SULAR®
and
TRIGLIDE™
Now Available through a National BPA

March 6, 2006

Dear Pharmacist:

On February 21, 2006, SULAR® (nisoldipine) and TRIGLIDE™ (fenofibrate) were made available to IHS Federal, Tribal, and Urban hospitals and clinics through an incentive agreement with the IHS through the National Supply Service Center resulting in a national BPA. The IHS National, Area, and local Pharmacy and Therapeutics Committees have the opportunity to review these products for addition to their formularies. Below is a brief summary of the clinical and economic information of each product:

SULAR® (nisoldipine) Costs

SULAR® 10 mg (100 tablets)	$31.00 plus PV discount
SULAR® 20 mg (100 tablets)	$31.00 plus PV discount
SULAR® 30 mg (100 tablets)	$31.00 plus PV discount
SULAR® 40 mg (100 tablets)	$31.00 plus PV discount

SULAR® is as Clinically Effective as NORVASC® and PLENDIL®

SULAR® has been shown in comparative studies to be as effective as NORVASC®[5, 6,7, 8] and PLENDIL®[9].

Achieves Therapeutic Effect Early in the Course of Treatment[10]

In 5 placebo controlled trials evaluating blood pressure reduction over time, the most pronounced reduction occurred during the first 2 weeks of nisoldipine therapy, with smaller reductions measured in weeks 2 to 4 and weeks 4 to 6.

By the end of week 1, an average of 81% of the ultimate blood pressure reduction had been achieved, and by the end of week 2, 88% had been achieved.

This compares favorably to a study by Hayduk et al. (1999) that suggested there was no advantage in an early increase in dosage of NORVASC® in terms of antihypertensive effect and that a dose increase should not be considered until after six weeks of treatment at 5 mg once daily.[11] Please note that the findings in the Hayduk study are not consistent with the titration and clinical information in the NORVASC® package insert.

SULAR® Significantly Reduces BP in Patients with Severe Hypertension

In a study by Radevski et al. (1999) that measured blood pressure reduction in black South African patients with severe hypertension, the authors observed that after 9 weeks of treatment with SULAR® that there was profound reduction in office BP and 24-hour day and night ambulatory blood pressure ($P<0.0001$).[12]

The mean reductions in 24 hour systolic/diastolic blood pressure with SULAR® were 35/24 mm Hg.

NORVASC® to SULAR® Conversion [13]

Conversion to SULAR® from NORVASC® is usually done by giving the recommended starting dose of SULAR® at the end of NORVASC®'s dosing interval. The dosage of SULAR® must be adjusted to each patient's need. Therapy usually should be initiated with 20 mg orally once daily, and then increased every week or longer intervals, to attain adequate control of blood pressure. The usual maintenance dosage is 20 to 40 mg once daily. Blood pressure response increases over the 10 to 60 mg daily dose range.

Patients over age 65, or patients with impaired liver function should be monitored closely during any dosage adjustment. A starting dose not exceeding 10 mg is recommended in these patient groups.

TRIGLIDE™ (fenofibrate) Costs

TRIGLIDE™ 50 mg (90 tablets)	$36.90 plus PV Discount
TRIGLIDE™ 160 mg (90 tablets)	$111.60 plus PV Discount

TRIGLIDE™ is Clinically Similar to TRICOR® and ANTARA™[2,3,4]

Triglide has been approved by the FDA in the same method as Tricor 145mg and Antara 130mg. The approval of all three products is based on the same reference listed drug; 200mg micronized fenofibrate (Tricor 200mg). In clinical trials, fenofibrate has been shown to decrease serum LDL, Triglycerides, Apo-B, and Total Cholesterol while raising HDL.

TRIGLIDE™ can be Taken with or without Food[2]

Per the FDA approved labeling, TRIGLIDE™ may be administered with or without food. This could provide convenience to patients with once daily dosing administration.

TRIGLIDE™ Utilizes a Unique Delivery System[1]

TRIGLIDE™ utilizes the patented Insoluble Drug Delivery™ Microparticle (IDD®-P) technology[1]. This unique delivery system decreases the overall size of the fenofibrate drug particles and then coats the surface of the particle with a natural phospholipid, lecithin. The result is increased surface area, physical stability, and overall bioavailability for fenofibrate, a highly water-insoluble drug.

TRIGLIDE™ is Generally Safe and Well-Tolerated when Used as Directed[2]

In double-blind, placebo controlled trials, increases in liver function tests were the most frequently observed adverse event, causing discontinuation of fenofibrate therapy in 1.6% of patients.

Starting Patients on TRIGLIDE™[2]

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRIGLIDE is 160mg per day. For patients with primary hypertriglyceridemia, the initial dose is 50mg to 160mg once daily. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 weeks intervals. The maximum dose is 160mg per day. Treatment with TRIGLIDE should be initiated at a dose of 50mg/day in patients with impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 50mg/day. Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRIGLIDE if lipid levels fall significantly below the targeted range.

Please see Full Prescribing Information enclosed with this letter.

