

Successful Outcomes

	1 Week Therapy			4 Weeks Therapy	
	At 1 wk (end of Rx)	At 4 wks (3 wk f/up)	At 6 wks (5 wk f/up)	At 4 wks (end of Rx)	At 6 wks (2 wk f/up)
sum	14% (11/79)	51% (40/78)	65% (51/78)	71% (94/133)	73% (97/132)
phytes	6% (5/79)	13% (10/75)	12% (8/69)	ND	ND
	ND	ND	ND	63% (84/133)	59% (79/134)

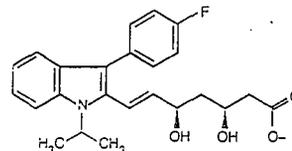
LESCOL®
(fluvastatin sodium)
Capsules

Caution: Federal law prohibits dispensing without prescription.

The following prescribing information is based on official labeling in effect on August 1, 1994.

DESCRIPTION

Lescol® (fluvastatin sodium), is a water soluble cholesterol lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Fluvastatin sodium is [R*, S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1-H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The structural formula is:



C₂₄H₂₅FO₄ Na

Mol. wt. 433.46

This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. Lescol® (fluvastatin sodium) is supplied as capsules containing fluvastatin sodium, equivalent to 20 mg or 40 mg of fluvastatin, for oral administration.

Active Ingredient: fluvastatin sodium

Inactive Ingredients: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch, red iron oxide, sodium lauryl sulfate, calc. titanium dioxide, yellow iron oxide, and other ingredients.

May Also Include: benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide and sodium propionate.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (a membrane transport complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was a multicenter, randomized, double-blind study involving 3,806 asymptomatic middle-aged men in the United States with Type II hyperlipoproteinemia treated with diet and cholestyramine. Results of this trial demonstrated that a statistically significant reduction of 19% in the incidence of definite myocardial infarction and/or coronary heart disease death was associated with an 8% decrease in blood cholesterol and 11% decrease in LDL-C levels. In other multicenter clinical trials, those pharmacologic and/or nonpharmacologic interventions that simultaneously lowered LDL-C and increased HDL-C also have reduced the rate of cardiovascular events (both fatal and nonfatal myocardial infarctions).

In patients with hypercholesterolemia, treatment with Lescol® (fluvastatin sodium) reduced Total-C, LDL-C, and apolipoprotein B. Lescol® (fluvastatin sodium) also moderately reduced triglycerides (TG) while producing an increase in HDL-C of variable magnitude. The agent had no consistent effect on either Lp(a) or fibrinogen. The effect of fluvastatin sodium-induced changes in lipoprotein levels on the evolution of atherosclerosis has not been established.

Mechanism of Action

Lescol® (fluvastatin sodium) is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

Pharmacokinetics/Metabolism

Lescol® (fluvastatin sodium) is administered orally in the active form. Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. In a fed state, even up to 4 hours post prandial, the drug is also completely absorbed, but at a reduced rate (C_{max} is reduced

day 7 of drug therapy. The duration of drug therapy should be for a minimum of 1 week and should not exceed 4 weeks. (See **CLINICAL STUDIES** and following Note.)

In the treatment of tinea cruris (jock itch) or tinea corporis (ringworm), Lamisil® Cream, 1% (terbinafine hydrochloride cream) should be applied to cover the affected and immediately surrounding areas once or twice daily until clinical signs and symptoms are significantly improved. In many patients this occurs by day 7 of drug therapy. The duration of drug therapy should be for a minimum of 1 week and should not exceed 4 weeks. (See **CLINICAL STUDIES** and following Note.)

Note:

Many patients treated with shorter durations of therapy (1-2 weeks) continue to improve during the 2-4 weeks after drug therapy has been completed. As a consequence, patients should not be considered therapeutic failures until they have been observed for a period of 2-4 weeks off therapy. (See **CLINICAL STUDIES**.)

If successful outcome is not achieved during the post-treatment observation period, the diagnosis should be reviewed.

