) can potentiate each other, less than the
169 usual dosage of the added drug is recommended and caution is advised when
170 they are administered concomitantly.

171 Use with caution in patients who are receiving atropine or related drugs
172 because of additive anticholinergic effects and also in patients who will be exposed
173 to extreme heat or phosphorus insecticides.

174 The use of alcohol should be avoided, since additive effects and hypotension
175 may occur. Patients should be cautioned that their response to alcohol may be
176 increased while they are being treated with TRILAFON products. The risk of

177 suicide and the danger of overdose may be increased in patients who use alcohol
178 excessively due to its potentiation of the drug's effect.

179 Blood counts and hepatic and renal functions should be checked periodically.
180 The appearance of signs of blood dyscrasias requires the discontinuance of the
181 drug and institution of appropriate therapy. If abnormalities in hepatic tests occur,
182 phenothiazine treatment should be discontinued. Renal function in patients on
183 long-term therapy should be monitored; if blood urea nitrogen (BUN) becomes
184 abnormal, treatment with the drug should be discontinued.

185 The use of phenothiazine derivatives in patients with diminished renal function
186 should be undertaken with caution.

187 Use with caution in patients suffering from respiratory impairment due to acute
188 pulmonary infections, or in chronic respiratory disorders such as severe asthma or
189 emphysema.

190 In general, phenothiazines, including perphenazine, do not produce psychic
191 dependence. Gastritis, nausea and vomiting, dizziness, and tremulousness have
192 been reported following abrupt cessation of high-dose therapy. Reports suggest
193 that these symptoms can be reduced by continuing concomitant antiparkinson
194 agents for several weeks after the phenothiazine is withdrawn.

195 The possibility of liver damage, corneal and lenticular deposits, and irreversible
196 dyskinesias should be kept in mind when patients are on long-term therapy.

197 Because photosensitivity has been reported, undue exposure to the sun should
198 be avoided during phenothiazine treatment.

199 **Drug Interactions:** Metabolism of a number of medications, including
200 antipsychotics, antidepressants, β -blockers, and antiarrhythmics, occurs through
201 the cytochrome P450 2D6 isoenzyme (debrisoquine hydroxylase). Approximately
202 10% of the Caucasian population has reduced activity of this enzyme, so-called
203 'poor' metabolizers. Among other populations the prevalence is not known. Poor
204 metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at
205 usual doses, which may correlate with emergence of side effects. In one study of
206 45 elderly patients suffering from dementia treated with perphenazine, the 5

207 patients who were prospectively identified as poor P450 2D6 metabolizers had
208 reported significantly greater side effects during the first 10 days of treatment than
209 the 40 extensive metabolizers, following which the groups tended to converge.
210 Prospective phenotyping of elderly patients prior to antipsychotic treatment may
211 identify those at risk for adverse events.

212 The concomitant administration of other drugs that inhibit the activity of
213 P450 2D6 may acutely increase plasma concentrations of antipsychotics. Among
214 these are tricyclic antidepressants and selective serotonin reuptake inhibitors,
215 e.g. fluoxetine, sertraline, and paroxetine. When prescribing these drugs to patients
216 already receiving antipsychotic therapy, close monitoring is essential and dose
217 reduction may become necessary to avoid toxicity. Lower doses than usually
218 prescribed for either the antipsychotic or the other drug may be required.

219 **Information for Patients:** This information is intended to aid in the safe and
220 effective use of this medication. It is not a disclosure of all possible adverse or
221 intended effects.

222 Given the likelihood that a substantial proportion of patients exposed
223 chronically to antipsychotics will develop tardive dyskinesia, it is advised that all
224 patients in whom chronic use is contemplated be given, if possible, full information
225 about this risk. The decision to inform patients and/or their guardians must
226 obviously take into account the clinical circumstances and the competency of the
227 patient to understand the information provided.

228 **Geriatric Use:** Clinical studies of TRILAFON products did not include sufficient
229 numbers of subjects aged 65 and over to determine whether elderly subjects
230 respond differently from younger subjects. Other reported clinical experience has
231 not identified differences in responses between the elderly and younger patients.
232 In general, dose selection for an elderly patient should be cautious, usually starting
233 at the low end of the dosing range, reflecting the greater frequency of decreased
234 hepatic function, concomitant disease or other drug therapy.