Sincerely,

John Edwards, MD
Marketing Medical Director
First Horizon Pharmaceutical® Corporation

Important Safety Information

Triglide™ is indicated as adjunctive therapy to diet for the reduction of LDL-C, Total-C, Triglycerides, and Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Triglide™ is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlidemia). Lipid altering agents should be used in addition to a diet restricted in saturated fat and cholesterol, when response to diet and non pharmacological interventions alone have been inadequate. Triglide™ administration is contraindicated for patients with a known hypersensitivity to fenofibrate or any of the formulation components, severe renal dysfunction, and/or pre-existing gallbladder disease. Caution should be exercised when coumarin anticoagulants are given in conjunction with Triglide™. The combined use of Triglide™ and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. The most commonly observed side effects seen in fenofibrate therapy are abnormal liver function test results, respiratory disorders, and abdominal pain.

SULAR® is indicated for the treatment of hypertension. In rare cases, some patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration, and/or severity of angina, or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. Safety of SULAR in patients with heart failure has not been established. SULAR should be administered cautiously in patients over the age of 65 and in those with severe hepatic dysfunction. Because nisoldipine, like other vasodilators, decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of SULAR is recommended. SULAR should not be taken with grapefruit products or in conjunction with a high-fat meal. The most common adverse events, reported in US placebo-controlled trials, were peripheral edema, headache, and dizziness.

TRIGLIDE™ is a trademark of First Horizon Pharmaceutical® Corporation.
TRICOR® is a registered trademark of Abbott Laboratories.
ANTARA™ is a trademark of Reliant Pharmaceuticals, LLC.
SULAR® is a registered trademark of First Horizon Pharmaceutical ™ Corporation.
NORVASC® is a registered trademark of Pfizer Inc.
PLENDIL® is a registered trademark of AstraZeneca group of companies.

References:

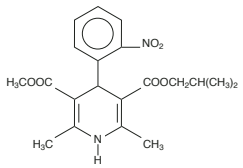
1 Solubilization Overview Page for IDD®-P Technology available at www.SkyePharma.com
2 TRIGLIDE™ (fenofibrate) prescribing information. First Horizon Pharmaceutical Corporation. Revision number: FF-PI-1 Rev 01/05.
3 ANTARA™ (fenofibrate) prescribing information. Reliant Pharmaceuticals, LLC. Revision number: October 2005.
4 TRICOR® (fenofibrate) prescribing information. Abbott Laboratories. Revision number: 04K-030-F534-1 Rev November 2004.
5 Punzi HA, Noveck R, Weiss RJ, et al. Are there differences in the effects of long-acting calcium antagonists on ambulatory blood pressure? Extended-release nisoldipine versus amlodipine as a model. *Blood Press Monit.* 1998 Aug;3(4):267-272.
6 Marazzi P. A study to demonstrate the equivalence in efficacy and safety of once-daily nisoldipine CC and amlodipine in the treatment of mild to moderate hypertension. *Acta Therapeutica.* 1996;22:23-35.
7 White WB, Saunders E, Noveck RJ, Ferdinand K. Comparative efficacy and safety of nisoldipine extended-release (ER) and amlodipine (CESNA-III study) in African American patients with hypertension. *Am J Hypertens.* 2003 Sep;16(9 Pt 1):739-45.
8 Lenz TL, Wurdeman RL, Hilleman DE. Comparison of 24-hour blood pressure profiles in patients with hypertension who were switched from amlodipine to nisoldipine. *Pharmacotherapy.* 2001 Aug;21(8):898-903.
9 Hoglund C, Hutchinson HG. A comparison of nisoldipine coat-core and felodipine in the treatment of mild-to-moderate hypertension. *Int J Clin Pract.* 1998 Jun;52(4):221-5.
10 Data on file. Integrated summary of efficacy, NDA, First Horizon Pharmaceuticals™, Alpharetta, Georgia.
11 Hayduk K, Adamczak M, Nowitzki G. Is initial dose titration of amlodipine worthwhile in patients with mild to moderate hypertension? *Curr Med Res Opin.* 1999;15(1):39-45.
12 Radevski I, Skudicky D, Candy G, et al. Antihypertensive monotherapy with nisoldipine CC is superior to enalapril in black patients with severe hypertension. *Am J Hypertens.* 1999 Feb;12(2 Pt 1):194-203.
13 SULAR® (nisoldipine) prescribing information. First Horizon Pharmaceutical™ Corporation. Revision number: SUL-PI-2 Rev 11/03A

SULAR® (Nisoldipine)

Extended Release Tablets
For Oral Use

DESCRIPTION

SULAR® (nisoldipine) is an extended release tablet dosage form of the dihydropyridine calcium channel blocker nisoldipine. Nisoldipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester, $C_{20}H_{24}N_2O_6$, and has the structural formula:



Nisoldipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 388.4. SULAR tablets consist of an external coat and an internal core. Both coat and core contain nisoldipine, the coat as a slow release formulation and the core as a fast release formulation. SULAR tablets contain either 10, 20, 30 or 40 mg of nisoldipine for once-a-day oral administration.

Inert ingredients in the formulation are: hydroxypropylcellulose, lactose, corn starch, crospovidone, microcrystalline cellulose, sodium lauryl sulfate, povidone and magnesium stearate. The inert ingredients in the film coating are: hypromellose, polyethylene glycol, ferric oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Nisoldipine is a member of the dihydropyridine class of calcium channel antagonists (calcium ion antagonists or slow channel blockers) that inhibit the transmembrane influx of calcium into vascular smooth muscle and cardiac muscle. It reversibly competes with other dihydropyridines for binding to the calcium channel. Because the contractile process of vascular smooth muscle is dependent upon the movement of extracellular calcium into the muscle through specific ion channels, inhibition of the calcium channel results in dilation of the arterioles. *In vitro* studies show that the effects of nisoldipine on contractile processes are selective, with greater potency on vascular smooth muscle than on cardiac muscle. Although, like other dihydropyridine calcium channel blockers, nisoldipine has negative inotropic effects *in vitro*, studies conducted in intact anesthetized animals have shown that the vasodilating effect occurs at doses lower than those that affect cardiac contractility.

