CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20356/S7

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-356/S-007, S-008

JAN 19 2000

Zeneca Pharmaceuticals
Attention: Mr. Anthony F. Rogers
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

Dear Mr. Anthony:

Please refer to your supplemental new drug applications dated March 14 (S-007) and December 23 (S-008), 1997, received March 21 and December 29, 1997, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sular (nisoldipine) Extended Release Tablets.

We acknowledge receipt of your submissions dated August 4 and November 18, 1999. Your submission of November 18, 1999 constituted a complete response to our July 14, 1998 action letter.

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

The following paragraph was added under **PRECAUTIONS: Drug Interactions**:

> 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.

The following sentence was added to the end of the **ADVERSE REACTIONS** section:

> Gynocomastia has been associated with the use of calcium channel blockers.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted November 18, 1999). Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Mr. David Roeder
Regulatory Project Manager
(301) 594-5332

Sincerely,

/S/ 1/19/00

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20356/S7

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-356/S-007
S-008

JUL 14 1998

Zeneca Pharmaceuticals
Attention: W.J. Kennedy, Ph.D.
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Dr. Kennedy:

Please refer to your March 14 (S-007) and December 23 (S-008), 1997 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sular (nisoldipine) Tablets.

These supplemental applications provide for draft labeling revised as follows:

S-007

The following paragraph was added to **PRECAUTIONS: Drug Interactions**:

> In a pharmacokinetic study, plasma concentrations of nisoldipine were considerably lower in epileptic patients on phenytoin therapy than in healthy volunteers. Since clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

S-008

The following sentence was added to the end of the **ADVERSE EXPERIENCES** section:

> Gynecomastia has been associated with the use of calcium channel blockers.

We have completed the review of these applications and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. Certain sections of the labeling should be identical in content to the enclosed marked-up draft

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

/S/ 7/14/98

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

Enclosure: Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20356/S007

FINAL PRINTED LABELING

991018

F.P.O.

Rev M 3/99

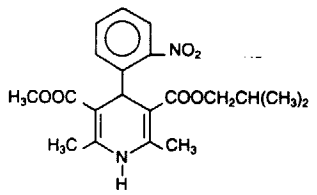
PROFESSIONAL INFORMATION BROCHURE

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: hydroxypropylmethylcellulose, 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

Labeling: original
NDA No. 20-356 Rcd. 1-19-99
Reviewed by: Revised 1-15-00

APPROVED
JAN 19 2000

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.

(CONTINUED ON REVERSE SIDE)

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 (post-implantation 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: Of the total number of subjects in the placebo-controlled clinical studies of nisoldipine for hypertension 12% were over 65 years of age.

Elderly patients have been found to have 2 to 3 fold higher plasma concentrations (C_{max} and AUC) than younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects (See CLINICAL PHARMACOLOGY-Special Population-Geriatrics).

Patients over 65 are expected to develop higher plasma concentrations of nisoldipine. In general, dose selection for an elderly patient should be cautious. A starting dose not exceeding 10 mg daily is recommended in this patient group. Blood pressure should be monitored closely during dose adjustment (See DOSAGE AND ADMINISTRATION).

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	Placebo	SULAR 10 mg	20 mg	30 mg	40 mg	60 mg
(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, watery eyes

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	891 on one side and ZENECA 10 on the other side.
20 mg	Yellow Cream	892 on one side and ZENECA 20 on the other side.
30 mg	Mustard	893 on one side and ZENECA 30 on the other side.
40 mg	Burnt Orange	894 on one side and ZENECA 40 on the other side.

SULAR Tablets are supplied in:

	Strength	NDC Code
Bottles of 100	10 mg	0310-0891-10
	20 mg	0310-0892-10
	30 mg	0310-0893-10
	40 mg	0310-0894-10
Unit Dose Packages of 100	10 mg	0310-0891-39
	20 mg	0310-0892-39
	30 mg	0310-0893-39

Protect from light and moisture. Store at controlled room temperature, 20-25°C (68-77°F) [see USP]. Dispense in tight, light-resistant containers.

ZENECA

Manufactured for:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437
By: Bayer AG, Leverkusen, Germany
Made in Germany

991018

Rev M 3/99

F.P.O.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20356/S007

CHEMISTRY REVIEW(S)

271

JAN 7 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-356
3. Name and Address of Applicant (City & State) Zeneca Limited - Macclesfield, England US Agent - Zeneca Pharmaceuticals 1800 Concord Pike, P.O. Box 15437 Wilmington, DE 19850-5437		4. Supplement(s) Number(s) Date(s) S-008 12/23/97 (LR)
5. Drug Name Sular Extended Release	6. Nonproprietary Name Nisoldipine	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Draft labeling information - gynecomastia.		
9. Pharmacological Category Hypertension	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Coat core (extended release) Tablets	13. Potency(ies) 10, 20, 30 and 40 mg	
14. Chemical Name and Structure		15. Records/Reports Current [ ] Yes [ ] No Reviewed [ ] Yes [ ] No

16. **Comments:**

Zeneca proposed to revise the Adverse Experiences section of the labeling to include the information on gynecomastia.