HOW SUPPLIED

Lamisil® Cream, 1% (terbinafine hydrochloride cream)
Tubes of 15 grams (NDC 0078-0170-40)
Tubes of 30 grams (NDC 0078-0170-46)
Store between 5° and 30°C (41° and 86°F).

CLINICAL STUDIES

In the following data presentations, the term "successful outcome" refers to those patients evaluated at a specific time point, who had both negative mycological results (culture and KOH preparation) and a total clinical score of less than 2. The clinical score is the sum of the scores of each sign and symptom graded on a scale from 0=absent to 3=severe. Mean clinical scores at entry ranged from 8-11 in the pivotal clinical trials. All studies included, at a minimum, clinical evaluation of erythema, desquamation, and pruritus.

A. Tinea Pedis

In 3 studies of Lamisil® Cream, 1% (terbinafine hydrochloride cream) used B.I.D. in the treatment of tinea pedis, 2 (combined in the table below) were vehicle-controlled (placebo) evaluations of 1 week treatment duration. The third study (see following table) was of 4 weeks therapy compared to another active drug. (See table above.)

B. Tinea Corporis/Cruris

Two studies (combined below) compared Lamisil® Cream, 1% (terbinafine hydrochloride cream) to vehicle (placebo), applied once daily for 1 week in the treatment of tinea corporis/cruris.

In the following table, sites of infection are separated into 2 groups: (1) tinea corporis and (2) tinea cruris. Patients with mixed tinea corporis/cruris are included in both groups.

Disease	Drug	Successful Outcomes after 1 Week of Therapy	
		At 1 wk (end of Rx)	At 4 wks (3 wk f/up)
Corporis	Lamisil®	21% (7/33)	83% (25/30)
	Vehicle	0% (0/31)	31% (4/13)
Cruris	Lamisil®	43% (21/49)	92% (45/49)
	Vehicle	9% (5/58)	25% (7/28)

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[REV: JUNE 1993 37352902]

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Sandoz—Cont.

by 40%-70%). The action of HMG-R inhibitors occurs within the liver. The absolute systemic bioavailability for this drug class is low. The absolute bioavailability of fluvastatin following a 10 mg oral dose was 24% (range 9%-50%). At doses above 20 mg, fluvastatin exhibits nonlinear kinetics, at least in the fasting state, resulting in dose normalized AUC values 20%-40% higher than expected for the 40 mg dose. The volume of distribution ($V_{D_{ss}}$) for the drug is calculated to be 34.4 liters. More than 98% of the circulating drug is bound to plasma proteins, and this binding is unaffected by drug concentration.

Biotransformation pathways for fluvastatin include: a) hydroxylation of the indole ring at the 5- and 6-positions; b) N-dealkylation; and c) beta-oxidation. The major circulating blood components are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically. Both enantiomers of fluvastatin are metabolized in a similar manner resulting in only minor differences in systemic exposure.

Following administration of 3H -fluvastatin sodium to healthy volunteers, excretion of radioactivity was about 5% in the urine and 90% in the feces. With the parent, fluvastatin, accounting for less than 2% of the total radioactivity excreted. The plasma clearance for fluvastatin in man is calculated to be 39.2 ± 4.4 liters per hour. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of 40 mg daily; however, after 6 days of dosing with 40 mg 3H -fluvastatin sodium solution, total radioactivity—which includes parent compound and pharmacologically inactive metabolites—accumulated by a factor of 2 based on C_{min} values. Following oral administration of 20 mg of fluvastatin sodium, the beta elimination half-life for fluvastatin is 1.2 hours (range of 0.53-3.1 hours). The bioavailability of Lescol® (fluvastatin sodium) 20 mg capsules is equivalent to a solution of fluvastatin sodium except that the time to peak under fasted conditions is about 0.7 hours following administration of the capsule compared to about 0.4 hours for the solution. Following ingestion of a single 20 mg Lescol® (fluvastatin sodium) capsule under fasted conditions, measurable plasma concentrations of fluvastatin appear systemically within 10 minutes after dosing and reach a peak of 147 ± 86 ng/mL at 0.66 ± 0.3 hours. Lescol® (fluvastatin sodium), like the other HMG-R inhibitors, has variable systemic bioavailability. The coefficient of variation (based on the inter-subject variability) was 47%-57% for AUC, and 58%-62% for C_{max} .

