16792 020

16792 015 018 019

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 16-792/S-020

Wyeth Laboratories
Attention: Roberta R. Acchione
170 North Radnor-Chester Road
St. David's, PA 19087-5221

MAY 1 2000

Dear Ms. Acchione:

Please refer to your supplemental new drug application dated August 27, 1998, received August 28, 1998, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surmontil (trimipramine maleate) capsules, 25 mg, 50 mg, and 100 mg.

Supplemental application S-020 provides draft labeling that incorporates new text in the CLINICAL PHARMACOLOGY and PRECAUTIONS sections. These additions describe the safety and efficacy of Surmontil in the geriatric population in accordance with 21 CFR 201.57(f)(10). The specific additions are as follows:

1. Under the CLINICAL PHARMACOLOGY section, a statement regarding a comparative pharmacokinetics study was added and it reads:

   "The single-dose pharmacokinetics of trimipramine were evaluated in a comparative study of 24 elderly subjects and 24 younger subjects; no clinically relevant differences were demonstrated based on age or gender."

2. Under PRECAUTIONS, a new Geriatric Use subsection was added and it reads:

   "Geriatric Use
   Clinical studies of Surmontil were not adequate to determine whether subjects aged 65 and over respond differently from younger subjects.

   The pharmacokinetics of trimipramine were not substantially altered in the elderly (see **CLINICAL PHARMACOLOGY**).

   Surmontil is known to be substantially excreted by the kidney. Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered (see **PRECAUTIONS-General**).
   Greater sensitivity (e.g., confusional states, sedation) of some older individuals cannot be ruled out (see **ADVERSE REACTIONS**). In general, dose selection for an elderly patient should be cautious, usually starting at a lower dose (see **DOSAGE AND ADMINISTRATION**)."

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated July 28, 1998 and submitted on August 27, 1998. Accordingly, the application is approved.

The final printed labeling (FPL) must be identical to the draft labeling text submitted on August 27, 1998. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Individually, mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplemental NDA S-020."

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" 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 Mr. Paul David, Regulatory Management Officer, at (301) 594-5530.

Sincerely,

/S/

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

cc:
Archival NDA 16-792
HFD-120/Div. File
HFD--120/M.Mille
HFD-120/EHearst/TLaughren:
HFD-120/RKatz:
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: mjm/ April 11, 2000
final:
filename: [redacted]

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

RMO REVIEW OF NDA FPL

NDA #:	**16-792**	Date Review Completed:	**04/11/00**
Supplement #:	**S-020**	Date of Submission:	**08-27-98**
Applicant's Name and Address:	**Wyeth Laboratories** 170 North Radnor-Chester Rd. St. David's, PA 19087-5221		
Product Trademark/: Generic Name:	**Surmontil** **trimipramine maleate**		
Dosage Form and Strength:	**25, 50, 100 mg Capsule**		
Pharmacological Category and/or Principal Indication:	**Antidepressant**		

Material Reviewed:

1. S-019: FPL (CI 3842-6) revised on July 18, 1996 and submitted on Oct. 7, 1996.
2. Draft Agency letter approving S-015, S-018, and S-019.
3. S-020: Draft labeling dated July 28, 1998 and submitted on Aug. 27, 1998.
4. Clinical review dated Jan. 9, 1995. (acceptable)

Evaluation: (See Attached Review Notes)

VI. RECOMMENDATIONS:

With clinical concurrence, a letter should issue approving S-020. Before, this letter issues, however, an approval action should be taken on S-019.

Merril J. Mille, RMO

cc: ORIG NDA 16-792
HFD-120
HFD-120/MMille
DOC#

Concur:

John S. Purvis
Chief, Project Management Staff

Review Notes

I. COMPARATIVE LABELING:

FPL (CI 3842-6) is the last reviewed labeling (See PM labeling review of S-019 completed on 04-03-00. Therefore, this labeling was used as comparative labeling in this review.

II. LABELING CHANGES

When draft labeling dated 7-28-98 was compared to FPL (CI 3842-6), the following changes to the labeling were noted and are listed below by section:

SECTION NOTE #	PREVIOUS FPL (CI 3842-6)	NEW Draft Labeling (7/28/98)
CLINICAL PHARMACOLOGY:		
Note #1		
[ADDITION]		The single-dose pharmacokinetics of trimipramine were evaluated in a comparative study of 24 elderly subjects and 24 younger subjects,; no clinically relevant differences were demonstrated based on age or gender.
PRECAUTIONS:		
Note #2		
[ADDITION]		**Geriatric Use** Clinical studies of Surmontil were not adequate to determine whether subjects aged 65 and over respond differently form younger subjects. The pharmacokinetics of trimipramine were not substantially altered in the elderly (see **CLINICAL PHARMACOLOGY**). Surmontil is known to be substantially excreted by the kidney. Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered (see **PRECAUTIONS-General**).

PRECAUTIONS:

Note #2 (Continued) - Greater sensitivity (e.g., confusional states, sedation) of some older individuals cannot be ruled out (see **ADVERSE REACTIONS**). In general, dose selection for an elderly patient should be cautious, usually starting at a lower dose (see **DOSAGE AND ADMINISTRATION**).

III. SUPPLEMENT S-020:

Supplemental application S-020 provides draft labeling (7/28/98) that proposes the addition of new text in the CLINICAL PHARMACOLOGY and PRECAUTIONS section. These additions describe the safety and efficacy of Surmontil in the geriatric population in accordance with 21 CFR 201.57(f)(10).
[See Notes #1 & 2]

IV. COMMENTS S-020:

A. A clinical review of this supplement is pending.

B. The draft labeling includes labeling changes put into effect under several unapproved labeling supplements (S-015, S-018, and S-019). These supplements have been reviewed and an approval letter will issue soon.

C. The review of the draft labeling did not reveal any text changes other than the changes acknowledged by the sponsor.

V. CONCLUSIONS:

A. Clinical concurrence is required before an action is taken on S-020.

B. If clinical concurrence is obtained, the labeling changes provided under S-020 may be approved.

C. Before S-020 is approved, however, the labeling changes implemented under supplements S-015, S-018, and S-019 should be approved. The approval letter for these supplements circulating for sign off at the time of this review.

D. There are no other regulatory issues that would prohibit approval of this FPL.

END of REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 16-792/S-015; S-018; S-019

APR 27 2000

Wyeth Laboratories
Attention: Roberta R. Acchione
170 North Radnor-Chester Road
St. David's, PA 19087-5221

Dear Ms. Acchione:

Please refer to your supplemental new drug applications dated September 14, 1989, December 28, 1994, and February 2, 1996, received September 14, 1989, January 3, 1995, and February 6, 1996, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surmontil (trimipramine maleate) capsules, 25 mg, 50 mg, and 100 mg.