235 Geriatric patients are particularly sensitive to the side effects of
236 antipsychotics, including TRILAFON. These side effects include extrapyramidal

237 symptoms (tardive dyskinesia, antipsychotic-induced parkinsonism, akathisia),
238 anticholinergic effects, sedation and orthostatic hypotension (See **WARNINGS**).
239 Elderly patients taking psychotropic drugs may be at increased risk for falling and
240 consequent hip fractures. Elderly patients should be started on lower doses and
241 observed closely.

242 **ADVERSE REACTIONS** Not all of the following adverse reactions have been
243 reported with this specific drug; however, pharmacological similarities among
244 various phenothiazine derivatives require that each be considered. With the
245 piperazine group (of which perphenazine is an example), the extrapyramidal
246 symptoms are more common, and others (eg, sedative effects, jaundice, and blood
247 dyscrasias) are less frequently seen.

248 **CNS Effects:** *Extrapyramidal reactions:* opisthotonus, trismus, torticollis,
249 retrocollis, aching and numbness of the limbs, motor restlessness, oculogyric
250 crisis, hyperreflexia, dystonia, including protrusion, discoloration, aching and
251 rounding of the tongue, tonic spasm of the masticatory muscles, tight feeling in the
252 throat, slurred speech, dysphagia, akathisia, dyskinesia, parkinsonism, and ataxia.
253 Their incidence and severity usually increase with an increase in dosage, but there
254 is considerable individual variation in the tendency to develop such symptoms.
255 Extrapyramidal symptoms can usually be controlled by the concomitant use of
256 effective antiparkinsonian drugs, such as benztropine mesylate, and/or by
257 reduction in dosage. In some instances, however, these extrapyramidal reactions
258 may persist after discontinuation of treatment with perphenazine.

259 *Persistent tardive dyskinesia:* As with all antipsychotic agents, tardive
260 dyskinesia may appear in some patients on long-term therapy or may appear after
261 drug therapy has been discontinued. Although the risk appears to be greater in
262 elderly patients on high-dose therapy, especially females, it may occur in either
263 sex and in children. The symptoms are persistent and in some patients appear to
264 be irreversible. The syndrome is characterized by rhythmical, involuntary
265 movements of the tongue, face, mouth, or jaw (eg, protrusion of tongue, puffing of
266 cheeks, puckering of mouth, chewing movements). Sometimes these may be

267 accompanied by involuntary movements of the extremities. There is no known
268 effective treatment for tardive dyskinesia; antiparkinsonism agents usually do not
269 alleviate the symptoms of this syndrome. It is suggested that all antipsychotic
270 agents be discontinued if these symptoms appear. Should it be necessary to
271 reinstitute treatment, or increase the dosage of the agent, or switch to a different
272 antipsychotic agent, the syndrome may be masked. It has been reported that fine,
273 vermicular movements of the tongue may be an early sign of the syndrome, and if
274 the medication is stopped at that time the syndrome may not develop.

275 *Other CNS effects* include cerebral edema; abnormality of cerebrospinal fluid
276 proteins; convulsive seizures, particularly in patients with EEG abnormalities or a
277 history of such disorders; and headaches.

278 Neuroleptic malignant syndrome has been reported in patients treated with
279 antipsychotic drugs (see **WARNINGS** section for further information).

280 Drowsiness may occur, particularly during the first or second week, after which
281 it generally disappears. If troublesome, lower the dosage. Hypnotic effects appear
282 to be minimal, especially in patients who are permitted to remain active.

283 Adverse behavioral effects include paradoxical exacerbation of psychotic
284 symptoms, catatonic-like states, paranoid reactions, lethargy, paradoxical
285 excitement, restlessness, hyperactivity, nocturnal confusion, bizarre dreams, and
286 insomnia.

287 Hyperreflexia has been reported in the newborn when a phenothiazine was
288 used during pregnancy.

289 **Autonomic Effects:** dry mouth or salivation, nausea, vomiting, diarrhea,
290 anorexia, constipation, obstipation, fecal impaction, urinary retention, frequency or
291 incontinence, bladder paralysis, polyuria, nasal congestion, pallor, myosis,
292 mydriasis, blurred vision, glaucoma, perspiration, hypertension, hypotension, and
293 change in pulse rate occasionally may occur. Significant autonomic effects have
294 been infrequent in patients receiving less than 24 mg perphenazine daily.

