CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20758/S16

APPROVAL LETTER
Bristol-Myers Squibb
Attention: Mary Ellen Norvitch, Ph.D.
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Dr. Norvitch:

Please refer to your supplemental new drug applications dated February 23, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avapro (irbesartan) Tablets, 75, 150, 300 mg and Avalide (irbesartan/hydrochlorothiazide) Tablets, 75/12.5, 150/12.5, 300/12.5 mg.

We note that these supplements were submitted as a “Special Supplement – Changes Being Effected” under 21 CFR 314.70(c).

These supplemental new drug applications provide for final printed labeling revised as follows:

1. Under ADVERSE REACTIONS, the Post-Marketing Experience subsection has been changed to add hyperkalemia as follows:

   The following adverse reactions have been reported in post-marketing experience: Rare cases of urticaria and angioedema (involving swelling of the face, lips, pharynx, and/or tongue); hyperkalemia.

2. The address information has been changed to reflect a new logo.

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 final printed labeling included in your February 23, 2000 submissions. Accordingly, these supplemental applications are approved effective on the date of this letter.
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, please contact:

Mr. Edward Fromm  
Regulatory Health Project  
(301) 594-5313

Sincerely,

/\S/  
Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  

5/9/00
AVALIDE®
(irbesartan-hydrochlorothiazide)
Tablets

1030229A1

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, AVALIDE should be discontinued as soon as possible. (See WARNINGS: Pregnancy, Fetal/Neonatal Morbidity and Mortality.)

DESCRIPTION
AVALIDE® (irbesartan-hydrochlorothiazide) Tablets is a combination of an angiotensin II receptor antagonist (ATI, irbesartan) and a thiazide diuretic. hydrochlorothiazide (HCT).

Irbesartan is a nonpeptide compound, chemically described as 2-butyl-3-[2′-({N′-[1H-1,2,4-benzothiadiazol-7-yl]ethyl[1H-1,2,4-benzothiadiazol-7-yl]methyl)-4-piperidinyl]-1,3-disaxoyl]4,4- dimethyl-1,2,4-oxadiazole (4,4- dimethyl-1,2,4-oxadiazole). Its empirical formula is C30H31N10O8 and its structural formula is:

\[
\text{Structural Formula of Irbesartan}
\]

Hydrochlorothiazide is a white to off-white crystalline powder with a molecular weight of 268.5. It is a nonpeptide compound with a partition coefficient (octanol/water) of 10.3 at pH 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

Hydrochlorothiazide is 6-chloro-2,4-dihydro-3H-1,2,4-benzothiadiazole-7-sulfonamide 1,1-dioxide. Its empirical formula is C10H10ClN2O5S and its structural formula is:

\[
\text{Structural Formula of Hydrochlorothiazide}
\]

Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.7. Hydrochlorothiazide is slightly soluble in water and freely soluble in sodium hydroxide solution.

AVALIDE is available as oral administration in tablets containing 150 mg or 300 mg of irbesartan combined with 12.5 mg of hydrochlorothiazide. Inactive ingredients include: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, tangerine red, tangerine yellow, sodium dodecyl, and magnesium stearate.

CLINICAL PHARMACOLOGY
Mechanisms of Action
Irbesartan
Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensinconverting enzyme (ACE, dipeptidyl carboxypeptidase). Angiotensin II is the principal vasoconstrictor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by several corticosteroid, cardiac contractility, renal reabsorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1, angiotensin II receptor. There is also an AT2 receptor in many tissues, but it is not involved in cardiovascular homeostasis.

Irbesartan is a specific competitive antagonist of AT1 receptors with a much greater affinity (more than 1000-fold) for the AT1 receptor than for the AT2 receptor, and no agonist activity.

Blockade of the AT1 receptor reverses the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of irbesartan on blood pressure.

Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in cardiovascular regulation of blood pressure and sodium homeostasis. Because irbesartan does not inhibit ACE, it does not affect the response to captopril; whether this has clinical relevance is not known.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, diuretically increasing secretion of sodium and chloride in approximately equal amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

Pharmacokinetics
Irbesartan
Irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 65-80%. Following oral administration of irbesartan, peak plasma concentrations of irbesartan are attained at 1.5-2 hours after dosing. Food does not affect the bioavailability of irbesartan.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range. The terminal elimination half-life of irbesartan averaged 11-15 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of irbesartan (Cmax) is observed in plasma upon repeated once-daily dosing.

Hydrochlorothiazide
When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.8 and 14.3 hours.

*Registered trademark of Sanofi

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**Metabolism and Elimination**

**Ibuprofen**

Ibuprofen is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of \(1^C\)-labeled ibuprofen, more than 95% of the dose appears in urine within 48 hours. The principal metabolites are the inactive ibuprofen glucuronide conjugate (approximately 60%) and ibuprofen carboxylic acid (approximately 4%). The primary renal excretion routes are the urine and the feces. Then renally metabolized dose is excreted by both the kidney and the liver. Following either oral or intravenous administration of \(1^C\)-labeled ibuprofen, about 20% of radioactivity is recovered in the urine and the remainder in the feces, re-respectively in ibuprofen glucuronide and unmetabolized ibuprofen.

**Ibuprofen**

In vitro studies of ibuprofen oxidation by cytochrome P450 isozymes indicated ibuprofen was oxidized primarily by CYP2C9, CYP2C19, and CYP3A4. However, the role of these enzymes in the metabolism of ibuprofen is unclear due to the marked interindividual variability associated with drug metabolism (T1, A1, 1A2, 2A1, 2A6, 2E1, 3A4).

**Hydrochlorothiazide**

Hydrochlorothiazide is not metabolized but is excreted rapidly by the kidney. At least 61 percent of the oral dose is excreted unchanged within 24 hours.

**Reservoir**

Reservoir intake is 5% to 15% of serum proteins (primarily albumin and \(\alpha\)-acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53 ± 43 L. Total plasma and renal clearances are in the range of 15 ± 7 and 3.0 ± 3.5 L/min, respectively. With repetitive dosing, reservoirs accumulate to clinically relevant levels.

*Studies in animals indicate that nephrotoxicity of ibuprofen weakly crosses the blood brain barrier and placenta.*

**Ibuprofen**

Ibuprofen crosses the placental but not the blood-brain barrier and is excreted in breast milk.

**Special Considerations**

- **Pediatric:** Ibuprofen pharmacokinetics have not been investigated in patients <18 years of age.
- **Gender:** No gender-related differences in pharmacokinetics were observed in healthy elderly (age 65-80 years) or in healthy young (age 18-40 years) subjects. In studies of hypertensive patients, there was no gender difference in \(C_{max}\) or \(AUC_{0-8h}\), but gender and age differences in trough plasma concentrations of ibuprofen were observed in females (17-74 years) at 30 mg/day; no gender-related dosage adjustment is necessary.

**Geriatric:** In elderly subjects (age 65-80 years), ibuprofen elimination half-life was not significantly different from those of younger adults (18-74 years). The drug dosage adjustment is necessary in the elderly.

**Renal Insufficiency:** The pharmacokinetics of ibuprofen were not altered in patients with renal impairment or in patients on hemodialysis. However, if ibuprofen is given to patients on hemodialysis, the dose should be adjusted.

**Liver Insufficiency:** In patients with severe cirrhosis, ibuprofen **Cmax** and **AUC** were increased; no dosage adjustment is necessary in the cirrhotic patient.

**Hepatic Insufficiency:** The pharmacokinetics of ibuprofen following repeated oral administration were not significantly different in patients with hepatic insufficiency compared to those with normal liver function. No dosage adjustment is necessary in patients with hepatic insufficiency.

**Drug Interactions:** (See PRECAUTIONS: Drug Interactions.)

**Pharmacodynamics**

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and antipyretic properties. Ibuprofen is available in oral forms (tablets, capsules, and suspension) and injectable forms (injection).