We also refer to an October 7, 1996 amendment to S-019.

Supplemental application S-015 provides revised FPL (3842-2) that includes a revision of the second sentence of the DESCRIPTION section of labeling. This revised sentence describes the product in terms of trimipramine base and reads:

> "Surmontil capsules contain trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg. of trimipramine as the base."

Supplemental application S-018 provides revised FPL (CI 3842-5) that incorporates text changes in the WARNINGS and PRECAUTIONS sections as well as labeling format changes. Specifically, the revised labeling includes:

A. the addition of a statement to the *Drug Interactions* subsection of PRECAUTIONS regarding potentially serious interactions resulting from the co-administration of tricyclic antidepressants with drugs capable of inhibiting the cytochrome P450 2D6. This change was made in response to an Agency letter dated June 15, 1994 to Dr. John Beary of PhRMA, and

B. an improved organization of the FPL by relocation of specific text, changes in titles of sections, and the addition of subsections to conform to 21 CFR 201.57.

Supplemental application S-019 provides new FPL (CI 3642-6) that incorporates changes to the OVERDOSAGE section of labeling in response to an Agency letter dated October 3, 1995, in order to describe current clinical toxicology recommendations on how to best manage overdoses with tricyclic antidepressants. The revised text was taken, in most part, from a core-labeling document submitted by Dr. John Siegfried of PhRMA on January 26, 1996.

We note that these supplemental applications were submitted as "Changes Being Effected" and the final printed labeling has been implemented.

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 final printed labeling (CT 3842-6) submitted on October 7,1996. Accordingly, the applications are approved.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" 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 Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

Russell G, 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

cc:
Archival NDA 16-792
HFD-120/Div. File
HFD-120/M.Mille
HFD-120/EHearst/TLaughren:
HFD-120/Rzeszotarski/Seevers:
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: mjm/ April 11, 2000
final:
filename:

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

RMO REVIEW OF NDA FPL

NDA #: **16-792**

Date Review Completed: **04/03/00**

Supplement #: **S-015; S-018; S-019**

Date of Submission: **09/14/89; 12/28/94; 10/07/96**

Applicant's Name and Address: **Wyeth Laboratories**
170 North Radnor-Chester Rd.
St. David's, PA 19087-5221

Product Trademark/: **Surmontil**
Generic Name: **trimipramine maleate**

Dosage Form and Strength: **25, 50, 100 mg Capsule**

Pharmacological Category and/or Principal Indication: **Antidepressant**

Material Reviewed: (See page 2)

Evaluation: (See Attached Review Notes)

IX. RECOMMENDATIONS:
A letter should issue approving S-015, S-018, and S-019.

Merril J. Mille, RMO

cc: ORIG NDA 16-792
HFD-120
HFD-120/MMille
DOC#

Concur:

John S. Purvis
Chief, Project Management Staff

Material Reviewed:

1. S-001: FPL (CI 2550-2) revised on Jan. 17, 1980 and approved on July 8, 1980.
2. Agency letter (FPL change request) dated Sep. 1, 1983.
3. P-002: FPL (CI 3479-1) revised on Jan. 22, 1986 and submitted on July 8, 19987.
4. S-011: N/A letter dated Jan. 22, 1988 Re: container labeling; approved on June 17, 1988.
5. S-014: N/A Agency letter dated April 19, 1989.
6. S-015: FPL (CI 3842-2) revised on May 31, 1989 and submitted on Sep. 14, 1989.
7. S-015: Chemistry review dated Oct. 3, 1989. (approvable)
8. Y-017: FPL (CI 3842-4) revised on July 30, 1992 and submitted on Aug. 30, 1993.
9. Y-017: Clinical and chemistry notes dated 9/9/93 and 9/23/93 (satisfactory).
9. S-018: FPL (CI3842-5) revised on July 15, 1994 and submitted on Dec. 28, 1994
10. S-018: Clinical review dated Jan. 9, 1995. (acceptable)
11. Agency letter to PhRMA dated June 15, 1994. (Attachment #2)
12. S-019: draft labeling FPL (C96-4) revised in Jan. '96 and submitted on Feb. 2, 1996.
13. S-019: Clinical review dated Mar. 6, 1996.
14. S-019: FPL (CI3842-6) revised in July 18, 1996 and submitted on Oct. 7, 1996.
15. S-019: Clinical review dated Oct. 30, 1996.

Review Notes

I. COMPARATIVE LABELING:

FPL (CI 2550-2) is the last approved labeling. Therefore, this labeling was used as comparative labeling in this review.

II. LABELING CHANGES

When draft labeling dated 7-28-98 was compared to FPL (CI 2550-2), the following changes to the labeling were noted and are listed below by section:

SECTION NOTE #	PREVIOUS FPL (CI 2550-2)	NEW FPL (CI 3842-6)
HEADING:		
Note #1		
A.H.F.S. Category 28:16.04		[DELETION]

DESCRIPTION:
Note #2A
[ADDITION]

Surmontil capsules contain trimipramine maleate equivalent to 25 mg, 50 mg or 100 mg of trimipramine as the base. The inactive ingredients present are FD&C Blue 1, gelatin, lactose, magnesium stearate and titanium dioxide. The 25 mg dosage strength also contains D&C Yellow 10 and FD&C Yellow 6; the 50 mg dosage strength also contains D&C Red 28, FD&C Red 40, and FD&C Yellow 6.

INDICATIONS AND USAGE:
Note #2B
[ADDITION] and Usage

WARNINGS:
Note #3A
[DELETION]

PRECAUTIONS:
Note #3B
[ADDITION] GENERAL

Note #4
[DELETION]

Note #4 (Continued)

Use in Pregnancy – Pregnancy Category C. Surmontil has show evidence of embryo-toxicity and/or increased incidence of major anomalies in rats or rabbits at doses 20 times the human dose. There are no adequate and well-controlled studies in pregnant women. Surmontil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Semen studies in man (four schizophrenics and nine normal volunteers) revealed no significant changes in sperm morphology. It is recognized that drugs having a parasympathetic effect, including tricyclic antidepressants, may alter the ejaculatory response.

Chronic animal studies showed occasional evidence of degeneration of seminiferous tubules at the highest dose of 60 mg/kg/day.

PRECAUTIONS:

Note #5

[ADDITION]

DRUG INTERACTIONS

Cimetidine

There is evidence that cimetidine inhibits the elimination of tricyclic antidepressants. Downward adjustment of Surmontil dosage may be required if cimetidine therapy is initiated, upward adjustment if cimetidine therapy is discontinued.