The effect of nisoldipine on blood pressure is principally a consequence of a dose-related decrease of peripheral vascular resistance. While nisoldipine, like other dihydropyridines, exhibits a mild diuretic effect, most of the antihypertensive activity is attributed to its effect on peripheral vascular resistance.

Pharmacokinetics and Metabolism

Nisoldipine pharmacokinetics are independent of the dose in the range of 20 to 60 mg, with plasma concentrations proportional to dose. Nisoldipine accumulation, during multiple dosing, is predictable from a single dose.

Nisoldipine is relatively well absorbed into the systemic circulation with 87% of the radiolabeled drug recovered in urine and feces. The absolute bioavailability of nisoldipine is about 5%. Nisoldipine's low bioavailability is due, in part, to pre-systemic metabolism in the gut wall, and this metabolism decreases from the proximal to the distal parts of the intestine. Food with a high fat content has a pronounced effect on the release of nisoldipine from the coat-core formulation and results in a significant increase in peak concentration (C_{max}) by up to 300%. Total exposure, however, is decreased about 25%, presumably because more of the drug is released proximally. This effect appears to be specific for nisoldipine in the controlled release formulation, as a less pronounced food effect was seen with the immediate release tablet. Concomitant intake of a high fat meal with SULAR should be avoided.

Maximal plasma concentrations of nisoldipine are reached 6 to 12 hours after dosing. The terminal elimination half-life (reflecting post absorption clearance of nisoldipine) ranges from 7 to 12 hours. C_{max} and AUC increase by factors of approximately 1.3 and 1.5, respectively, from first dose to steady state. After oral administration, the concentration of (+) nisoldipine, the active enantiomer, is about 6 times higher than the (-) inactive enantiomer. The plasma protein binding of nisoldipine is very high, with less than 1% unbound over the plasma concentration range of 100 ng/mL to 10 mcg/mL.

Nisoldipine is highly metabolized; 5 major urinary metabolites have been identified. Although 60 - 80% of an oral dose undergoes urinary excretion, only traces of unchanged nisoldipine are found in urine. The major biotransformation pathway appears to be the hydroxylation of the isobutyl ester. A hydroxylated derivative of the side chain, present in plasma at concentrations approximately equal to the parent compound, appears to be the only active metabolite, and has about 10% of the activity of the parent compound. Cytochrome P_{450} enzymes are believed to play a major role in the metabolism of nisoldipine. The particular isoenzyme system responsible for its metabolism has not been identified, but other dihydropyridines are metabolized by cytochrome P_{450} IIIA4. Nisoldipine should not be administered with grapefruit juice as this has been shown, in a study of 12 subjects, to interfere with nisoldipine metabolism, resulting in a mean increase in C_{max} of about 3-fold (ranging up to about 7-fold) and AUC of almost 2-fold (ranging up to about 5-fold). A similar phenomenon has been seen with several other dihydropyridine calcium channel blockers.

Special Populations

Renal Dysfunction: Because renal elimination is not an important pathway, bioavailability and pharmacokinetics of SULAR were not significantly different in patients with various degrees of renal impairment. Dosing adjustments in patients with mild to moderate renal impairment are not necessary.

Geriatric: Elderly patients have been found to have 2 to 3 fold higher plasma concentrations (C_{max} and AUC) than young subjects. This should be reflected in more cautious dosing (See DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: In patients with liver cirrhosis given 10 mg SULAR, plasma concentrations of the parent compound were 4 to 5 times higher than those in healthy young subjects. Lower starting and maintenance doses should be used in cirrhotic patients (See DOSAGE AND ADMINISTRATION).

Gender and Race: The effect of gender or race on the pharmacokinetics of nisoldipine has not been investigated.

Disease States: Hypertension does not significantly alter the pharmacokinetics of nisoldipine.

Pharmacodynamics

Hemodynamic Effects

Administration of a single dose of nisoldipine leads to decreased systemic vascular resistance and blood pressure with a transient increase in heart rate. The change in heart rate is greater with immediate release nisoldipine preparations. The effect on blood pressure is directly related to the initial degree of elevation above normal. Chronic administration of nisoldipine results in a sustained decrease in vascular resistance and small increases in stroke index and left ventricular ejection fraction. A study of the immediate release formulation showed no effect of nisoldipine on the renin-angiotensin-aldosterone system or on plasma norepinephrine concentration in normals. Changes in blood pressure in hypertensive patients given SULAR were dose related over the range of 10 - 60 mg/day.

Nisoldipine does not appear to have significant negative inotropic activity in intact animals or humans, and did not lead to worsening of clinical heart failure in three small studies of patients with asymptomatic and symptomatic left ventricular dysfunction. There is little information, however, in patients with severe congestive heart failure, and all calcium channel blockers should be used with caution in any patient with heart failure.