**Ibuprofen**

In healthy subjects, single and multiple doses of up to 400 mg produced dose-dependent inhibition of the pressor effect of angiotensin II (AII). Inhibition was complete (0.04 mg) for higher oral doses at 150 mg or 300 mg and partial inhibition was sustained for 24 hours (50% and 30 mg at 150 mg and 30 mg, respectively). No toxicity was noted. At doses up to 1,200 mg, no ibuprofen has been found to be significantly affected at recommended doses.

**Ibuprofen**

In hypertensive patients, blood pressure was lowered by 5-10 mm Hg in the first 2 hours of treatment. In multiple dose studies in hypertensive patients, there were clinically significant effects in lowering systemic arterial pressure, heart rate, diastolic arterial pressure, and arterial compliance. These effects were observed in patients receiving ibuprofen alone or in combination with other antihypertensive agents.

**Hydrochlorothiazide**

**Ibuprofen**

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 5 to 12 hours.

**Clinical Studies**

The antihypertensive effects of ibuprofen were examined in seven (7) major placebo-controlled 8-12 week trials in patients with baseline diastolic blood pressure readings of 100 ± 20 mm Hg. The trials included a range of 12 mg to 400 mg of ibuprofen daily. The primary endpoint was the change in diastolic blood pressure over 12 weeks. The ibuprofen dose was increased at 4-week intervals in order to achieve a target dose of 400 mg/day. A total of 1,307 patients were randomized to the ibuprofen treatment groups and 1,294 patients were randomized to the placebo group. The results of these studies are presented in Table 1.

**Ibuprofen**

The antihypertensive effects of hydrochlorothiazide were examined in four (4) major placebo-controlled 8-12 week trials in patients with baseline diastolic blood pressure readings of 100 ± 20 mm Hg. The trials included a range of 12 mg to 400 mg of ibuprofen daily. The primary endpoint was the change in diastolic blood pressure over 12 weeks. The ibuprofen dose was increased at 4-week intervals in order to achieve a target dose of 400 mg/day. A total of 1,307 patients were randomized to the ibuprofen treatment groups and 1,294 patients were randomized to the placebo group. The results of these studies are presented in Table 2.

**Ibuprofen**

The antihypertensive effects of ibuprofen were examined in seven (7) major placebo-controlled 8-12 week trials in patients with baseline diastolic blood pressure readings of 100 ± 20 mm Hg. The trials included a range of 12 mg to 400 mg of ibuprofen daily. The primary endpoint was the change in diastolic blood pressure over 12 weeks. The ibuprofen dose was increased at 4-week intervals in order to achieve a target dose of 400 mg/day. A total of 1,307 patients were randomized to the ibuprofen treatment groups and 1,294 patients were randomized to the placebo group. The results of these studies are presented in Table 1.

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discontinued due to increases or decreases in serum potassium. Overall, the combination of ibresinat and hydrochlorothiazide had no effect on serum potassium. Higher doses of ibresinat ameliorated the hyperuricemic response to hydrochlorothiazide.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Although hyperkalemia has not been observed for clinical benefit, the development of hyperkalemia is particularly important when the patient is normalizing and is predisposed to develop symptoms of hyperkalemia. Ascites and areas of cutaneous atrophy in the absence of cause, including edema of the hand, tarsal, weakness, atrophy, edema, cutaneous atrophy, restlessness, confusion, seizures, muscle pain or cramps, muscular twitching, hypotension, dyspnea, or respiratory arrest, may occur. Moreover, hypoglycemia may develop, especially with brisk diarrhea, when severe diarrhea is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmias and may also exacerbate or aggravate the response of the heart to the toxic effects of digitalis.

Although any chloride deficit is generally mild and usually does not require specific treatment except under extrarenal conditions and replaces may be required in the treatment of metabolic alkalosis.