Results from an overnight pharmacokinetic evaluation following steady-state administration of Lescol® (fluvastatin sodium) with the evening meal or 4 hours after the evening meal for 15 weeks showed that administration of fluvastatin sodium with the evening meal results in a two-fold decrease in C_{max} and more than a two-fold increase in t_{max} as compared to patients receiving the drug 4 hours after the evening meal. No significant difference in AUC was observed between the 2 treatment groups, and there were no differences in the lipid-lowering effects of fluvastatin sodium administered with the evening meal or 4 hours after the evening meal.

The effects of gender and age on the pharmacokinetics of fluvastatin sodium were evaluated in 4 patient subgroups; young and elderly males and females. All patients were administered 20 mg fluvastatin daily, at least 2 hours after the evening meal, for 21 days. Results from an overnight pharmacokinetic evaluation indicate that for the general patient population plasma concentrations of fluvastatin do not vary either as a function of age or gender. Due to their generally smaller body weight, young female patients show higher fluvastatin plasma concentrations after administration of 10-40 mg of fluvastatin compared to young males.

Since fluvastatin is eliminated primarily via the biliary route and is subject to significant presystemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency. In a single-dose study the kinetics of fluvastatin sodium in subjects with cirrhosis ($n=11$) and in healthy age- and sex-matched subjects ($n=11$) were compared. The mean AUC and C_{max} parameters were about 2.5 times higher in the subjects with hepatic insufficiency. There was a 28% decrease in plasma clearance and a 31% smaller volume of distribution. No apparent difference was observed in the plasma elimination half-lives for the 2 groups. Caution should be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion (see WARNINGS).

Clinical Studies

Lescol® (fluvastatin sodium) has been studied in 4 controlled Phase 3 trials. These studies involved 1605 North American patients with Type IIa or IIb hyperlipoproteinemia. Lescol® (fluvastatin sodium) was administered to 946 patients in these trials of 24-54 weeks duration. In the largest single randomized study with Lescol® (fluvastatin sodium) ($n=292$), treatment at a dose of 20 mg QPM resulted

in a highly significant decrease in LDL-C of 22.2% after 9 weeks of study. In the largest single study ($n=210$) of patients randomized to 40 mg daily and limited to FH patients, a mean LDL-C reduction of 24.0% was observed. Reductions in Apo B were also seen as a result of treatment with Lescol® (fluvastatin sodium). Small but statistically significant increases in HDL-C and corresponding decreases in TG were also noted. No consistent effect on Lp(a) was found.

INDICATIONS AND USAGE

Lescol® (fluvastatin sodium) is indicated as an adjunct to diet in the treatment of elevated total cholesterol (total-C) and LDL-C levels in patients with primary hypercholesterolemia (Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate.

Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, or other medication, or alcoholism, have been excluded. Prior to initiation of fluvastatin sodium, a lipid profile should be performed to measure Total-C, HDL-C and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

$$LDL-C = Total-C - HDL-C - \frac{1}{5} TG$$

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients LDL-C may be low or normal despite elevated Total-C. In such cases, Lescol® (fluvastatin sodium) is not indicated.

Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

Definite Atherosclerotic Disease*	Two or More Other Risk Factors**	LDL-Cholesterol mg/dL (mmol/L)	
		Initiation Level	Goal
NO	NO	≥ 190 (≥ 4.9)	<160 (<4.1)
NO	YES	≥ 160 (≥ 4.1)	<130 (<3.4)
YES	YES or NO	≥ 130 (≥ 3.4)	≤ 100 (≤ 2.6)

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

** Other risk factors for coronary heart disease (CHD) include: age (males: ≥ 45 years; females: ≥ 55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥ 60 mg/dL (≥ 1.6 mmol/L).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that the LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations	
		Major	Minor
I (rare)	Chylomicrons	TG	1 → C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	1 → C
V (rare)	Chylomicrons, VLDL	TG	1 → C

C = cholesterol

TG = triglycerides

LDL = low density lipoprotein

VLDL = very low density lipoprotein

IDL = intermediate density lipoprotein

Lescol® (fluvastatin sodium) has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e. hyperlipoproteinemia Types I, III, IV, or V).