Electrophysiologic Effects

Nisoldipine has no clinically important chronotropic effects. Except for mild shortening of sinus cycle, SA conduction time and AH intervals, single oral doses up to 20 mg of immediate release nisoldipine did not significantly change other conduction parameters. Similar electrophysiologic effects were seen with single iv doses, which could be blunted in patients pre-treated with beta-blockers. Dose and plasma level related flattening or inversion of T-waves have been observed in a few small studies. Such reports were concentrated in patients receiving rapidly increased high doses in one study; the phenomenon has not been a cause of safety concern in large clinical trials.

Clinical Studies in Hypertension

The antihypertensive efficacy of SULAR was studied in 5 double-blind, placebo-controlled, randomized studies, in which over 600 patients were treated with SULAR as monotherapy and about 300 with placebo; 4 of the five studies compared 2 or 3 fixed doses while the fifth allowed titration from 10 - 40 mg. Once daily administration of SULAR produced sustained reductions in systolic and diastolic blood pressures over the 24 hour dosing interval in both supine and standing positions. The mean placebo-subtracted reductions in supine systolic and diastolic blood pressure at trough, 24 hours post-dose, in these studies, are shown below. Changes in standing blood pressure were similar:

MEAN SUPINE TROUGH SYSTOLIC AND DIASTOLIC BLOOD PRESSURE CHANGES (mm Hg)

SULAR Dose (mg/day)	10 mg	20 mg	30 mg	40 mg	60 mg	10-40 mg titrated
Systolic	8	11	11	14	15	15
Diastolic	3	5	7	7	10	8

In patients receiving atenolol, supine blood pressure reductions with SULAR at 20, 40 and 60 mg once daily were 12/6, 19/8 and 22/10 mm Hg, respectively. The sustained antihypertensive effect of SULAR was demonstrated by 24 hour blood pressure monitoring and examination of peak and trough effects. The trough/peak ratios ranged from 70 to 100% for diastolic and systolic blood pressure. The mean change in heart rate in these studies was less than one beat per minute. In 4 of the 5 studies, patients received initial doses of 20 - 30 mg SULAR without incident (excessive effects on blood pressure or heart rate). The fifth study started patients on lower doses of SULAR.

Patient race and gender did not influence the blood pressure lowering effect of SULAR. Despite the higher plasma concentration of nisoldipine in the elderly, there was no consistent difference in their blood pressure response except that the 10 mg dose was somewhat more effective than in non-elderly patients. No postural effect on blood pressure was apparent and there was no evidence of tolerance to the antihypertensive effect of SULAR in patients treated for up to one year.

INDICATIONS AND USAGE

SULAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

SULAR is contraindicated in patients with known hypersensitivity to dihydropyridine calcium channel blockers.

WARNINGS

Increased angina and/or myocardial infarction in patients with coronary artery disease: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration and/or severity of angina, or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been established. In controlled studies of SULAR in patients with angina this was seen about 1.5% of the time in patients given nisoldipine, compared with 0.9% in patients given placebo.

PRECAUTIONS

General

Hypotension: Because nisoldipine, like other vasodilators, decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of SULAR is recommended. Close observation is especially important for patients already taking medications that are known to lower blood pressure. Although in most patients the hypotensive effect of SULAR is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment.

Congestive Heart Failure: Although acute hemodynamic studies of nisoldipine in patients with NYHA Class II-IV heart failure have not demonstrated negative inotropic effects, safety of SULAR in patients with heart failure has not been established. Caution therefore should be exercised when using SULAR in patients with heart failure or compromised ventricular function, particularly in combination with a beta-blocker.

Patients with Hepatic Impairment: Because nisoldipine is extensively metabolized by the liver and, in patients with cirrhosis, it reaches blood concentrations about 5 times those in normals, SULAR should be administered cautiously in patients with severe hepatic dysfunction (See DOSAGE AND ADMINISTRATION).

Information for Patients: SULAR is an extended release tablet and should be swallowed whole. Tablets should not be chewed, divided or crushed. SULAR should not be administered with a high fat meal. Grapefruit juice, which has been shown to increase significantly the bioavailability of nisoldipine and other dihydropyridine type calcium channel blockers, should not be taken with SULAR.

Laboratory Tests: SULAR is not known to interfere with the interpretation of laboratory tests.

Drug Interactions: A 30 to 45% increase in AUC and C_{max} of nisoldipine was observed with concomitant administration of cimetidine 400 mg twice daily. Ranitidine 150 mg twice daily did not interact significantly with nisoldipine (AUC was decreased by 15 - 20 %). No pharmacodynamic effects of either histamine H_2 receptor antagonist were observed.