295 Adynamic ileus occasionally occurs with phenothiazine therapy and if severe
296 can result in complications and death. It is of particular concern in psychiatric
297 patients, who may fail to seek treatment of the condition.

298 **Allergic Effects:** urticaria, erythema, eczema, exfoliative dermatitis, pruritus,
299 photosensitivity, asthma, fever, anaphylactoid reactions, laryngeal edema, and
300 angioneurotic edema; contact dermatitis in nursing personnel administering the
301 drug; and in extremely rare instances, individual idiosyncrasy or hypersensitivity to
302 phenothiazines has resulted in cerebral edema, circulatory collapse, and death.

303 **Endocrine Effects:** lactation, galactorrhea, moderate breast enlargement in
304 females and gynecomastia in males on large doses, disturbances in the menstrual
305 cycle, amenorrhea, changes in libido, inhibition of ejaculation, syndrome of
306 inappropriate ADH (antidiuretic hormone) secretion, false positive pregnancy tests,
307 hyperglycemia, hypoglycemia, glycosuria.

308 **Cardiovascular Effects:** postural hypotension, tachycardia (especially with
309 sudden marked increase in dosage), bradycardia, cardiac arrest, faintness, and
310 dizziness. Occasionally the hypotensive effect may produce a shock-like
311 condition. ECG changes, nonspecific (quinidinelike effect) usually reversible, have
312 been observed in some patients receiving phenothiazine antipsychotics.

313 Sudden death has occasionally been reported in patients who have received
314 phenothiazines. In some cases the death was apparently due to cardiac arrest; in
315 others, the cause appeared to be asphyxia due to failure of the cough reflex. In
316 some patients, the cause could not be determined nor could it be established that
317 the death was due to the phenothiazine.

318 **Hematological Effects:** agranulocytosis, eosinophilia, leukopenia, hemolytic
319 anemia, thrombocytopenic purpura, and pancytopenia. Most cases of
320 agranulocytosis have occurred between the fourth and tenth weeks of therapy.
321 Patients should be watched closely, especially during that period, for the sudden
322 appearance of sore throat or signs of infection. If white blood cell and differential
323 cell counts show significant cellular depression, discontinue the drug and start

324 appropriate therapy. However, a slightly lowered white count is not in itself an
325 indication to discontinue the drug.

326 **Other Effects:** Special considerations in long-term therapy include
327 pigmentation of the skin, occurring chiefly in the exposed areas; ocular changes
328 consisting of deposition of fine particulate matter in the cornea and lens,
329 progressing in more severe cases to star-shaped lenticular opacities; epithelial
330 keratopathies; and pigmentary retinopathy. Also noted: peripheral edema,
331 reversed epinephrine effect, increase in PBI not attributable to an increase in
332 thyroxine, parotid swelling (rare), hyperpyrexia, systemic lupus erythematosuslike
333 syndrome, increases in appetite and weight, polyphagia, photophobia, and muscle
334 weakness.

335 Liver damage (biliary stasis) may occur. Jaundice may occur, usually between
336 the second and fourth weeks of treatment, and is regarded as a hypersensitivity
337 reaction. Incidence is low. The clinical picture resembles infectious hepatitis but
338 with laboratory features of obstructive jaundice. It is usually reversible; however,
339 chronic jaundice has been reported.

340 Side effects with intramuscular TRILAFON **Injection** have been infrequent and
341 transient. Dizziness or significant hypotension after treatment with TRILAFON
342 **Injection** is a rare occurrence.

343 **DOSAGE AND ADMINISTRATION** Dosage must be individualized and adjusted
344 according to the severity of the condition and the response obtained. As with all
345 potent drugs, the best dose is the lowest dose that will produce the desired clinical
346 effect. Since extrapyramidal symptoms increase in frequency and severity with
347 increased dosage, it is important to employ the lowest effective dose. These
348 symptoms have disappeared upon reduction of dosage, withdrawal of the drug, or
349 administration of an antiparkinsonian agent.

350 Prolonged administration of doses exceeding 24 mg daily should be reserved
351 for hospitalized patients or patients under continued observation for early detection
352 and management of adverse reactions. An antiparkinsonian agent, such as

353 trihexyphenidyl hydrochloride or benztropine mesylate, is valuable in controlling
354 drug-induced extrapyramidal symptoms.