The effect of fluvastatin sodium-induced changes in lipoprotein levels on cardiovascular morbidity or mortality has not been established.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. Lescol® (fluvastatin sodium) is contraindicated in

patients with active liver disease or unexplained persistent elevations in serum transaminase (see WARNINGS).

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. Fluvastatin sodium should be administered to women of childbearing age only when such patients are highly unlikely to become pregnant and have been informed of the potential hazards. If a patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. A small number of patients treated with Lescol® (fluvastatin sodium) in United States clinical trials ($N=17$, 1.1%) developed persistent elevations of aminase levels to more than 3 times the upper limit of normal. Ten of these patients (0.7%) were discontinued therapy. Most of these (10/17) abnormalities occurred during the first 6 weeks of treatment and resolved rapidly to treatment values. In a long-term open-label extension study of 824 (0.6%) patients exposed to Lescol® (fluvastatin sodium) at a dose of 40 mg developed persistent transaminase elevations. Only 2 of these patients were discontinued from the study. The majority of these abnormal biochemical findings were asymptomatic.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter (e.g., semiannually). Liver enzyme changes usually occur in the first 3 months of treatment with fluvastatin sodium. Patients who develop increased transaminase levels should be monitored with a second evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater occur, withdrawal of fluvastatin sodium therapy is recommended. Active liver disease or unexplained transaminase elevations are contraindications to the use of Lescol® (fluvastatin sodium) (see CONTRAINDICATIONS). Caution should be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol consumption (see CONTRAINDICATIONS).

CLINICAL PHARMACOLOGY: Pharmacokinetics. See above. **Skeletal Muscle**
Rhabdomyolysis with renal dysfunction secondary to acute glomerulonephritis has been reported with other drugs in this class. To date, this has not occurred with fluvastatin sodium. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, has been reported in 1 fluvastatin sodium patient who was related to physical exertion. An additional patient reported in a patient receiving placebo.

Myopathy should be considered in any patient with unexplained myalgias, muscle tenderness or weakness, or elevation of CPK. Patients should be advised to discontinue promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Fluvastatin sodium therapy should be discontinued if myopathy or CPK levels occur or myopathy is diagnosed. Fluvastatin sodium therapy should also be discontinued if held in any patient experiencing an acute or severe condition predisposing to the development of rhabdomyolysis secondary to rhabdomyolysis, e.g., severe trauma; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy. The risk of myopathy during treatment with fluvastatin sodium was found to be similar to that of placebo. Fluvastatin sodium was found to be bioequivalent to fluvastatin sodium when administered with either cyclosporine, gemfibrozil, erythromycin, or diltiazem. Fluvastatin sodium was administered concurrently with niacin in a clinical trial in 74 patients who were treated with fluvastatin sodium and niacin.

Uncomplicated myalgia has been observed in patients treated with Lescol® (fluvastatin sodium) and is indistinguishable from placebo. The use of fibrates alone may occasionally cause myopathy. The combined use of HMG-CoA reductase inhibitors and fibrates should generally be avoided.

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Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Concomitant Therapy

Fluvastatin sodium has been administered concurrently with cholestyramine and nicotinic acid. No adverse reactions unique to the combination or in addition to those previously reported for this class of drugs alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See **WARNINGS: Skeletal Muscle.**)

OVERDOSAGE

The approximate oral LD₅₀ is greater than 2 g/kg in mice and greater than 0.7 g/kg in rats.

The maximum single oral dose received by healthy volunteers was 60 mg. No clinically significant adverse experiences were seen at this dose. There has been a single report of 2 children, one 2 years old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium that could have been ingested was 80 mg (4 × 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems.