Coadministration of phenytoin with 40 mg SULAR tablets in epileptic patients lowered the nisoldipine plasma concentrations to undetectable levels. Coadministration of SULAR with phenytoin or any known CYP3A4 inducer should be avoided and alternative antihypertensive therapy should be considered. Pharmacokinetic interactions between nisoldipine and beta-blockers (atenolol, propranolol) were variable and not significant. Propranolol attenuated the heart rate increase following administration of immediate release nisoldipine. The blood pressure effect of SULAR tended to be greater in patients on atenolol than in patients on no other antihypertensive therapy. Quinidine at 648 mg bid decreased the bioavailability (AUC) of nisoldipine by 26%, but not the peak concentration. The immediate release, but not the coat-core formulation of nisoldipine increased plasma quinidine concentrations by about 20%. This interaction was not accompanied by ECG changes and its clinical significance is not known. No significant interactions were found between nisoldipine and warfarin or digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Dietary administration of nisoldipine to male and female rats for up to 24 months (mean doses up to 82 and 111 mg/kg/day, 16 and 19 times the maximum recommended human dose (MRHD) on a mg/m^2 basis, respectively) and female mice for up to 21 months (mean doses of up to 217 mg/kg/day, 20 times the MRHD on a mg/m^2 basis) revealed no evidence of tumorigenic effect of nisoldipine. In male mice receiving a mean dose of 163 mg nisoldipine/kg/day (16 times the MRHD of 60 mg/day on a mg/m^2 basis), an increased frequency of stomach papilloma, but still within the historical range, was observed. No evidence of stomach neoplasia was observed at lower doses (up to 58 mg/kg/day). Nisoldipine was negative when tested in a battery of genotoxicity assays including the Ames test and the CHO/HGRPT assay for mutagenicity and the *in vivo* mouse micronucleus test and *in vitro* CHO cell test for clastogenicity.

When administered to male and female rats at doses of up to 30 mg/kg/day (about 5 times the MRHD on a mg/m^2 basis) nisoldipine had no effect on fertility.

Pregnancy Category C: Nisoldipine was neither teratogenic nor fetotoxic at doses that were not maternally toxic. Nisoldipine was fetotoxic but not teratogenic in rats and rabbits at doses resulting in maternal toxicity (reduced maternal body weight gain). In pregnant rats, increased fetal resorption (postimplantation loss) was observed at 100 mg/kg/day and decreased fetal weight was observed at both 30 and 100 mg/kg/day. These doses are, respectively, about 5 and 16 times the MRHD when compared on a mg/m^2 basis. In pregnant rabbits, decreased fetal and placental weights were observed at a dose of 30 mg/kg/day, about 10 times the MRHD when compared on a mg/m^2 basis. In a study in which pregnant monkeys (both treated and control) had high rates of abortion and mortality, the only surviving fetus from a group exposed to a maternal dose of 100 mg nisoldipine/ kg/day (about 30 times the MRHD when compared on a mg/m^2 basis) presented with forelimb and vertebral abnormalities not previously seen in control monkeys of the same strain. There are no adequate and well controlled studies in pregnant women. SULAR should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether nisoldipine is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made to discontinue nursing, or to discontinue SULAR, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Clinical studies of nisoldipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Patients over 65 are expected to develop higher plasma concentrations of nisoldipine. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE EXPERIENCES

More than 6000 patients world-wide have received nisoldipine in clinical trials for the treatment of hypertension, either as the immediate release or the SULAR extended release formulation. Of about 1,500 patients who received SULAR in hypertension studies, about 55% were exposed for at least 2 months and about one third were exposed for over 6 months, the great majority at doses of 20 to 60 mg daily.

SULAR is generally well-tolerated. In the U.S. clinical trials of SULAR in hypertension, 10.9% of the 921 SULAR patients discontinued treatment due to adverse events compared with 2.9% of 280 placebo patients. The frequency of discontinuations due to adverse experiences was related to dose, with a 5.4% discontinuation rate at 10 mg daily and a 10.9% discontinuation rate at 60 mg daily.

The most frequently occurring adverse experiences with SULAR are those related to its vasodilator properties; these are generally mild and only occasionally lead to patient withdrawal from treatment. The table below, from U.S. placebo-controlled parallel dose response trials of SULAR using doses from 10 - 60 mg once daily in patients with hypertension, lists all of the adverse events, regardless of the causal relationship to SULAR, for which the overall incidence on SULAR was both >1% and greater with SULAR than with placebo.

Adverse Event	Nisoldipine (%) (n=663)	Placebo (%) (n=280)
Peripheral Edema	22	10
Headache	22	15
Dizziness	5	4
Pharyngitis	5	4
Vasodilation	4	2
Sinusitis	3	2
Palpitation	3	1
Chest Pain	2	1
Nausea	2	1
Rash	2	1

Only peripheral edema and possibly dizziness appear to be dose related.

Adverse Event		SULAR				
	Placebo	10mg	20mg	30mg	40mg	60mg
(Rates in %)	N=280	N=30	N=170	N=105	N=139	N=137
Peripheral Edema	10	7	15	20	27	29
Dizziness	4	7	3	3	4	10

The common adverse events occurred at about the same rate in men as in women, and at a similar rate in patients over age 65 as in those under that age, except that headache was much less common in older patients. Except for peripheral edema and vasodilation, which were more common in whites, adverse event rates were similar in blacks and whites.

The following adverse events occurred in ≤1% of all patients treated for hypertension in U.S. and foreign clinical trials, or with unspecified incidence in other studies. Although a causal relationship of SULAR to these events cannot be established, they are listed to alert the physician to a possible relationship with SULAR treatment.