355 TRILAFON Tablets

356 Suggested dosages for **Tablets** for various conditions follow:

357 *Moderately disturbed nonhospitalized patients with schizophrenia: Tablets* 4 to
358 8 mg tid initially; reduce as soon as possible to minimum effective dosage.

359 *Hospitalized patients with schizophrenia: Tablets* 8 to 16 mg bid to qid; avoid
360 dosages in excess of 64 mg daily.

361 *Severe nausea and vomiting in adults: Tablets* 8 to 16 mg daily in divided
362 doses; 24 mg occasionally may be necessary; early dosage reduction is desirable.

363 TRILAFON Injection

364 Intramuscular Administration

365 The injection is used when rapid effect and prompt control of acute or
366 intractable conditions is required or when oral administration is not feasible.
367 **TRILAFON Injection**, administered by deep intramuscular injection, is well
368 tolerated. The injection should be given with the patient seated or recumbent, and
369 the patient should be observed for a short period after administration.

370 Therapeutic effect is usually evidenced in 10 minutes and is maximal in 1 to 2
371 hours. The average duration of effective action is 6 hours, occasionally 12 to 24
372 hours.

373 Pediatric dosage has not yet been established. Pediatric patients over 12 years
374 may receive the lowest limit of adult dosage.

375 The usual initial dose is 5 mg (1 mL). This may be repeated every 6 hours.
376 Ordinarily, the total daily dosage should not exceed 15 mg in ambulatory patients
377 or 30 mg in hospitalized patients. When required for satisfactory control of
378 symptoms in severe conditions, an initial 10-mg intramuscular dose may be given.
379 Patients should be placed on oral therapy as soon as practicable. Generally, this
380 may be achieved within 24 hours. In some instances, however, patients have been
381 maintained on injectable therapy for several months. It has been established that

382 TRILAFON **Injection** is more potent than TRILAFON **Tablets**. Therefore, equal or
383 higher dosage should be used when the patient is transferred to oral therapy after
384 receiving the injection.

385 *Schizophrenia:* While 5 mg of the **Injection** has a definite tranquilizing effect, it
386 may be necessary to use 10-mg doses to initiate therapy in severely agitated
387 schizophrenic states. Most patients will be controlled and amenable to oral therapy
388 within a maximum of 24 to 48 hours. Acute schizophrenic conditions (hysteria,
389 panic reaction) often respond well to a single dose, whereas in chronic conditions,
390 several injections may be required. When transferring patients to oral therapy, it is
391 suggested that increased dosage be employed to maintain adequate clinical
392 control. This should be followed by gradual reduction to the minimal maintenance
393 dose which is effective.

394 *Severe nausea and vomiting in adults:* To obtain rapid control of vomiting,
395 administer 5 mg (1 mL); in rare instances it may be necessary to increase the dose
396 to 10 mg; in general, higher doses should be given only to hospitalized patients.

397 Intravenous Administration

398 The intravenous administration of TRILAFON **Injection** is seldom required.
399 This route of administration should be used with particular caution and care, and
400 only when absolutely necessary to control severe vomiting, intractable hiccoughs,
401 or acute conditions, such as violent retching during surgery. Its use should be
402 limited to recumbent hospitalized adults in doses not exceeding 5 mg. When
403 employed in this manner, intravenous injection ordinarily should be given as a
404 diluted solution by either fractional injection or a slow drip infusion. In the surgical
405 patient, slow infusion of not more than 5 mg is preferred. When administered in
406 divided doses, TRILAFON **Injection** should be diluted to 0.5 mg/mL (1mL mixed
407 with 9 mL of physiologic saline solution), and not more than 1 mg per injection
408 given at not less than 1- to 2-minute intervals. Intravenous injection should be
409 discontinued as soon as symptoms are controlled and should not exceed 5 mg.
410 The possibility of hypotensive and extrapyramidal side effects should be

411 considered and appropriate means for management kept available. Blood pressure
412 and pulse should be monitored continuously during intravenous administration.

413 Pharmacologic and clinical studies indicate that intravenous administration of
414 norepinephrine should be useful in alleviating the hypotensive effect.