Diuretic use in edematous patients in hot weather: adequate therapy is water restriction, rather than administration of salt except in rare instances when the hyperosmolality is life-threatening. In acetate administration, 75% of the dose should be given during the first two hours. Hyperkalemia may occur or frank gout may be precipitated in certain patients receiving theophylline. Barbiturates, in diabetics patient dosage adjustments of insulin and oral hypoglycemics appear to be required. Hypertension may occur with thiazide diuretics. Thus marked diastolic dissection may be manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathetic patient. Progression renal impairment becomes evident, consider withdrawal or decreasing diuretic use.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Theophylline may decrease urinary calcium excretion. Thiazides may cause intercurrent and slight elevation of serum uric acid in the absence of brown colors of diet and physical activity. Marked hyperkalemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Impaired Renal Function

As a consequence of inducing the non-steroid analgesic activity, changes in renal function may be anticipated in susceptible patients. In patients whose renal function may depend on the activity of the renin-angiotensin system, hypertension may occur or frank gout may be precipitated in certain patients receiving theophylline. Barbiturates, in diabetics patient dosage adjustments of insulin and oral hypoglycemics appear to be required. Hypertension may occur with thiazide diuretics. Thus marked diastolic dissection may be manifest during thiazide therapy.

Specific Use For Prevention of Postoperative Nausea and Vomiting

Ibresinat is occasionally used in patients aged 70 years and over.

Ibresinat is not known to be carcinogenic in human tests. The use of ibresinat in human, animal or other experience is limited. In vitro studies in the Ames Salmonella/Mammalian Microsome assay, the Escherichia coli Mutagenesis assay, and the Chinese Hamster Ovary Test for chromosomal aberrations, in B6C3F1 mice and males mice, has shown no evidence of an increase in the frequency of mutations or chromosome aberrations.

Ibresinat had no adverse effects on the fertility of mice and rats of either sex in studies when administered orally to sperm at doses up to 100 mg/kg or in males and female rats at doses of up to 150 mg/kg.

Ibresinat did not significantly affect body weight, sperm motility, sperm survival, or litter size in mouse or rat fertility studies. The administration of ibresinat to pregnant rats at doses up to 500 mg/kg/day did not result in histological findings that would indicate an embryo-fetal toxicity. In a study on the effects of ibresinat on the ability of inbred DBA strain mice to reproduce, there was no evidence of any adverse effects on fertility or on other reproductive parameters.

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Skin eruptions multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis.

Special Sensitivity: transient blurred vision, vertigo.

Post-Marketing Experience
The following adverse reactions have been reported in post-marketing experience: Rare cases of urticaria and angioedema (involving swelling of the face, lips, pharynx, and/or tongue); hypokalemia.

Laboratory Test Findings
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of AVALDE (isradipine-hydrochlorothiazide) Tablets.

Creatinine: Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3% and 1.1% patient respectively, of patients with essential hypertension treated with AVALDE alone. No patient discontinued taking AVALDE due to increased BUN. One patient discontinued taking AVALDE due to a minor increase in serum creatinine.

Hemoglobin: Mean decreases of approximately 0.2 g/dl occurred in patients treated with AVALDE alone, but were rarely of clinical importance. This compared to a mean of 0.4 g/dl in patients receiving placebo. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with AVALDE alone, one patient was discontinued due to elevated liver enzymes.

Serum Electrolytes: (See PRECAUTIONS.)

OVERDOSAGE
Isradipine
No data are available in regard to overdosage in humans. However, daily doses of 800 mg for 9 weeks were well-tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdosage. Isradipine is not removed by hemodialysis.

To obtain up-to-date information about the treatment of overdosage, a good resource is the certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibilities of multiple-cause interactions, drug-drug interactions, and unusual drug toxicities in the patient.

Laboratory determinations of serum levels of isradipine are not widely available, and such determinations have, in any event, not established a role in the management of isradipine overdosage.

Acute oral toxicity studies with isradipine in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg. AUC was 25- and 30-fold the maximum recommended human dose (300 mg) on a mg/m² basis, respectively.

Hydrochlorothiazide
The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hypernatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered the symptoms of digitalis toxicity may be accentuated. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD₅₀ of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

DOSE AND ADMINISTRATION
The recommended initial dose of isradipine is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.