Alcohol

Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggerated effects.

Catecholamines/Anticholinergics

It has been reported that tricyclic antidepressants can potentiate the effects of catecholamines. Similarly, atropinelike effects may be more pronounced in patients receiving anticholinergic therapy. Therefore, particular care should be exercised when it is necessary to administer tricyclic antidepressants with sympathomimetic amines, local decongestants, local anesthetics containing epinephrine, atropine or drugs with an anticholinergic effect. In resistant cases of depression in adults, a dose of 2.5 mg/kg/day may have to be exceeded. If a higher dose is needed, ECG monitoring should be maintained during the initiation of therapy and at appropriate intervals during stabilization of dose.

PRECAUTIONS:

Note #5 (continued)

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7%-10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of the isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecanide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of the inhibition. The extent to which SSRIs TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressants or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required.

It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be inhibitor of P450 2D6.

PRECAUTIONS:

Note #5 (Continued) CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Semen studies in man (four schizophrenics and nine normal volunteers) revealed no significant changes in sperm morphology. It is recognized that drugs having a parasympathetic effect, including tricyclic antidepressants, may alter the ejaculatory response.

Chronic animal studies showed occasional evidence of degeneration of seminiferous tubules at the highest dose of 60 mg/kg/day.

PREGNANCY

Teratogenic Effects - Pregnancy Category C.

Surmontil has show evidence of embryotoxicity and/or increased incidence of major anomalies in rats or rabbits at doses 20 times the human dose. There are no adequate and well-controlled studies in pregnant women. Surmontil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE

This drug is not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

ADVERSE REACTIONS:

Note #6

[ADDITION] syndrome of inappropriate ADH (antidiuretic hormone) secretion.

OVERDOSAGE:

Note #7

Sign and Symptoms – The response of the patient to toxic overdosage of tricyclic antidepressants may vary in severity and is conditioned by factors such as age, amount ingested, amount absorbed, interval between ingestion and start of treatment. Surmontil is not recommended for infants or young children. Should accidental ingestion occur in any amount, it should be regarded as serious and potentially fatal. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of

[See Attachment #1 for complete text of the revised OVERDOSAGE section.]

OVERDOSAGE:

Note #7 (Continued) -

impaired conduction, and signs of congestive failure. Other symptoms may include respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, and diaphoresis.

Treatment is supportive and symptomatic as no specific antidote is known. Depending upon need the following measure can be considered:

[Please refer to FPL CI 2550-2 (item # 7) for reminder of text.]

HOW SUPPLIED:

Note #8

Surmontil (trimipramine maleate) Capsules are available as:
25 mg in bottles of 100 opaque blue and yellow capsules.
50 mg in bottles of 100 opaque blue and orange capsules.

Surmontil (trimipramine maleate) Capsules are available in the following dosage strengths:
25 mg NDC 0008-4132, opaque blue and yellow capsules marked "Wyeth" and "4132",in bottles of 100 capsules.
50 mg NDC 0008-4133, opaque blue and orange capsules marked "Wyeth" and "4133",in bottles of 100 capsules.
100 mg NDC 0008-4158, opaque blue and white capsules marked "Wyeth" and "4158",in bottles of 100 capsules.
Store at room temperature, approximately 25 °C (77°F).
Keep bottles tightly closed.
Dispense in a tight container.
Protect capsules packaged in blister strips from moisture.

III. Periodic Adverse Drug Experience Report (P-002):
In a Periodic ADE report dated July 8, 1987, the sponsor provided FPL (CI 3479-1) that includes:

A. the listing of the adverse event "syndrome of inappropriate ADH (antidiuretic hormone)" under the *Neurological* subsection of the ADVERSE REACTIONS section, and

B. the disclosure of inactive ingredients in the DESCRIPTION section. A review of the NDA file did not uncover any acknowledgment by the sponsor of this labeling change.

COMMENTS-P-002:

A. The inclusion of the adverse event in the *Neurological* subsection was in response to a 'FPL Change Request' letter issued by the Agency on September 1, 1983. [See Note # 6]

B. A review of the NDA file did not uncover any acknowledgment by the sponsor that inactive ingredients were included in the DESCRIPTION section of labeling. [See Note #2A]

C. A chemistry review of S-015 indicates that the DESCRIPTION section (containing inactive ingredients) is satisfactory. [See Note #2A]

IV. SUPPLEMENT S-015:

Supplemental application S-015 provides revised FPL (3842-2) that includes a revision of the second sentence of the DESCRIPTION section of labeling. This revised sentences describes the product in terms of trimipramine base and reads:

> "Surmontil capsules contain trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg. of trimipramine as the base."

COMMENTS S-015:

A. The chemistry review dated Oct. 3, 1989 indicates that the changes in the DESCRIPTION section are satisfactory and, therefore, the S-015 is approvable. [See Note #2A]

B. The only other changes noted in this labeling are minor changes in packaging description in the HOW SUPPLIED section. [See Note #8]

C. The labeling changes under S-015 qualify for implementation prior to Agency approval.

V. Annual Report Y-017:

Annual Report Y-017 provides FPL (CI-3842-4) that includes:

A. a new storage temperature statement at the end of the package insert which reads:

> "Store at room temperature, approximately 25 °C (77°F)."

B. a storage temperature statement which reads:

> "Protect capsules packaged in blister strips from moisture."

C. other minor editorial changes to labeling.

COMMENTS-Y-017:

A. The new storage temperature statement was approved on June 17, 1988 under S-011 which provides FPL container labels. [See Note #8]

B. The inclusion of the "moisture" statement to the end of labeling was requested by the Agency in a letter (S-014) dated April 19, 1989. [See Note #8]

C. There are no objections (clinical or chemistry) to the labeling changes reported in Y-017. (See reviewer notes dated 9/9/93 and 9/29/93, respectively.)

VI. SUPPLEMENT S-018:

Supplemental application S-018 provides revised FPL (CI 3842-5) that incorporates text changes in the WARNINGS and PRECAUTIONS sections as well as labeling format changes. Specifically, the revised labeling includes:

A. the addition of a statement to the *Drug Interactions* subsection of PRECAUTIONS regarding potentially serious interactions resulting from the co-administration of tricyclic antidepressants with drugs capable of inhibiting the cytochrome P450 2D6. This change was made in response to an Agency letter dated June 15, 1994 to Dr. John Beary of PhRma;

B. an improved organization of the FPL by relocation of specific text, changes in titles of sections, and the addition of subsections to conform to 21 CFR 201.57;

C. [redacted]

COMMENTS-S-018:

A. The new text added to the *Drug Interactions* subsection was taken verbatim from an Agency letter dated March 22, 1993. [See Note #5 and Attachment #2]

B. The revised format and relocation of specific text is in compliance with labeling format requirements under 21 CFR 201.57.
[Notes #2B & 3B indicate format changes. Notes # 3A (E) & 4 (A, B, C, D) indicate text relocation.]