415 **Elderly patients:** With increasing age, plasma concentrations of perphenazine
416 per daily ingested dose increase. Geriatric dosages of perphenazine preparations
417 have not been established, but initiation of lower dosages is recommended.
418 Optimal clinical effect or benefit may require lower doses for a longer duration.
419 Dosing of perphenazine may occur before bedtime, for agitation, if required.

420 **OVERDOSAGE** In the event of overdose, emergency treatment should be
421 started immediately. Consultation with a poison center should be considered. All
422 patients suspected of having taken an overdose should be hospitalized as soon as
423 possible.

424 **Manifestations** The toxic effects of perphenazine are typically mild to
425 moderate with death occurring in cases involving a large overdose. Overdosage of
426 perphenazine primarily involves the extrapyramidal mechanism and produces the
427 same side effects described under **ADVERSE REACTIONS**, but to a more marked
428 degree. It is usually evidenced by stupor or coma; children may have convulsive
429 seizures. Signs of arousal may not occur for 48 hours. The primary effects of
430 medical concern are cardiac in origin including tachycardia, prolongation of the
431 QRS or QTc intervals, atrioventricular block, torsade de pointes, ventricular
432 dysrhythmia, hypotension or cardiac arrest, which indicate serious poisoning.
433 Deaths by deliberate or accidental overdose have occurred with this class of
434 drugs.

435 **Treatment** Treatment is symptomatic and supportive. Induction of emesis is
436 not recommended because of the possibility of a seizure, CNS depression, or
437 dystonic reaction of the head or neck and subsequent aspiration. Gastric lavage
438 (after intubation, if the patient is unconscious) and administration of activated
439 charcoal together with a laxative should be considered. There is no specific
440 antidote. The patient should be induced to vomit even if emesis has occurred

441 spontaneously. Pharmacologic vomiting by the administration of ipecac syrup is a
442 preferred method. It should be noted that ipecac has a central mode of action in
443 addition to its local gastric irritant properties, and the central mode of action may
444 be blocked by the antiemetic effect of TRILAFON products. Vomiting should not be
445 induced in patients with impaired consciousness. The action of ipecac is facilitated
446 by physical activity and by the administration of 8 to 12 fluid ounces of water. If
447 emesis does not occur within 15 minutes, the dose of ipecac should be repeated.
448 Precautions against aspiration must be taken, especially in infants and children.
449 Following emesis, any drug remaining in the stomach may be adsorbed by
450 activated charcoal administered as a slurry with water. If vomiting is unsuccessful
451 or contraindicated, gastric lavage should be performed. Isotonic and one-half
452 isotonic saline are the lavage solutions of choice. Saline cathartics, such as milk of
453 magnesia, draw water into the bowel by osmosis and therefore, may be valuable
454 for their action in rapid dilution of bowel content.

455 Standard measures (oxygen, intravenous fluids, corticosteroids) should be
456 used to manage circulatory shock or metabolic acidosis. An open airway and
457 adequate fluid intake should be maintained. Body temperature should be
458 regulated. Hypothermia is expected, but severe hyperthermia may occur and must
459 be treated vigorously. (See **CONTRAINDICATIONS**.)

460 An electrocardiogram should be taken and close monitoring of cardiac function
461 instituted if there is any sign of abnormality. Cardiac arrhythmias may be treated
462 with neostigmine, pyridostigmine, or propranolol. Digitalis should be considered for
463 cardiac failure. Close monitoring of cardiac function is advisable for not less than
464 five days. Vasopressors such as norepinephrine may be used to treat hypotension,
465 but epinephrine should NOT be used.

466 Anticonvulsants (an inhalation anesthetic, diazepam, or paraldehyde) are
467 recommended for control of convulsions, since perphenazine increases the central
468 nervous system depressant action, but not the anticonvulsant action of
469 barbiturates.

470 If acute parkinson like symptoms result from perphenazine intoxication,
471 benztrapine mesylate or diphenhydramine may be administered.

472 Central nervous system depression may be treated with nonconvulsant doses
473 of CNS stimulants. Avoid stimulants that may cause convulsions (eg, picrotoxin
474 and pentylenetetrazol).

475 Signs of arousal may not occur for 48 hours.

476 Hemodialysis and peritoneal dialysis is of no value because of low plasma
477 concentrations of the drug.

478 Since overdosage is often deliberate, patients may attempt suicide by other
479 means during the recovery phase. Deaths by deliberate or accidental overdosage
480 have occurred with this class of drugs.

