10.775/SLR.029 rsp.
11.213/SLR.021 rsp.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 10-775/SLR-029
NDA 11-213/SLR-021

Schering Corporation
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 December 20, 2000, received December 22, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trilafon (perphenazine) tablets and injection.

These "Changes Being Effected" supplemental new drug applications provide for the labeling changes 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 these supplemental applications 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 December 20, 2000). 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.

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
3/15/01 08:37:51 AM

APPEARS THIS WAY
ON ORIGINAL

Review and Evaluation of Clinical Data
NDA # 10-775

Sponsor:	Schering Corporation
Drug:	Trilafon Tablets
Proposed Indication:	Schizophrenia
Material Submitted:	Geriatric Labeling Supplement: SLR-030
Correspondence Date:	January 25, 2001
Date Received:	January 26, 2001
Related Submission:	NDA 11-213, SLR-022 (Trilafon Injection)

I. Background

These submissions provide for the addition of information regarding geriatric use to Trilafon labeling in accordance with the final rule published in the Federal Register on August 27, 1997, and with 21 CFR 201.57(f)(10).

II. Clinical Data

The sponsor examined a listing of all post-marketing adverse event reports in their Drug Safety and Surveillance database involving patients age 65 and older. This listing is presented as Attachment 3 to this submission. They concluded that these events were of the same type as those observed in younger patients.

Additionally, the sponsor performed a literature search on June 20, 2000, using a number of databases (including MedLine, EmBase, Biosis, ToxLine, and Scholar) to locate data relevant to the use of perphenazine in geriatric patients. The results of this search are provided as Attachment 4 to this submission. Complete copies of those articles felt to be most relevant to their proposed labeling changes are included as Attachment 5.

III. Proposed Labeling Changes

Proposed labeling changes are as follows:

- under the Tardive Dyskinesia subsection of WARNINGS, the following statement would be added to the first paragraph:

"Older patients may be at increased risk for development of tardive dyskinesia, and it is more likely to be persistent or severe."

- the following would be added to a Drug Interactions subsection under PRECAUTIONS to describe potential interactions via P450 2D6:

"Metabolism of a number of medications, including antipsychotics, antidepressants, beta-blockers, and antiarrhythmics, occurs through the cytochrome P450 2D6 isoenzyme (debrisoquine hydroxylase). Approximately 10% of the Caucasian population has reduced activity of this enzyme, so-called "poor" metabolizers. Among other populations the prevalence is not known. Poor metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of side effects. In one study of 45 elderly patients suffering from dementia treated with perphenazine, the 5 patients who were prospectively identified as poor P450 2D6 metabolizers had significantly greater side effects than the 40 extensive metabolizers.

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

- The Geriatric Use subsection under PRECAUTIONS will contain the following text:

"Clinical studies of TRILAFON did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (1/4 of the usual adult dose), reflecting the greater frequency of decreased hepatic function, concomitant disease or other drug therapy.

Geriatric patients are particularly sensitive to the side effects of antipsychotics, including TRILAFON. These side effects include extrapyramidal symptoms (tardive dyskinesia, neuroleptic-induced parkinsonism, akathisia), anticholinergic effects, sedation and orthostatic hypotension (See WARNINGS). Elderly patients taking psychotropic drugs may be at increased risk for falling."

• A subsection entitled "Elderly Patients" will follow suggested dosages under DOSAGE AND ADMINISTRATION and will contain the text below:

"With increasing age, plasma concentrations of perphenazine per daily ingested dose increase. Geriatric dosages of perphenazine preparations have not been established, but initiation of lower dosages is recommended . Optimal clinical effect or benefit may require lower doses for a longer duration. Dosing of perphenazine may occur before bedtime, in case of agitation."

Literature articles supporting the above changes are included as Attachment 5 of the submission.

IV. Conclusions and Recommendations

In general, the labeling changes proposed by the sponsor are acceptable. However, some of the specific language merits further justification:

1) In the WARNINGS statement, the cited references do not provide the data which support their assertion that

" compared to younger patients. While this may be true, it is reasonable to ask the sponsor to provide these data before permitting this statement to be added to labeling.

2) In the Drug Interactions subsection of PRECAUTIONS, the description of the study of perphenazine in poor and extensive P450 2D6 metabolizers should be qualified by adding that the poor metabolizers had reported significantly greater side effects during the first 10 days of treatment. Thereafter, the poor and extensive metabolizer groups tended to converge, according to the supporting literature article (Pollock BG, et al. Psychopharm Bull 1995;31(2):327-332).