No specific information on the treatment of overdosage can be recommended. Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The dialyzability of fluvastatin sodium and of its metabolites in humans is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lescol® (fluvastatin sodium) and should continue on this diet during treatment with Lescol® (fluvastatin sodium). (See NCEP Treatment Guidelines for details on dietary therapy.)

The recommended starting dose for the majority of patients is 20 mg once daily at bedtime. The recommended dosing range is 20-40 mg/day as a single dose in the evening. Splitting the 40 mg QPM dose into a BID regimen provides a modest improvement in LDL-C response. Lescol® (fluvastatin sodium) may be taken without regard to meals, since there are no apparent differences in the lipid-lowering effects of fluvastatin sodium administered with the evening meal or 4 hours after the evening meal. Since the maximal reductions in LDL-C of a given dose are seen within 4 weeks, periodic lipid determinations should be performed during this time with dosage adjusted according to the patient's response to therapy and established treatment guidelines. The therapeutic effect of Lescol® (fluvastatin sodium) is maintained with prolonged administration.

Concomitant Therapy

Lipid-lowering effects on total cholesterol and LDL cholesterol are additive when Lescol® (fluvastatin sodium) is combined with a bile-acid binding resin or niacin. When administering a bile-acid resin (e.g., cholestyramine) and fluvastatin sodium, Lescol® (fluvastatin sodium) should be administered at bedtime, at least 2 hours following the resin to avoid a significant interaction due to drug binding to resin. (See also **ADVERSE REACTIONS: Concomitant Therapy.**)

Dosage in Patients with Renal Insufficiency

Since fluvastatin sodium is cleared hepatically with less than 5% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not necessary. Caution should be exercised with severe impairment.

HOW SUPPLIED**Lescol® (fluvastatin sodium) Capsules****20 mg**

Brown and light brown imprinted twice with "A" and "20" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.

Bottles of 100 capsules (NDC 0078-0176-05)

Bottles of 30 capsules (NDC 0078-0176-15)

40 mg

Brown and gold imprinted twice with "A" and "40" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.

Bottles of 100 capsules (NDC 0078-0234-05)

Bottles of 30 capsules (NDC 0078-0234-15)

Store and Dispense

Below 86°F (30°C) in a tight container. Protect from light.

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Shown in Product Identification Guide, page 328

MELLARIL®*

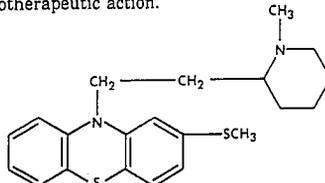
[mel'ah-rii']
(thioridazine HCl) TABLETS, USP
(thioridazine HCl) ORAL SOLUTION, USP
MELLARIL-S®
(thioridazine) ORAL SUSPENSION, USP
FOR ORAL ADMINISTRATION

CAUTION: Federal law prohibits dispensing without prescription.

The following prescribing information is based on official labeling in effect on August 1, 1994.

DESCRIPTION

Mellaril® (thioridazine) is 2-methylmercapto-10-[2-(N-methyl-2-piperidyl) ethyl] phenothiazine. The presence of a thiomethyl radical (S-CH₃) in position 2, conventionally occupied by a halogen, is unique and could account for the greater toleration obtained with recommended doses of thioridazine as well as a greater specificity of psychotherapeutic action.



10 mg, 15 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg Tablets

Active Ingredient: thioridazine HCl, USP

10 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, carnauba wax, D&C Yellow #10, FD&C Blue #1, FD&C Yellow #6, gelatin, lactose, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

15 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, carnauba wax, D&C Red #7, gelatin, lactose, methylparaben, povidone, propylparaben, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

25 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, carnauba wax, gelatin, lactose, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, synthetic iron oxide, talc, titanium dioxide, and other ingredients.