C. The deletion of the reference to the A.H.F.S. is consistent with an Agency request for product labeling. [See Note #1]

D. This supplement was submitted as "Changes Being Effected."

VII. SUPPLEMENT S-019

Supplemental application S-019 provides new FPL (C(3642-6) that incorporates changes to the OVERDOSAGE section of labeling in response to an Agency letter dated October 3, 1995, in order to describe current clinical toxicology recommendations on how to best manage overdoses with tricyclic antidepressants. The revised text was taken, in most part, from a core-labeling document submitted by Dr. John Siegfried of PhRMA on January 26, 1996.

COMMENTS S-019:

A. The revision of the OVERDOSAGE section was considered in basic agreement with the Poisindex recommendations and, therefore, was considered acceptable by the clinical reviewer in a review dated 10/30/96. (See Note #7 and Attachment #1]

B. The only other changes noted in this labeling were minor changes in packaging description in the HOW SUPPLIED section. [See Note #8]

C. This supplement was submitted as "Changes Being Effected."

VIII. CONCLUSIONS:

A. The revisions to the labeling text are adequately supported and there are no objections to their implementation.

B. All required clinical and chemistry reviews are complete.

C. There are no objections to the implementation of the revised labeling prior to Agency approval.

D. There are no objections to the approval of S-015, S-018 and S-019.

END of REVIEW

APPEARS THIS WAY
ON ORIGINAL

Labeling: SLR-019 (13-)

NDA No: 16-792 Rec'd. 10-11-9 c

Reviewed by: _____

Surmontil®
(trimipramine maleate)

CI 3842-6

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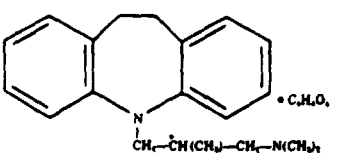
CODE INSERTED HERE

-APPROVED
APR 27 2000

Surmontil®
(trimipramine maleate)

Description

Surmontil (trimipramine maleate) is 5-(3-dimethylamino-2-methylpropyl)-10,11-dihydro-5H-dibenz (b,f) azepine acid maleate (racemic form).



Molecular Formula: $C_{20}H_{26}N_2 \cdot C_4H_4O_4$ Molecular Weight: 410.5

Surmontil capsules contain trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg of trimipramine as the base. The inactive ingredients present are FD&C Blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25 mg dosage strength also contains D&C Yellow 10 and FD&C Yellow 6; the 50 mg dosage strength also contains D&C Red 28, FD&C Red 40, and FD&C Yellow 6.

Trimipramine maleate is prepared as a racemic mixture which can be resolved into levorotatory and dextrorotatory isomers. The asymmetric center responsible for optical isomerism is marked in the formula by an asterisk. Trimipramine maleate is an almost odorless, white or slightly cream-colored, crystalline substance, melting at 140°-144° C. It is very slightly soluble in ether and water, is slightly soluble in ethyl alcohol and acetone, and freely soluble in chloroform and methanol at 20° C.

Clinical Pharmacology

Surmontil is an antidepressant with an anxiety-reducing sedative component to its action. The mode of action of Surmontil on the central nervous system is not known. However, unlike amphetamine-type compounds it does not act primarily by stimulation of the central nervous system. It does not act by inhibition of the monoamine oxidase system.

Indications and Usage

Surmontil is indicated for the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states. In studies with neurotic outpatients, the drug appeared to be equivalent to amitriptyline in the less-depressed patients but somewhat less effective than amitriptyline in the more severely depressed patients. In hospitalized depressed patients, trimipramine and imipramine were equally effective in relieving depression.

Contraindications

Surmontil is contraindicated in cases of known hypersensitivity to the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind. Surmontil should not be given in conjunction with drugs of the monoamine oxidase inhibitor class (e.g., tranylcypromine, isocarboxazid or phenelzine sulfate). The concomitant use of monoamine oxidase inhibitors (MAOI) and tricyclic compounds similar to Surmontil has caused severe hyperpyretic reactions, convulsive crises, and death in some patients. At least two weeks should elapse after cessation of therapy with MAOI before instituting therapy with Surmontil. Initial dosage should be low and increased gradually with caution and careful observation of the patient. The drug is contraindicated during the acute recovery period after a myocardial infarction.

Warnings

GENERAL CONSIDERATION FOR USE

Extreme caution should be used when this drug is given to patients with any evidence of cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes, and tachycardia.

Caution is advised in patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties; hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity; patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold; patients receiving guanethidine or similar agents, since Surmontil may block the pharmacologic effects of these drugs.

Since the drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

Precautions

GENERAL

The possibility of suicide is inherent in any severely depressed patient and persists until a significant remission occurs. When a patient with a serious suicidal potential is not hospitalized, the prescription should be for the smallest amount feasible.

In schizophrenic patients activation of the psychosis may occur and require reduction of dosage or the addition of a major tranquilizer to the therapeutic regime.

Manic or hypomanic episodes may occur in some patients, in particular those with cyclic-type disorders. In some cases therapy with Surmontil must be discontinued until the episode is relieved, after which therapy may be reinstituted at lower dosages if still required.

Concurrent administration of Surmontil and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to those patients for whom it is essential. When possible, discontinue the drug for several days prior to elective surgery.

Surmontil should be used with caution in patients with impaired liver function.

Chronic animal studies showed occasional occurrence of hepatic congestion, fatty infiltration, or increased serum liver enzymes at the highest dose of 60 mg/kg/day.

Both elevation and lowering of blood sugar have been reported with tricyclic antidepressants.

DRUG INTERACTIONS

Cimetidine

There is evidence that cimetidine inhibits the elimination of tricyclic antidepressants. Downward adjustment of Surmontil dosage may be required if cimetidine therapy is initiated; upward adjustment if cimetidine therapy is discontinued.

Alcohol

Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggerated effects.

Catecholamines/Anticholinergics

It has been reported that tricyclic antidepressants can potentiate the effects of catecholamines. Similarly, atropinelike effects may be more pronounced in patients receiving anticholinergic therapy. Therefore, particular care should be exercised when it is necessary to administer tricyclic antidepressants with sympathomimetic amines, local decongestants, local anesthetics containing epinephrine, atropine or drugs with an anticholinergic effect. In resistant cases of depression in adults, a dose of 2.5 mg/kg/day may have to be exceeded. If a higher dose is needed, ECG monitoring should be maintained during the initiation of therapy and at appropriate intervals during stabilization of dose.