3) In the Geriatric Use subsection of PRECAUTIONS, the rationale for recommending that ——— is not clear. For some psychotropic agents (e.g., Paxil), the starting dose in the elderly is one-half of the usual adult dose and it is not clear why such a recommendation couldn't be made for perphenazine. Also, an option would be to simply recommend that perphenazine be started at a lower dose in the elderly and allow the clinician, who will usually be familiar with the individual patient, to use his discretion in selecting a starting dose. Their proposal merits justification.

4) In the DOSAGE AND ADMINISTRATION section, the last sentence of their proposal is puzzling ("Dosing of perphenazine may occur before bedtime, in case of agitation."). Does this statement imply that agitation is a distinct indication for perphenazine? Does it mean that if a schizophrenic patient becomes agitated, the dose should be given at bedtime? The intended meaning is unclear. Also, since perphenazine is moderately sedating, it seems reasonable to administer the dose before bedtime in most patients, regardless of age or presence of agitation. The sponsor should clarify what is intended and reword this sentence to more clearly communicate that intention.

It is recommended that the above comments be conveyed to the sponsor. Upon resolution of the above concerns, these supplements may be approved.

Gregory M. Dubitsky, M.D.
March 6, 2001

cc: NDA # 10-775
NDA # 11-213
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/SHardeman

/s/

Greg Dubitsky
3/6/01 02:47:36 PM
MEDICAL OFFICER

Thomas Laughren
3/7/01 07:35:08 AM
MEDICAL OFFICER
The reference to agitation should be deleted.--TPL

Review and Evaluation of Clinical Data
NDA #10-775

Sponsor:	Schering Corporation
Drug:	Trilafon Tablets
Proposed Indication:	Schizophrenia
Material Submitted:	SLR-029: Response to Request for Labeling Change
Correspondence Date:	December 20, 2000
Date Received:	December 22, 2000
Related Submissions:	NDA #11-213 (Injection), SLR-021 NDA #11-557 (Concentrate), SLR-024

On 9-25-00, the Division issued a letter to all holders of NDA's for antipsychotic drug products that requested modification of labeling text to more clearly indicate that these agents are indicated for the treatment of schizophrenia. The above submissions contain the response from Schering with respect to Trilafon.

Additionally, the sponsor has taken this opportunity to make the following modifications to labeling:

1) add new formulation information from their reformulation supplement (S-026), that was approved on 5-23-00, to the DESCRIPTION section of product labeling.

2) correct formulation information that was submitted in S-026 in the DESCRIPTION and HOW SUPPLIED sections of labeling.

The sponsor has previously informed us that they will be withdrawing their NDA for Trilafon Concentrate once all products in distribution have expired.[1] Hence, labeling changes relevant only to the Concentrate have not been implemented.

Other changes pursuant to our 9-25-00 request are acceptable. Revised CMC information was examined by Robert Seevers, Ph.D., Team Leader in the Office of New Drug Chemistry, and found to be acceptable.

[1] This information was communicated to the undersigned by Steve Hardeman, Project Manager, in an E-Mail dated 11-15-00.

It is recommended that the above supplements be approved.

Gregory M. Dubitsky, M.D.
January 24, 2001

APPEARS THIS WAY
ON ORIGINAL

cc: NDA #10-775 (Tablets)
NDA #11-213 (Injection)
NDA #11-557 (Oral Solution)
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/SHardeman

/s/

Greg Dubitsky
1/24/01 02:14:43 PM
MEDICAL OFFICER

Thomas Laughren
1/24/01 03:57:53 PM
MEDICAL OFFICER
I agree that these supplements may be approved.--TPL

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 10-775/S-030
NDA 11-213/S-022

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

Dear Ms. Nehring:

Please refer to your supplemental new drug applications dated January 25, 2001, received January 26, 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 submissions dated July 2, 2001, July 5, 2001, and August 31, 2001. Your submission of August 31, 2001 constituted a complete response to our March 15, 2001 action letter.

These supplemental new drug applications provide for labeling changes relevant to geriatric use.

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 agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 31, 2001 - attached).

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 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, these submissions should be designated "FPL for approved supplement NDA 10-775/S-030, 11-213/S-022." Approval of these submissions 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
10/18/01 10:06:59 AM
Signed for Russell Katz, M.D.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 10-775/SLR-030
NDA 11-213/SLR-022

Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your supplemental new drug applications dated January 25, 2001, received January 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trilafon (perphenazine) tablets and injection.