481 **HOW SUPPLIED TRILAFON Tablets (2 mg):** gray, sugar-coated tablets branded
482 in black with the Schering trademark and the numbers, 1229; bottles of 100 (NDC
483 0085-1229-01). **Store between 2° and 25°C (36° and 77°F).**

484 **TRILAFON Tablets (4 mg):** gray, sugar-coated tablets branded in green with the
485 Schering trademark and the numbers, 1232; bottles of 100 (NDC 0085-1232-01).
486 **Store between 2° and 25°C (36° and 77°F).**

487 **TRILAFON Tablets (8 mg):** gray, sugar-coated tablets branded in blue with the
488 Schering trademark the numbers, 1251; bottles of 100 (NDC 0085-1251-01). **Store**
489 **between 2° and 25°C (36° and 77°F).**

490 **TRILAFON Tablets (16 mg):** gray, sugar-coated tablets branded in red with the
491 Schering trademark and the numbers, 1237; bottles of 100 (NDC 0085-1237-01).
492 **Store between 2° and 25°C (36° and 77°F).**

493 **TRILAFON Injection, 5 mg per mL, 1-mL ampule** for intramuscular or intravenous
494 use, box of 100 (NDC 0085-0012-04). **Store between 2° and 30°C (36° and**
495 **86°F).** Keep package closed to protect from light. Exposure may cause
496 discoloration. Slight yellowish discoloration will not alter potency or therapeutic
497 efficacy; if markedly discolored, ampule should be discarded. **Protect from light.**
498 **Store in carton until completely used.**

499

500 TRILAFON®

501 brand of perphenazine, USP

502 **Tablets,**

503 **Injection**

504 Schering Corporation

505 Kenilworth, NJ 07033 USA

506 Rev. 11/00 ~~4/02~~

507

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/s/

Russell Katz
5/10/02 08:06:04 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

**APPLICATION NUMBER: 10-775/S-031
11-213/S-024**

MEDICAL REVIEW

Review and Evaluation of Clinical Data
NDA 10-775

Sponsor: Schering Corporation
Drug: Trilafon Tablets
Proposed Indication: Schizophrenia
Material Submitted: Supplement SLR-031: Overdosage
Correspondence Dates: September 28, 2001
Dates Received: October 1, 2001
Related Submission: NDA 11-213, SLR-024 (Trilafon Inj.)

I. Background

The sponsor is submitting these labeling supplements to update the "Overdosage" section of Trilafon labeling.

II. Proposed Labeling Changes

Basically, the sponsor is proposing the following additions to and deletions from the "Overdosage" section of labeling:

ADD

- consider consultation with a poison center.
- toxic effects of perphenazine are typically mild to moderate with death occurring in cases involving a large overdose.
- primary effects of medical concern are cardiac in origin, including tachycardia, prolongation of the QRS or QTc intervals, atrioventricular block, torsade de pointes, ventricular dysrhythmia, hypotension or cardiac arrest indicating serious poisoning.

-
- specify that hemodialysis and peritoneal dialysis are of no value.

DELETE

III. Conclusions and Recommendations

The sponsor provided no supportive data for these revisions to labeling.

I evaluated the proposed revisions for this section vis-a-vis information regarding phenothiazine overdose contained in POISINDEX.¹ POISINDEX was chosen as the reference source because it has been regarded as reflecting current thinking by "experts" in the field of toxicology.²

The changes proposed by the sponsor are acceptable with one exception. The second sentence under the "Treatment" subsection

_____") should be replaced with the following language to more explicitly discourage the induction of emesis and to specifically suggest the use of activated charcoal and gastric lavage:

Induction of emesis is not recommended because of the possibility of a seizure, CNS depression, or dystonic reaction of the head or neck and subsequent aspiration. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

When the sponsor agrees to add the above language or similar text, these supplements may be approved.

¹ As accessed via WebLern under the Micromedex® Healthcare Series.

² According to a personal conversation between the undersigned reviewer and Dan Spyker, M.D., an Agency consultant in overdose issues, in February 1998.

Gregory M. Dubitsky, M.D.
October 16, 2001

cc: NDA #10-775
NDA #11-213
HFD-120 (Division Files)
HFD-120/GDubitsky
/TLaughren

/SHardeman

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