Body As A Whole: cellulitis, chills, facial edema, fever, flu syndrome, malaise

Cardiovascular: atrial fibrillation, cerebrovascular accident, congestive heart failure, first degree AV block, hypertension, hypotension, jugular venous distension, migraine, myocardial infarction, postural hypotension, ventricular extrasystoles, supraventricular tachycardia, syncope, systolic ejection murmur, T wave abnormalities on ECG (flattening, inversion, nonspecific changes), venous insufficiency

Digestive: abnormal liver function tests, anorexia, colitis, diarrhea, dry mouth, dyspepsia, dysphagia, flatulence, gastritis, gastrointestinal hemorrhage, gingival hyperplasia, glossitis, hepatomegaly, increased appetite, melena, mouth ulceration

Endocrine: diabetes mellitus, thyroiditis

Hemic and Lymphatic: anemia, ecchymoses, leukopenia, petechiae

Metabolic and Nutritional: gout, hypokalemia, increased serum creatine kinase, increased nonprotein nitrogen, weight gain, weight loss

Musculoskeletal: arthralgia, arthritis, leg cramps, myalgia, myasthenia, myositis, tenosynovitis

Nervous: abnormal dreams, abnormal thinking and confusion, amnesia, anxiety, ataxia, cerebral ischemia, decreased libido, depression, hypesthesia, hypertonia, insomnia, nervousness, paresthesia, somnolence, tremor, vertigo

Respiratory: asthma, dyspnea, end inspiratory wheeze and fine rales, epistaxis, increased cough, laryngitis, pharyngitis, pleural effusion, rhinitis, sinusitis

Skin and Appendages: acne, alopecia, dry skin, exfoliative dermatitis, fungal dermatitis, herpes simplex, herpes zoster, maculopapular rash, pruritus, pustular rash, skin discoloration, skin ulcer, sweating, urticaria

Special Senses: abnormal vision, amblyopia, blepharitis, conjunctivitis, ear pain, glaucoma, itchy eyes, keratoconjunctivitis, otitis media, retinal detachment, tinnitus, watery eyes, taste disturbance, temporary unilateral loss of vision, vitreous floater

Urogenital: dysuria, hematuria, impotence, nocturia, urinary frequency, increased BUN and serum creatinine, vaginal hemorrhage, vaginitis.

The following postmarketing event has been reported very rarely in patients receiving SULAR: systemic hypersensitivity reaction which may include one or more of the following; angioedema, shortness of breath, tachycardia, chest tightness, hypotension, and rash. A definite causal relationship with SULAR has not been established. An unusual event observed with immediate release nisoldipine but not observed with SULAR was one case of photosensitivity. Gynecomastia has been associated with the use of calcium channel blockers.

OVERDOSAGE

There is no experience with nisoldipine overdosage. Generally, overdosage with other dihydropyridines leading to pronounced hypotension calls for active cardiovascular support including monitoring of cardiovascular and respiratory function, elevation of extremities, judicious use of calcium infusion, pressor agents and fluids. Clearance of nisoldipine would be expected to be slowed in patients with impaired liver function. Since nisoldipine is highly protein bound, dialysis is not likely to be of any benefit; however, plasmapheresis may be beneficial.

DOSAGE AND ADMINISTRATION

The dosage of SULAR must be adjusted to each patient's needs. Therapy usually should be initiated with 20 mg orally once daily, then increased by 10 mg per week or longer intervals, to attain adequate control of blood pressure. Usual maintenance dosage is 20 to 40 mg once daily. Blood pressure response increases over the 10 - 60 mg daily dose range but adverse event rates also increase. Doses beyond 60 mg once daily are not recommended. SULAR has been used safely with diuretics, ACE inhibitors, and beta-blocking agents. Patients over age 65, or patients with impaired liver function are expected to develop higher plasma concentrations of nisoldipine. Their blood pressure should be monitored closely during any dosage adjustment. A starting dose not exceeding 10 mg daily is recommended in these patient groups. SULAR tablets should be administered orally once daily. Administration with a high fat meal can lead to excessive peak drug concentration and should be avoided. Grapefruit products should be avoided before and after dosing. SULAR is an extended release dosage form and tablets should be swallowed whole, not bitten, divided or crushed.

HOW SUPPLIED

SULAR extended release tablets are supplied as 10 mg, 20 mg, 30 mg, and 40 mg round film coated tablets. The different strengths can be identified as follows:

Strength	Color	Markings
10 mg	Oyster	440 on one side and FH 10 on the other side.
20 mg	Yellow Cream	441 on one side and FH 20 on the other side.
30 mg	Mustard	442 on one side and FH 30 on the other side.
40 mg	Burnt Orange	443 on one side and FH 40 on the other side.

SULAR Tablets are supplied in:

	Strength	NDC Code
Bottles of 100	10 mg	59630-440-10
	20 mg	59630-441-10
	30 mg	59630-442-10
	40 mg	59630-443-10

Protect from light and moisture. Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Dispense in tight, light-resistant containers.

] **Only**

Manufactured for:
First Horizon Pharmaceutical™ Corporation
Alpharetta, GA 30005
By: Bayer AG, Leverkusen, Germany
Made in Germany SUL-PI-3 Rev 03/04

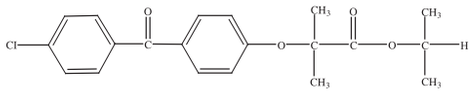
Code 953A00 Printed in U.S.A.

Triglide™
(fenofibrate) tablets

Rx Only

DESCRIPTION

TRIGLIDE™ (fenofibrate) tablets, is a lipid-regulating agent available as tablets for oral administration.
Each tablet contains 50 mg or 160 mg of fenofibrate.
The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water.
The melting point is 79°C to 82°C. Fenofibrate is a white solid that is stable under ordinary conditions.