50 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, carnauba wax, gelatin, lactose, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

100 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, carnauba wax, D&C Yellow #10, FD&C Blue #1, FD&C Blue #2, FD&C Yellow #6, lactose, povidone, sodium benzoate, sorbitol, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

150 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, carnauba wax, D&C Yellow #10, FD&C Green #3, FD&C Yellow #6, lactose, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

200 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, carnauba wax, D&C Red #7, gelatin, lactose, magnesium stearate, methylparaben, povidone, propylparaben, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

30 mg and 100 mg Concentrate

Active Ingredient: thioridazine HCl, USP.

30 mg Concentrate

Inactive Ingredients: alcohol, 3.0%, flavor, methylparaben, propylparaben, purified water, and sorbitol solution. May contain sodium hydroxide or hydrochloric acid to adjust the pH.

100 mg Concentrate

Inactive Ingredients: alcohol, 4.2%, flavor, glycerin, methylparaben, propylparaben, purified water, sorbitol solution, and sucrose. May contain sodium hydroxide or hydrochloric acid to adjust pH.

25 mg and 100 mg Oral Suspension

Active Ingredient: each 5 mL contains thioridazine, USP, equivalent to 25 mg and 100 mg thioridazine HCl, USP respectively.

*Also known as Mellerettes and Mallorol.

25 mg Oral Suspension

Inactive Ingredients: carbomer 934, flavor, purified water, sodium hydroxide, and sucrose.

100 mg Oral Suspension

Inactive Ingredients: carbomer 934, D&C Yellow #6, flavor, polysorbate 80, purified hydroxide, and sucrose.

CLINICAL PHARMACOLOGY

Mellaril® (thioridazine) is effective in reducing hypermotility, abnormal initiative, affective agitation through its inhibitory effect on beta-receptors. Successful modification of such a prerequisite for, and often the beginning of, recovery in patients exhibiting mental and physical disturbances.

Thioridazine's basic pharmacological activity, that of other phenothiazines, and certain have come to light which support the clinical spectrum of this drug shows significant differences from those of the other agents of this class. Emetic activity and minimal extrapyramidal effects, notably pseudoparkinsonism, are distinctive of this drug.

INDICATIONS

For the management of manifestations of anxiety.

For the short-term treatment of moderate to severe anxiety with variable degrees of anxiety in the treatment of multiple symptoms such as anxiety, depressed mood, tension, sleep disturbances in geriatric patients.

For the treatment of severe behavioral problems marked by combativeness and/or explosive behavior (out of proportion to immediate precipitants) in the short-term treatment of hyperactive patients who show excessive motor activity with accompanying disorders consisting of some or all of the following: impulsivity, difficulty sustaining attention, mood lability, and poor frustration tolerance.

CONTRAINDICATIONS

In common with other phenothiazines, Mellaril® (thioridazine) is contraindicated in severe central depression or comatose states from any drug induced central nervous system depression. (See **WARNINGS**). It should also be noted that hypotensive heart disease of extreme degree is a contraindication of phenothiazine administration.

WARNINGS**Tardive Dyskinesia**

Tardive dyskinesia, a syndrome consisting of irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic drugs. Although the prevalence of the syndrome is highest among the elderly, especially those who are on long-term neuroleptic treatment, it is likely to develop in the syndrome. Whether products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and that it will become irreversible are believed to increase with the duration of treatment and the total amount of neuroleptic drugs administered to the patient. However, the syndrome can develop, although rarely, after relatively brief treatment.

There is no known treatment for tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is discontinued. The signs and symptoms, however, may persist. The effect that symptomatic suppression has on the long-term course of the syndrome is unknown.

Given these considerations, neuroleptic treatment should be reserved for patients with a chronic illness that, 1) is known to be potentially less harmful if treated, and 2) for whom alternative therapy is not available or is not considered appropriate. In patients who do require neuroleptic treatment, the shortest duration and the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be used. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia are present on neuroleptic drug discontinuation. However, some patients may be able to discontinue the neuroleptic drug in the presence of the syndrome. (For further information about tardive dyskinesia and its clinical detection, see **Information for Patients** and **REACTIONS**.)

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