Drugs Metabolized by P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7-10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of the isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Semen studies in man (four schizophrenics and nine normal volunteers) revealed no significant changes in sperm morphology. It is recognized that drugs having a parasympathetic effect, including tricyclic antidepressants, may alter the ejaculatory response.

Chronic animal studies showed occasional evidence of degeneration of seminiferous tubules at the highest dose of 60 mg/kg/day.

PREGNANCY

Teratogenic Effects—Pregnancy Category C

Surmontil has shown evidence of embryotoxicity and/or increased incidence of major anomalies in rats or rabbits at doses 20 times the human dose. There are no adequate and well-controlled studies in

the potential benefit outweighs the potential risk to the fetus.

PEDIATRIC USE

This drug is not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Adverse Reactions

Note: The pharmacological similarities among the tricyclic antidepressants require that each of the reactions be considered when Surmontil is administered. Some of the adverse reactions included in this listing have not in fact been reported with Surmontil.

CARDIOVASCULAR

Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

PSYCHIATRIC

Confusional states (especially the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

NEUROLOGICAL

Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

ANTICHOLINERGIC

Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis, constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

ALLERGIC

Skin rash, petechiae, urticaria, itching, photosensitization, edema of face and tongue.

HEMATOLOGIC

Bone-marrow depression including agranulocytosis, eosinophilia; purpura; thrombocytopenia. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathological neutrophil depression.

GASTROINTESTINAL

Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue.

ENDOCRINE

Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood-sugar levels.

OTHER

Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness, and fatigue; headache; parotid swelling; alopecia.

WITHDRAWAL SYMPTOMS

Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Dosage and Administration

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. It is not possible to prescribe a single dosage schedule of Surmontil that will be therapeutically effective in all patients. The physical psychodynamic factors contributing to depressive symptomatology are very complex; spontaneous remissions or exacerbations of depressive symptoms may occur with or without drug therapy. Consequently, the recommended dosage regimens are furnished as a guide which may be modified by factors such as the age of the patient, chronicity and severity of the disease, medical condition of the patient, and degree of psychotherapeutic support.

Most antidepressant drugs have a lag period of ten days to four weeks before a therapeutic response is noted. Increasing the dose will not shorten this period but rather increase the incidence of adverse reactions.

USUAL ADULT DOSE

Outpatients and Office Patients—Initially, 75 mg/day in divided doses, increased to 150 mg/day. Dosages over 200 mg/day are not recommended. Maintenance therapy is in the range of 50 to 150 mg/day. For convenient therapy and to facilitate patient compliance, the total dosage requirement may be given at bedtime.

Hospitalized Patients—Initially, 100 mg/day in divided doses. This may be increased gradually in a few days to 200 mg/day, depending upon individual response and tolerance. If improvement does not occur in 2 to 3 weeks, the dose may be increased to the maximum recommended dose of 250 to 300 mg/day.

Adolescent and Geriatric Patients—Initially, a dose of 50 mg/day is recommended, with gradual increments up to 100 mg/day, depending upon patient response and tolerance.

Maintenance—Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission. Maintenance therapy is preferably administered as a single dose at bedtime. To minimize relapse, maintenance therapy should be continued for about three months.

Overdosage

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

MANIFESTATIONS

Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are [illegible] tion, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under **Adverse Reactions**.

MANAGEMENT

General

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Plasma drug levels may not reflect the severity of the poisoning. Therefore, monitoring of plasma drug levels alone should not guide management of the patient.

Gastrointestinal Decontamination

All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of ≥ 0.10 seconds has been associated with an increased incidence of seizures. A QRS duration of ≥ 0.16 seconds has been associated with an increased incidence of ventricular dysrhythmias. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a pCO_2 < 20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

**Poisindex® Toxicologic Management.* Topic: Antidepressants, Tricyclic Micromedex Inc. Vol.85.

How Supplied

Surmontil® (trimipramine maleate) Capsules are available in the following dosage strengths:

25 mg, NDC 0008-4132, opaque blue and yellow capsule marked "WYETH" and "4132", in bottles of 100 capsules.

50 mg, NDC 0008-4133, opaque blue and orange capsule marked "WYETH" and "4133", in bottles of 100 capsules.

100 mg, NDC 0008-4158, opaque blue and white capsule marked "WYETH" and "4158", in bottles of 100 capsules.

Store at room temperature, approximately 25°C (77°F).

Keep bottles tightly closed.

Dispense in a tight container.

Protect capsules packaged in blister strips from moisture.

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories.

by arrangement with Rhone-Poulenc Rorer France

Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101
CI 3842-6 Revised July 18, 1996 Printed in USA

A.H.F.S. Category 28:16.04

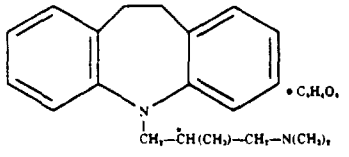
Wyeth

Surmontil®

(trimipramine maleate)

Description

Surmontil (trimipramine maleate) is 5-(3-dimethylamino-2-methylpropyl)-10,11-dihydro-5H-dibenz (b,f) azepine acid maleate (racemic form).



MOLECULAR FORMULA: $C_{20}H_{26}N_2 \cdot C_4H_4O_4$

MOLECULAR WEIGHT: 410.5

Surmontil capsules contain trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg of trimipramine as the base. The inactive ingredients present are FD&C Blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25 mg dosage strength also contains D&C Yellow 10 and FD&C Yellow 6; the 50 mg dosage strength also contains D&C Red 28, FD&C Red 40, and FD&C Yellow 6.

Trimipramine maleate is prepared as a racemic mixture which can be resolved into levorotatory and dextrorotatory isomers. The asymmetric center responsible for optical isomerism is marked in the formula by an asterisk. Trimipramine maleate is an almost odorless, white or slightly cream-colored, crystalline substance, melting at 140-144° C. It is very slightly soluble in ether and water, is slightly soluble in ethyl alcohol and acetone, and freely soluble in chloroform and methanol at 20° C.

Clinical Pharmacology

Surmontil is an antidepressant with an anxiety-reducing sedative component to its action. The mode of action of Surmontil on the central nervous system is not known. However, unlike amphetamine-type compounds it does not act primarily by stimulation of the central nervous system. It does not act by inhibition of the monoamine oxidase system.