Inactive Ingredients: Each tablet also contains crospovidone, lactose monohydrate, mannitol, maltodextrin, carboxymethylcellulose sodium, egg lecithin, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate, and monobasic sodium phosphate.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high-density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo A-I and apo A-II) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of TC, LDL-C, and triglycerides (TG), and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering TG on the risk of cardiovascular morbidity and mortality has not been determined. Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apo AI and apo AII. The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in TG produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics

Absorption
The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, after fenofibrate is dissolved, fenofibrate is well absorbed from the gastrointestinal tract. Peak plasma levels of fenofibric acid occurs an average of 3 hours after administration.

TRIGLIDE 160 mg tablet exhibits a similar extent of absorption but 32% higher rate of absorption compared to the 200 mg micronized fenofibrate capsule under low-fat fed conditions.

Effect of Food on Absorption
Fenofibrate is insoluble in water and its bioavailability is optimized when taken with meals.

The extent of absorption of TRIGLIDE (AUC) is comparable between fed and fasted conditions. Food increases the rate of absorption of TRIGLIDE approximately 55%.
(See DOSAGE AND ADMINISTRATION.)

Distribution
In healthy volunteers administered nonmicronized formulation of fenofibrate, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of daily dosing with single oral doses and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% bound to plasma proteins in normal and hyperlipidemic subjects.

Metabolism
Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma of healthy subjects following fenofibrate administration. Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (*e.g.*, cytochrome P450) to a significant extent.

Excretion
After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabeled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces. Fenofibric acid is eliminated with a half-life of approximately 16 hours, allowing once daily administration in a clinical setting.

Pharmacokinetics in Special Populations

Geriatrics
TRIGLIDE has not been investigated in adequate and well-controlled trials in geriatric patients. However, a previous study using nonmicronized formulation shows that the oral clearance of fenofibric acid is similar to that of young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics
TRIGLIDE has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender
No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race
The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal Insufficiency
TRIGLIDE has not been investigated in patients with renal impairment. In a study using nonmicronized formulation in patients with severe renal impairment (creatinine clearance <50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults. Therefore, the dosage of TRIGLIDE should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic Insufficiency
No pharmacokinetic studies have been conducted in patients with hepatic insufficiency.

Drug-Drug Interactions
In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome P450 (CYP) isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

(See WARNINGS and PRECAUTIONS.)

CLINICAL TRIALS

In a single-dose pharmacokinetics study in healthy volunteers, TRIGLIDE 160 mg tablet was shown to have comparable bioavailability to a single dose of 200 mg fenofibrate capsule, micronized.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose comparable to 200 mg micronized fenofibrate per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1

Mean Percent Change in Lipid Parameters at End of Treatment†

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C>160 mg/dL and TG<150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C>160 mg/dL And TG≥150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

* p=<0.05 vs. placebo
† Duration of study treatment was 3 to 6 months.

In a subset of the subjects, measurements of apo B were conducted. Fenofibrate treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials (Goldberg et al., 1989) of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 200 mg micronized fenofibrate (comparable to 160 mg TRIGLIDE) per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2

Effects of Fenofibrate in Patients With Fredrickson Type IV/V Hyperlipidemia**

Study 1	Placebo				Fenofibrate**			
Baseline TG levels 350 to 499 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4.0	27	34	40	19.6*
LDL Cholesterol	28	120	129	12.0	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*
Study 2	**Placebo**				**Fenofibrate****			
Baseline TG levels 500 to 1500 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

* p=<0.05 vs. placebo
** Equivalent to 200 mg fenofibrate capsules, micronized. Dosage comparable to 160 mg TRIGLIDE.

The effect of fenofibrate on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia
TRIGLIDE is indicated as adjunctive therapy to diet for the reduction of LDL-C, Total-C, Triglycerides and Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb).
Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia
TRIGLIDE is indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention. Markedly elevated levels of serum triglycerides (*e.g.,* >2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRIGLIDE therapy on reducing this risk has not been studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low-density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia (Nikkila, 1983).

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure.

Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia.

In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS.)

Fredrickson Classification of Hyperlipoproteinemias

Type	Lipoprotein Elevated	Lipid Elevation	
		Major	Minor
I (rare)	Chylomicrons	TG	↑↔C
IIa	LDL	C	–
IIb	LDL,VLDL	C	TG
III (rare)	IDL	C, TG	–
IV	VLDL	TG	↑↔C
V (rare)	Chylomicrons, VLDL	TG	↑↔

C = cholesterol; IDL = intermediate density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides; VLDL = very low-density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ risk factors (10-year risk ≤20%	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD = coronary heart disease
†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this category.
††† Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

CONTRAINDICATIONS

TRIGLIDE administration is contraindicated in the following conditions:
- Hypersensitivity to fenofibrate or any of the formulation components
- Severe renal dysfunction
- Hepatic dysfunction, including primary biliary cirrhosis and unexplained persistent liver function abnormality
- Pre-existing gallbladder disease

(See WARNINGS.)

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 134 mg to 200 mg micronized fenofibrate per day (at the highest dose, comparable to 160 mg TRIGLIDE) has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)].