These supplements propose geriatric labeling changes pursuant to 21 CFR 201.57(f)(10).

We have completed the review of these applications, and they are approvable. In general, the proposed labeling changes are acceptable. Before these applications may be approved, however, it will be necessary for you to address the following:

- In the WARNINGS statement, the cited references do not provide the data which support the assertion that tardive dyskinesia in the elderly is "more likely to be persistent or severe" compared to younger patients. While this may be true, we request that you provide these data for review.

- In the Drug Interactions subsection of PRECAUTIONS, the description of the study of perphenazine in poor and extensive P450 2D6 metabolizers should be qualified by adding that the poor metabolizers had reported significantly greater side effects during the first 10 days of treatment. Thereafter, the poor and extensive metabolizer groups tended to converge, according to the supporting literature article (Pollock BG, et al. Psychopharm Bull 1995;31(2):327-332).

- In the Geriatric Use subsection of PRECAUTIONS, the rationale for recommending that [redacted]. For some psychotropic agents (e.g., Paxil), the starting dose in the elderly is one-half of the usual adult dose and it is not clear why such a recommendation couldn't be made for perphenazine. Also, an option would be to simply recommend that perphenazine be started at a lower dose in the elderly and allow the clinician, who will usually be familiar with the individual patient, to use his or her discretion in selecting a starting dose.

- In the DOSAGE AND ADMINISTRATION section, we request that you delete the reference to agitation. This statement implies that agitation is a distinct indication for perphenazine.

In addition, it will be necessary for you to submit revised draft labeling. 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.

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

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 314.110. 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

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Russell Katz
3/15/01 10:18:36 AM

APPEARS THIS WAY
ON ORIGINAL

Review and Evaluation of Clinical Data
NDA 10-775

Sponsor:	Schering Corporation
Drug:	Trilafon Tablets
Proposed Indication:	Schizophrenia
Material Submitted:	Geriatric Labeling Supplement: SLR-030-BL
Correspondence Dates:	July 5, 2001; August 31, 2001
Dates Received:	July 6, 2001; September 4, 2001
Related Submission:	NDA 11-213, SLR-022-BL (Trilafon Injection)

I. Background

On January 25, 2001, the sponsor submitted supplements to add information relevant to geriatric use to the labeling for Trilafon tablets (NDA 10-775/SLR-030) and Trilafon Injection (NDA 11-213/SLR-022).

These supplements were reviewed and it was concluded that further information and action was required before they could be approved. The following specific requests were conveyed in a March 15, 2001, approvable letter from the Division:

Request #1: In the WARNINGS statement, the cited references did not provide the data which support their assertion that ——— ——— compared to younger patients. The supporting data were requested.

Request #2: In the Drug Interactions subsection of PRECAUTIONS, we asked that the description of the study of perphenazine in poor and extensive P450 2D6 metabolizers be qualified by adding that the poor metabolizers had reported significantly greater side effects during the first 10 days of treatment. Thereafter, the poor and extensive metabolizer groups tended to converge, according to the supporting literature article.

Request #3: In the Geriatric Use subsection of PRECAUTIONS, the rationale for recommending that ——— ———

was not clear. For some psychotropic agents (e.g., Paxil), the starting dose in the elderly is one-half of the usual adult dose and it was not clear why such a recommendation couldn't be made for perphenazine. Also, an option would be to simply recommend that perphenazine be started at a lower dose in the elderly and allow the clinician, who will usually be familiar with the individual patient, to use his discretion in selecting a starting dose. We asked that they justify their proposal.

Request #4: In the DOSAGE AND ADMINISTRATION section, we requested that they delete the reference to agitation. This statement implied that agitation was a distinct indication for perphenazine.

Schering responded to the above concerns in a submission dated July 5, 2001. A review of that submission revealed one continuing concern (see Request #1 below), which was telephonically conveyed to the sponsor's representative (Yvette Henderson) on July 30, 2001. A subsequent submission dated August 31, 2001, addressed that particular concern.

II. Responses to Agency Requests

A. Request #1

In their July 5, 2001, submission, the sponsor submitted two literature articles to support their previously proposed statement under WARNINGS/Tardive Dyskinesia that

compared to younger patients.[1,2]

Both articles were reviewed by the undersigned and were not deemed to support the proposed statement. Yvette Henderson, the sponsor's point of contact, was reached by telephone on 7-23-01 and was requested to locate the supporting statements in these articles.