Indications

Surmontil is indicated for the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states. In studies with neurotic outpatients, the drug appeared to be equivalent to amitriptyline in the less-depressed patients but somewhat less effective than amitriptyline in the more severely depressed patients. In hospitalized depressed patients, trimipramine and imipramine were equally effective in relieving depression.

Contraindications

Surmontil is contraindicated in cases of known hypersensitivity to the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind. Surmontil should not be given in conjunction with drugs of the monoamine oxidase inhibitor class (e.g., tranylcypromine, isocarboxazid or phenelzine sulfate). The concomitant use of monoamine oxidase inhibitors (MAOI) and tricyclic compounds similar to Surmontil has caused severe hyperpyretic reactions, convulsive crises, and death in some patients. At least two weeks should elapse after cessation of therapy with MAOI before instituting therapy with Surmontil. Initial dosage should be low and increased gradually with caution and careful observation of the patient. The drug is contraindicated during the acute recovery period after a myocardial infarction.

Warnings

USE IN CHILDREN

This drug is not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

GENERAL CONSIDERATION FOR USE

Extreme caution should be used when this drug is given to patients with any evidence of cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes, and tachycardia.

Caution is advised in patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties; hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity; patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold; patients receiving guanethidine or similar agents, since Surmontil may block the pharmacologic effects of these drugs.

Since the drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

Precautions

The possibility of suicide is inherent in any severely depressed patient and persists until a significant remission occurs. When a patient with a serious suicidal potential is not hospitalized, the prescription should be for the smallest amount feasible.

In schizophrenic patients activation of the psychosis may occur and require reduction of dosage or the addition of a major tranquilizer to the therapeutic regime.

Manic or hypomanic episodes may occur in some patients, in particular those with cyclic-type disorders. In some cases therapy with Surmontil must be discontinued until the episode is relieved, after which therapy may be reinstituted at lower dosages if still required.

Concurrent administration of Surmontil and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to those patients for whom it is essential. When possible, discontinue the drug for several days prior to elective surgery.

There is evidence that cimetidine inhibits the elimination of tricyclic antidepressants. Downward adjustment of Surmontil dosage may be required if cimetidine therapy is initiated; upward adjustment if cimetidine therapy is discontinued.

Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggerated effects.

It has been reported that tricyclic antidepressants can potentiate the effects of catecholamines. Similarly, atropinelike effects may be more pronounced in patients receiving anticholinergic therapy. Therefore, particular care should be exercised when it is necessary to administer tricyclic antidepressants with sympathomimetic amines, local decongestants, local anesthetics containing epinephrine, atropine or drugs with an anticholinergic effect. In resistant cases of depression in adults, a dose of 2.5 mg/kg/day may have to be exceeded. If a higher dose is needed, ECG monitoring should be maintained during the initiation of therapy and at appropriate intervals during stabilization of dose.

USAGE IN PREGNANCY

Pregnancy Category C

Surmontil has shown evidence of embryo-toxicity and/or increased incidence of major anomalies in rats or rabbits at doses 20 times the human dose. There are no adequate and well-controlled studies in pregnant women. Surmontil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Semen studies in man (four schizophrenics and nine normal volunteers) revealed no significant changes in sperm morphology. It is recognized that drugs having a parasympathetic effect, including tricyclic antidepressants, may alter the ejaculatory response.

Chronic animal studies showed occasional evidence of degeneration of seminiferous tubules at the highest dose of 60 mg/kg/day.

Surmontil should be used with caution in patients with impaired liver function.

Chronic animal studies showed occasional occurrence of hepatic congestion, fatty infiltration, or increased serum liver enzymes at the highest dose of 60 mg/kg/day.

Both elevation and lowering of blood sugar have been reported with tricyclic antidepressants.

Adverse Reactions

Note: The pharmacological similarities among the tricyclic antidepressants require that each of the reactions be considered when Surmontil is administered. Some of the adverse reactions included in this listing have not in fact been reported with Surmontil.

CARDIOVASCULAR

Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

PSYCHIATRIC

Confusional states (especially the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

NEUROLOGICAL

Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

ANTICHOLINERGIC

Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis, constipation, paralytic

ileus, urinary retention, delayed micturition, dilation of the urinary tract.

ALLERGIC

Skin rash, petechiae, urticaria, itching, photosensitization, edema of face and tongue

HEMATOLOGIC

Bone-marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathological neutrophil depression.

GASTROINTESTINAL

Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue.

ENDOCRINE

Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling, elevation or depression of blood-sugar levels.

OTHER

Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness, and fatigue; headache; parotid swelling; alopecia.

WITHDRAWAL SYMPTOMS

Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Dosage and Administration

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. It is not possible to prescribe a single dosage schedule of Surmontil that will be therapeutically effective in all patients. The physical psychodynamic factors contributing to depressive symptomatology are very complex; spontaneous remissions or exacerbations of depressive symptoms may occur with or without drug therapy. Consequently, the recommended dosage regimens are furnished as a guide which may be modified by factors such as the age of the patient, chronicity and severity of the disease, medical condition of the patient, and degree of psychotherapeutic support.

Most antidepressant drugs have a lag period of ten days to four weeks before a therapeutic response is noted. Increasing the dose will not shorten this period but rather increase the incidence of adverse reactions.

USUAL ADULT DOSE

Outpatients and Office Patients—Initially, 75 mg/day in divided doses, increased to 150 mg/day. Dosages over 200 mg/day are not recommended. Maintenance therapy is in the range of 50 to 150 mg/day. For convenient therapy and to facilitate patient compliance, the total dosage requirement may be given at bedtime.

Hospitalized Patients—Initially, 100 mg/day in divided doses. This may be increased gradually in a few days to 200 mg/day, depending upon individual response and tolerance. If improvement does not occur in 2 to 3 weeks, the dose may be increased to the maximum recommended dose of 250 to 300 mg/day.

Adolescent and Geriatric Patients—Initially, a dose of 50 mg/day is recommended, with gradual increments up to 100 mg/day, depending upon patient response and tolerance.

Maintenance—Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission. Maintenance therapy is preferably administered as a single dose at bedtime. To minimize relapse, maintenance therapy should be continued for about three months.

Overdosage

SIGNS AND SYMPTOMS

The response of the patient to toxic overdosage of tricyclic antidepressants may vary in severity and is conditioned by factors such as age, amount ingested, amount absorbed, interval between ingestion and start of treatment. Surmontil is not recommended for infants or young children. Should accidental ingestion occur in any amount, it should be regarded as serious and potentially fatal.

CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive failure. Other symptoms may include respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, and diaphoresis.