In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminase related to fenofibrate therapy appears to be dose-related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 134 mg to 200 mg micronized fenofibrate per day and was 0% in those receiving dosages equivalent to 34 mg or 67 mg micronized fenofibrate per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Baseline and regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRIGLIDE, and therapy should be discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated and TRIGLIDE therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRIGLIDE because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors (Statins): The combined use of TRIGLIDE and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone including fenofibrate, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRIGLIDE and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRIGLIDE therapy should be stopped.

Mortality: The effect of fenofibrate on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations: Because of chemical, pharmacological, and clinical similarities between fenofibrate and other products in this pharmacological class, adverse findings from other fibrate drugs (clofibrate and gemfibrozil) may also apply to fenofibrate products.

Clofibrate: In one large randomized, placebo-controlled clinical study (Coronary Drug Project) conducted in patients with previous myocardial infarction, no differences in mortality between patients treated with clofibrate for 5 years (N=1103) and patients receiving placebo (N=2789) were reported, but twice as many patients given clofibrate developed cholelithiasis and cholecystisis (3.0% versus 1.8%). In another study conducted by the World Health Organization (WHO) in 5000 patients without known coronary heart disease who were treated with clofibrate for 5 years and followed 1 year beyond, a statistically significant higher age-adjusted total mortality in the group of patients treated with clofibrate compared to the placebo-treated control group (N=5000) was reported (5.70% versus 3.96%, p<0.01). The excess mortality causes included malignancy, post-cholecystectomy complications, and pancreatitis. A higher risk for gallbladder disease in patients administered clofibrate was reported.

In a follow-up study, which included almost 8 years of observation after the study ended, no differences in cancer rates were reported when both groups were standardized for age.

Gemfibrozil: The Helsinki Heart Study was a large (N=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR =1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study. A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The

rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial Therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting therapy with fenofibrate. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued Therapy: Periodic determination of serum lipids should be obtained to determine the lowest effective dose of fenofibrate. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during postmarketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of fenofibrate administration.

Skeletal Muscle Changes: Treatment with drugs of the fibrate class, including fenofibrate, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions:

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRIGLIDE. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.
HMG-CoA Reductase Inhibitors (Statins): The combined use of TRIGLIDE and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (See WARNINGS).
Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take TRIGLIDE at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.
Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRIGLIDE, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRIGLIDE with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD, based on mg/meter^2 of surface area). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinoma was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD based on mg/meter^2 surface area) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD (200 mg/kg/day).

A carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg; 2 times the human dose), and gemfibrozil (250 mg/kg; 2 times the human dose, multiples based on mg/meter^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 0.7 and 3 times the MRHD on the basis of mg/meter^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18 month study at same doses, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been conducted, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following four tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy: Teratogenic Effects, Pregnancy Category C: Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and embryocidal in rabbits when given at 9 times the MRHD (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of approximately 9 times the MRHD of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of approximately 10 times the MRHD of fenofibrate to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of approximately 7 times the MRHD to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight at birth, as well as on days 4 and 21 post-partum.

Administration of fenofibrate at 9 to 18 times the MRHD to female rabbits caused abortions in 10% to 25% of dams, and death in 7% of fetuses at 18 times the MRHD.

Nursing Mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (n=439)	Placebo (n=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4%**	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 200 mg fenofibrate capsules, micronized. Dosage comparable to 160 mg TRIGLIDE.
**Significantly different from placebo.

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.

CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.

DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.

ENDOCRINE SYSTEM: Diabetes mellitus

HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.

METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.

MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.

RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis.

SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.

SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.

UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

Laboratory Tests/Altered Laboratory Findings: In patients treated with fenofibrate, the following has been reported:
- Increases in serum transaminase and isolated cases of hepatitis
- Decreases in plasma alkaline phosphatase
- Increases in plasma creatinine, urea, and creatine phosphokinase

OVERDOSAGE

There is no specific treatment for overdose with TRIGLIDE. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRIGLIDE and should continue on this diet during treatment with TRIGLIDE.

TRIGLIDE may be administered with or without food.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRIGLIDE is 160 mg per day.
For adult patients with hypertriglyceridemia, the initial dose is 50 mg to 160 mg once daily.
Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals.
The maximum dose is 160 mg per day.
Treatment with TRIGLIDE should be initiated at a dose of 50 mg/day in patients with impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 50 mg/day. Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRIGLIDE if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRIGLIDE (fenofibrate) tablets, is available as a tablet in two strengths:
50 mg round off-white tablets debossed with “FH 50” are available in bottles of 90 tablets (NDC 59630-480-90).
160 mg round off-white tablets debossed with “FH 160” are available in bottles of 90 tablets (NDC 59630-485-90).
Storage: Store at 20 – 25°C (68 – 77°F); excursions permitted between 15 – 30°C (59 – 86°F). (See USP Controlled Room Temperature).
Protect from light and moisture.
Manufactured for First Horizon Pharmaceutical® Corporation by SkyePharma Production SAS, France. Made in France.

SkyePharma

REFERENCES

Goldberg AC, et al. Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. Clinical Therapeutics 1989; 11: 69-83.

Nikkila EA. Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In: Stanbury JB, ed. The metabolic basis of inherited disease: McGraw-Hill, 1983; 622-642.

Brown WV, et al. Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. Arteriosclerosis, 1986; 6: 670-678.

FIRST HORIZON PHARMACEUTICAL® CORPORATION

FF-PI-1 Rev. 01/05