After further consideration of this request, the sponsor elected to delete the above phrase and simply state that "Older patients are at increased risk for development of

[1] Jeste DV. Tardive Dyskinesia in Older Patients. J Clin Psychiatry 2000;61[suppl 4]:27-32. (see Attachment 2 of submission).
[2] Caligiuri MP, et al. Antipsychotic-Induced Movement Disorders in the Elderly. Drugs and Aging 2000;17:363-384. (see Attachment 3 of submission).

tardive dyskinesia." This change to the proposed labeling is conveyed in submissions dated August 31, 2001, which were forwarded to NDA 10-775 (Trilafon tablets) and NDA 11-213 (Trilafon Injection).

B. Request #2

The sponsor revised the description of the study of perphenazine in poor and extensive P450 2D6 metabolizers in the Drug Interactions subsection to indicate that poor metabolizers had significantly greater side effects during the first 10 days of treatment, after which the poor and extensive metabolizer groups tended to converge.

C. Request #3

The subsection Geriatric Use was modified to suggest that elderly patients be started on lower doses and be observed closely. This is consistent with the recommendations under DOSAGE AND ADMINISTRATION.

D. Request #4

Under the DOSAGE AND ADMINISTRATION section, the reference to agitation was deleted as we had requested.

III. Conclusions and Recommendations

The proposed labeling revisions, as amended in the sponsor's August 31, 2001, submission to both NDA's, are acceptable. It is recommended that this labeling supplement be approved.

Gregory M. Dubitsky, M.D.
September 27, 2001

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Greg Dubitsky
9/27/01 06:04:36 PM
MEDICAL OFFICER

Thomas Laughren
9/28/01 07:43:39 AM
MEDICAL OFFICER
I agree that this supplement can now be approved.--TPL

TRILAFON ®

brand of perphenazine, USP

Tablets,

Injection

DESCRIPTION TRILAFON products contain perphenazine, USP (4-[3-(2-chlorophenothiazin-10-yl)propyl]-1-piper-azineethanol), a piperazinyl phenothiazine having the chemical formula, $C_{21}H_{26}ClN_3OS$. They are available as **Tablets**, 2, 4, 8, and 16 mg; and **Injection**, perphenazine 5 mg per 1 mL.

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

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

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

Parameter	Perphenazine	7-Hydroxyperphenazine
Cmax (pg/mL)	984 (43)	509 (25)
Cmin (pg/mL)	442 (76)	350 (56)

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

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

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

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

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

WARNINGS Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. [redacted] dyskinesia. 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 antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic 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 antipsychotic 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 antipsychotic treatment is withdrawn. Antipsychotic 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, [redacted], antipsychotics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic 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 antipsychotics, 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 **Information for Patients** and **ADVERSE REACTIONS**.)

TRILAFON **Injection** 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 is seen more frequently in asthmatic than in nonasthmatic people.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

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

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (eg, 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 reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

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

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

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

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

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

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

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

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

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

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

third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

Drug Interactions: [redacted]

[redacted]

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

Given the likelihood that a substantial proportion of patients exposed chronically to antipsychotics 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.

[redacted]

[redacted]

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

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

Persistent 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. Although the risk appears to be greater in elderly patients on high-dose therapy, especially females, it may occur in either sex and in children. 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 (eg, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TRILAFON **Tablets**

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

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

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

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

TRILAFON **Injection**

Intramuscular Administration

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

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

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

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

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

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

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

Intravenous Administration

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

considered and appropriate means for management kept available. Blood pressure and pulse should be monitored continuously during intravenous administration. Pharmacologic and clinical studies indicate that intravenous administration of norepinephrine should be useful in alleviating the hypotensive effect.

[redacted]

OVERDOSAGE In the event of overdosage, emergency treatment should be started immediately. [redacted] All patients suspected of having taken an overdose should be hospitalized as soon as possible.

Manifestations [redacted] Overdosage of perphenazine primarily involves the extrapyramidal mechanism and produces the same side effects described under **ADVERSE REACTIONS**, but to a more marked degree. It is usually evidenced by stupor or coma; children may have convulsive seizures. [redacted]

Treatment Treatment is symptomatic and supportive. [redacted] There is no specific antidote. ~~The patient should be induced to vomit even if emesis has occurred~~

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

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

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

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

~~If acute parkinson-like symptoms result from perphenazine intoxication, benztropine mesylate or diphenhydramine may be administered.~~

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

~~Signs of arousal may not occur for 48 hours~~.

[redacted] dialysis is of no value because of low plasma concentrations of the drug.

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

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

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

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

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

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

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/s/

Russell Katz
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