Treatment is supportive and symptomatic as no specific antidote is known. Depending upon need the following measures can be considered:

1. Surmontil is not recommended for use in infants and children. Hospitalization with continuous cardiac monitoring for up to 4 days is recommended for children who have ingested Surmontil in any amount. This is based on the reported greater sensitivity of children to acute overdosage with tricyclic antidepressants.

2. Blood and urine levels may not reflect the severity of the poisoning and are mostly of diagnostic value.

3. CNS involvement, respiratory depression, or cardiac arrhythmia can occur suddenly; hospitalization and close observation are necessary, even when the amount ingested is thought to be small or initial toxicity appears slight. Patients with any alteration of ECG should have continuous cardiac monitoring for at least 72 hours and be observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery.

4. The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the cardiovascular and CNS effects of overdosage with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, start with 0.5 mg and repeat at 5-minute intervals to determine the minimum effective dose; do not exceed 2.0 mg. Avoid rapid injection, to reduce the possibility of physostigmine-induced convulsions. Because of the short duration of action of physostigmine, it may be necessary to repeat doses at 30- to 60-minute intervals as necessary.

5. In the alert patient, empty the stomach rapidly by induced emesis, followed by lavage. In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Instillation of activated-charcoal slurry may help reduce absorption of trimipramine.

6. Minimize external stimulation to reduce the tendency to convulsions. If anticonvulsants are necessary, diazepam, short-acting barbiturates, paraldehyde, or methocarbamol may be useful. Do not use barbiturates if MAO inhibitors have been taken recently.

7. Maintain adequate respiratory exchange. Do not use respiratory stimulants.

8. Shock should be treated with supportive measures, such as intravenous fluids, oxygen, and corticosteroids. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised.

9. Hyperpyrexia should be controlled by whatever external means available, including ice packs and cooling sponge baths if necessary.

10. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have been generally reported as ineffective in tricyclic poisoning.

How Supplied

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Keep tightly closed.
Dispense in tight container.

The appearance of these capsules is a trademark of Wyeth Laboratories.

by arrangement with RHONE-POULENC France

Wyeth Laboratories Inc., Philadelphia, PA 19101
CI 3842-2 Revised May 31, 1989
Printed in USA

Surmontil®
(trimipramine maleate)
CI 3842-5

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APPROVED
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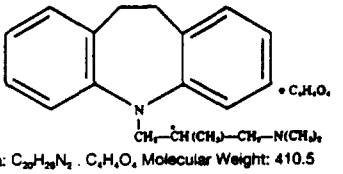
Surmontil®
(trimipramine maleate)

Description

Surmontil (trimipramine maleate) is 5-(3-dimethylamino-2-methylpropyl)-10,11-dihydro-5H-dibenz (b,f) azepine acid maleate (racemic form).



Molecular Formula: $C_{20}H_{26}N_2 \cdot C_4H_4O_4$ Molecular Weight: 410.5

Surmontil capsules contain trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg of trimipramine as the base. The inactive ingredients present are FD&C Blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25 mg dosage strength also contains D&C Yellow 10 and FD&C Yellow 6; the 50 mg dosage strength also contains D&C Red 28, FD&C Red 40, and FD&C Yellow 6.

Trimipramine maleate is prepared as a racemic mixture which can be resolved into levorotatory and dextrorotatory isomers. The asymmetric center responsible for optical isomerism is marked in the formula by an asterisk. Trimipramine maleate is an almost odorless, white or slightly cream-colored, crystalline substance, melting at 140-144° C. It is very slightly soluble in ether and water, is slightly soluble in ethyl alcohol and acetone, and freely soluble in chloroform and methanol at 20° C.

Clinical Pharmacology

Surmontil is an antidepressant with an anxiety-reducing sedative component to its action. The mode of action of Surmontil on the central nervous system is not known. However, unlike amphetamine-type compounds it does not act primarily by stimulation of the central nervous system. It does not act by inhibition of the monoamine oxidase system.

Indications and Usage

Surmontil is indicated for the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states. In studies with neurotic outpatients, the drug appeared to be equivalent to amitriptyline in the less-depressed patients but somewhat less effective than amitriptyline in the more severely depressed patients. In hospitalized depressed patients, trimipramine and imipramine were equally effective in relieving depression.

Contraindications

Surmontil is contraindicated in cases of known hypersensitivity to the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind. Surmontil should not be given in conjunction with drugs of the monoamine oxidase inhibitor class (e.g., tranylcypromine, isocarboxazid or phenelzine sulfate). The concomitant use of monoamine oxidase inhibitors (MAOI) and tricyclic compounds similar to Surmontil has caused severe hyperpyretic reactions, convulsive crises, and death in some patients. At least two weeks should elapse after cessation of therapy with MAOI before instituting therapy with Surmontil. Initial dosage should be low and increased gradually with caution and careful observation of the patient. The drug is contraindicated during the acute recovery period after a myocardial infarction.

Warnings

GENERAL CONSIDERATION FOR USE

Extreme caution should be used when this drug is given to patients with any evidence of cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes, and tachycardia.

Caution is advised in patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties; hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity; patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold; patients receiving guanethidine or similar agents, since Surmontil may block the pharmacologic effects of these drugs.

Since the drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

Precautions

GENERAL

The possibility of suicide is inherent in any severely depressed patient and persists until a significant remission occurs. When a patient with a serious suicidal potential is not hospitalized, the prescription should be for the smallest amount feasible.

In schizophrenic patients activation of the psychosis may occur and require reduction of dosage or the addition of a major tranquilizer to the therapeutic regime.

Manic or hypomanic episodes may occur in some patients, in particular those with cyclic-type disorders. In some cases therapy with Surmontil must be discontinued until the episode is relieved, after which therapy may be reinstituted at lower dosages if still required.

Concurrent administration of Surmontil and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to those patients for whom it is essential. When possible, discontinue the drug for several days prior to elective surgery.

Surmontil should be used with caution in patients with impaired liver function.

Chronic animal studies showed occasional occurrence of hepatic congestion, fatty infiltration, or increased serum liver enzymes at the highest dose of 60 mg/kg/day.

Both elevation and lowering of blood sugar have been reported with tricyclic antidepressants.

DRUG INTERACTIONS

Cimetidine

There is evidence that cimetidine inhibits the elimination of tricyclic antidepressants. Downward adjustment of Surmontil dosage may be required if cimetidine therapy is initiated; upward adjustment if cimetidine therapy is discontinued.

Alcohol

Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggerated effects.