A lower initial dose of isradipine (75 mg) is recommended in patients with diastolic blood pressure greater than 120 mm Hg and in those with evidence of congestive heart failure, recent stroke, or other serious conditions. Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive additional benefit from a higher dose of once-daily dosing.

Hydrochlorothiazide is effective at doses of 12.5 to 50 mg once daily. To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

The side effects (see WARNINGS) of isradipine are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (e.g., electrolyte loss). The former is much more common than the latter. Therapy with any combination of isradipine and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

AVALDE may be administered with other antianginal agents. AVALDE may be administered with or without food.

Replacement Therapy
The combination may be substituted for the titrated components.

Dose Titration by Clinical Effect
A patient whose blood pressure is inadequately controlled by isradipine or hydrochlorothiazide alone may be switched to once-daily AVALDE. The recommended doses of AVALDE, in order of increasing mean effect, are isradipine-hydrochlorothiazide 150/25 mg, 300/25 mg, and 300/50 mg (two 150/25 mg tablets). The latest incremental effect will likely be in the transition from monotherapy to 150/25 mg. (See CLINICAL PHARMACOLOGY:Clinical Study.) It takes about 4-6 weeks for the blood pressure to stabilize after a change in the dose of AVALDE.

The usual dose of AVALDE is one tablet once daily. More than two tablets once daily is not recommended. The maximum antihypertensive effect is attained about 2-4 weeks after initiation of therapy.

In Patients with Renal Impairment
The usual regimen of therapy with AVALDE may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with severe renal impairment, dosing intervals are preferred to thrice-daily doses, so AVALDE is not recommended.

Patients with Hepatic Impairment
No dosage adjustment is necessary in patients with hepatic impairment.

HOW SUPPLIED
AVALDE (isradipine-hydrochlorothiazide) Tablets are peach, biconvex, and oval with a heart debossed on one side and 2775 or 2776 on the reverse, supplied as follows:

<table>
<thead>
<tr>
<th>Isradipine (mg)</th>
<th>Hydrochlorothiazide (mg)</th>
<th>30 tablets bottle of 100 tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>12.5</td>
<td>2775-31</td>
</tr>
<tr>
<td>300</td>
<td>12.5</td>
<td>2776-31</td>
</tr>
</tbody>
</table>

Storage
Store at a temperature between 15 °C and 30 °C (59 °F and 86 °F) (See USP).

Manufactured and Distributed by
Bristol-Myers Squibb Company
Princeton, NJ 08543-4500
Comaxtrated by:
Sanofi-Synthelabo Inc.
New York, NY 10016

Bristol-Myers
Squibb Company
sanofi-synthelabo

1003291

Revised November 1998
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20758/S16

ADMINISTRATIVE DOCUMENTS
CSO Review of Final Printed Labeling

Application: NDA 20-757/S-015
NDA 20-758/S-016

Applicant: Bristol-Myers Squibb

Document Dates: February 23, 2000 (S-015 & S-016)
Receipt Dates: February 28, 2000 (S-015 & S-016)

Product Names: Avapro (irbesartan) Tablets, 75, 150, 300 mg
Avalide (irbesartan/hydrochlorothiazide) Tablets, 75/12.5, 150/12.5, 300/12.5 mg

Background: These supplemental applications were submitted as “Changes Being Effectuated” in response to our supplement request letter of August 23, 1999 that asked the sponsor to add hyperkalemia to the list of adverse reactions associated with irbesartan use.

Review: The sponsor has submitted final printed labeling (for both supplements) revised as follows:

1. Under ADVERSE REACTIONS, the Post-Marketing Experience subsection has been changed from:

[ ]

to:

The following adverse reactions have been reported in post-marketing experience: Rare cases of urticaria and angioedema (involving swelling of the face, lips, pharynx, and/or tongue); hyperkalemia.

2. The address information has been changed to reflect a new logo.

There are no other changes from the last approved package inserts.

Comments/Recommendations: An approval letter should issue for these supplements as set forth under 21 CFR 314.70 (c)(i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction].

/Edward Fromm/
Consumer Safety Officer

Ef/4-11-2000