Catecholamines/Anticholinergics

It has been reported that tricyclic antidepressants can potentiate the effects of catecholamines. Similarly, atropinelike effects may be more pronounced in patients receiving anticholinergic therapy. Therefore, particular care should be exercised when it is necessary to administer tricyclic antidepressants with sympathomimetic amines, local decongestants, local anesthetics containing epinephrine, atropine or drugs with an anticholinergic effect. In resistant cases of depression in adults, a dose of 2.5 mg/kg/day may have to be exceeded. If a higher dose is needed, ECG monitoring should be maintained during the initiation of therapy and at appropriate intervals during stabilization of dose.

Drugs Metabolized by P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7-10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from cotherapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Semen studies in man (four schizophrenics and nine normal volunteers) revealed no significant changes in sperm morphology. It is recognized that drugs having a parasympathetic effect, including tricyclic antidepressants, may alter the ejaculatory response.

Chronic animal studies showed occasional evidence of degeneration of seminiferous tubules at the highest dose of 60 mg/kg/day.

PREGNANCY

Teratogenic Effects—Pregnancy Category C

Surmontil has shown evidence of embryo-toxicity and/or increased incidence of major anomalies in rats or rabbits at doses 20 times the human dose. There are no adequate and well-controlled studies in

pregnant women. Surmontil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE

This drug is not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Adverse Reactions

Note: The pharmacological similarities among the tricyclic antidepressants require that each of the reactions be considered when Surmontil is administered. Some of the adverse reactions included in this listing have not in fact been reported with Surmontil.

CARDIOVASCULAR

Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

PSYCHIATRIC

Confusional states (especially the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

NEUROLOGICAL

Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

ANTICHOLINERGIC

Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis, constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

ALLERGIC

Skin rash, petechiae, urticaria, itching, photosensitization, edema of face and tongue.

HEMATOLOGIC

Bone-marrow depression including agranulocytosis, eosinophilia; purpura; thrombocytopenia. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathological neutrophil depression.

GASTROINTESTINAL

Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue.

ENDOCRINE

Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood-sugar levels.

OTHER

Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness, and fatigue; headache; parotid swelling; alopecia.

WITHDRAWAL SYMPTOMS

Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Dosage and Administration

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. It is not possible to prescribe a single dosage schedule of Surmontil that will be therapeutically effective in all patients. The physical psychodynamic factors contributing to depressive symptomatology are very complex; spontaneous remissions or exacerbations of depressive symptoms may occur with or without drug therapy. Consequently, the recommended dosage regimens are furnished as a guide which may be modified by factors such as the age of the patient, chronicity and severity of the disease, medical condition of the patient, and degree of psychotherapeutic support.

Most antidepressant drugs have a lag period of ten days to four weeks before a therapeutic response is noted. Increasing the dose will not shorten this period but rather increase the incidence of adverse reactions.

USUAL ADULT DOSE

Outpatients and Office Patients—Initially, 75 mg/day in divided doses, increased to 150 mg/day. Dosages over 200 mg/day are not recommended. Maintenance therapy is in the range of 50 to 150 mg/day. For convenient therapy and to facilitate patient compliance, the total dosage requirement may be given at bedtime.

Hospitalized Patients—Initially, 100 mg/day in divided doses. This may be increased gradually in a few days to 200 mg/day, depending upon individual response and tolerance. If improvement does not occur in 2 to 3 weeks, the dose may be increased to the maximum recommended dose of 250 to 300 mg/day.

Adolescent and Geriatric Patients—Initially, a dose of 50 mg/day is recommended, with gradual increments up to 100 mg/day, depending upon patient response and tolerance.

Maintenance—Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission. Maintenance therapy is preferably administered as a single dose at bedtime. To minimize relapse, maintenance therapy should be continued for about three months.

Overdosage

SIGNS AND SYMPTOMS

The response of the patient to toxic overdosage of tricyclic antidepressants may vary in severity and is conditioned by factors such as age, amount ingested, amount absorbed, interval between ingestion and start of treatment. Surmontil is not recommended for infants or young children. Should accidental ingestion occur in any amount, it should be regarded as serious and potentially fatal.

CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive failure. Other symptoms may include respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, and diaphoresis.

Treatment is supportive and symptomatic as no specific antidote is known. Depending upon need the following measures can be considered:

1. Surmontil is not recommended for use in infants and children. Hospitalization with continuous cardiac monitoring for up to 4 days is recommended for children who have ingested Surmontil in any amount. This is based on the reported greater sensitivity of children to acute overdosage with tricyclic antidepressants.

2. Blood and urine levels may not reflect the severity of the poisoning and are mostly of diagnostic value.

3. CNS involvement, respiratory depression, or cardiac arrhythmia can occur suddenly; hospitalization and close observation are necessary, even when the amount ingested is thought to be small or initial toxicity appears slight. Patients with any alteration of ECG should have continuous cardiac monitoring for at least 72 hours and be observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery.

4. The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the cardiovascular and CNS effects of overdosage with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, start with 0.5 mg and repeat at 5-minute intervals to determine the minimum effective dose; do not exceed 2.0 mg. Avoid rapid injection, to reduce the possibility of physostigmine-induced convulsions. Because of the short duration of action of physostigmine, it may be necessary to repeat doses at 30- to 60-minute intervals as necessary.

5. In the alert patient, empty the stomach rapidly by induced emesis, followed by lavage. In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Instillation of activated-charcoal slurry may help reduce absorption of trimipramine.

6. Minimize external stimulation to reduce the tendency to convulsions. If anticonvulsants are necessary, diazepam, short-acting barbiturates, paraldehyde, or methocarbamol may be useful. Do not use barbiturates if MAO inhibitors have been taken recently.

7. Maintain adequate respiratory exchange. Do not use respiratory stimulants.

8. Shock should be treated with supportive measures, such as intravenous fluids, oxygen, and corticosteroids. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised.

9. Hyperpyrexia should be controlled by whatever external means available, including ice packs and cooling sponge baths if necessary.

10. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have been generally reported as ineffective in tricyclic poisoning.

How Supplied

Surmontil® (trimipramine maleate) Capsules are available in the following dosage strengths:

25 mg, NDC 0008-4132, opaque blue and yellow capsule marked "WYETH" and "4132", in bottles of 100 capsules.

50 mg, NDC 0008-4133, opaque blue and orange capsule marked "WYETH" and "4133", in bottles of 100 capsules and in Redipak® cartons of 100 capsules (10 blister strips of 10).

100 mg, NDC 0008-4158, opaque blue and white capsule marked "WYETH" and "4158", in bottles of 100 capsules.

Store at room temperature, approximately 25° C (77° F).

Keep bottles tightly closed.

Dispense in a tight container.

Protect capsules packaged in blister strips from moisture.

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories.

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