Labeling is satisfactory for DESCRIPTION and HOW SUPPLIED sections.

17. **Conclusions and Recommendations:**

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. **REVIEWER**

Name	Signature	Date Completed
Danute G. Cunningham	/S/	January 6, 1998

Distribution:

[X] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO [ ] District

20356S08.SUP

/S/ Short
1/7/98

DEC 1 1999

CHEMIST'S REVIEW	1.ORGANIZATION HFD-110	2. NDA Number 20-356
3. Name and Address of Applicant (City & State) Zeneca Limited - Macclesfield, England US Agent - Zeneca Pharmaceuticals 1800 Concord Pike, P.O. Box 15437 Wilmington, DE 19850-5437		4. Supplement(s) Number(s) Date(s) SLR-007 & SLR-008 (AF) -(AF) 11/18/99
5. Drug Name Sular Extended Release	6. Nonproprietary Name Nisoldipine	8. Amendments & Other (reports, etc) Dates
7. Supplement Provides For: Final printed labeling.		
9. Pharmacological Category Hypertension	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Coat core (extended release) Tablets	13. Potency(ies) 10, 20, 30 and 40 mg	
14. Chemical Name and Structure 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester		15. Records/Reports Current [ ] Yes [ ] No Reviewed [ ] Yes [ ] No

16. Comments:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

Insert - 991018 Rev. M 3/99 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.

17. Conclusions and Recommendations:

Labeling is satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	/S/	November 24, 1999

Distribution: [X] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO

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APR 2 1997

CHEMIST'S_REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-356
3. Name and Address of Applicant (City & State) Zeneca Limited - Macclesfield, England US Agent - Zeneca Pharmaceuticals 1800 Concord Pike, P.O. Box 15437 Wilmington, DE 19850-5437		4. Supplement(s) Number(s) Date(s) S-007 3/14/97
5. Drug Name Sular Extended Release	6. Nonproprietary Name Nisoldipine	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Labeling changes.		
9. Pharmacological Category Hypertension	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Coat core (extended release) Tablets	13. Potency(ies) 10, 20, 30 and 40 mg	
14. Chemical Name and Structure		15. Records/Reports Current [ ] Yes [ ] No Reviewed [ ] Yes [ ] No

16. Comments:

Submitted in response to the Agency's letter 12/5/95 which requested the addition of safety information concerning phenytoin-nisoldipine drug interaction.

Proposed changes are in PRECAUTION section.

There were no changes in DESCRIPTION and HOW SUPPLIED sections.

17. Conclusions and Recommendations:

DESCRIPTION and HOW SUPPLIED sections are satisfactory.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	/S/	April 2, 1997

Distribution:

[X] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO [ ] District

20356S07.SUP

/S/ 4/2/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20356/S7

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR - 6 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-356
Supplement
Nisoldipine C.C. tablets
Sular®
Zeneca Pharmaceuticals.

Submission date: March 14,1997

Reviewer: Patrick J Marroum.

Type of submission: Drug-drug interaction study with phenytoin.

Background:

Nisoldipine C.C. (SULAR®) is a once a day dihydropyridine calcium channel blocker currently approved for the treatment of hypertension. The formulation consists of a slow dissolving coat and a fast releasing core.
Since nisoldipine is a substrate of CYP3A4, its plasma concentrations might be affected by inducers of this enzyme system. To confirm this hypothesis, the sponsor conducted a drug-drug interaction study between nisoldipine C.C. and epileptic subjects which are on chronic phenytoin therapy. Enclosed in this submission are the results of the pharmacokinetic study entitled:"A study to compare the relative bioavailability of Nisoldipine C.C. in epileptic patients undergoing long term phenytoin therapy in comparison to a group of healthy volunteers matched with respect to age and gender." The sponsor is also requesting to revise package insert for Sular to incorporate the findings of this study.
Enclosed in Appendix I is a summary of the study report as well as a copy of the revised package insert.

Comments:

1-The results of the study that the sponsor conducted, indicate that phenytoin greatly reduces the nisoldipine plasma levels since except for 4 time points, the plasma levels were below the detection limits. In view of this finding, these two drugs should not be administered concomitantly. Alternative antihypertensive therapy should be sought for patients who are on phenytoin or any known inducers of CYP3A4.

2-The proposed paragraph that the sponsor intends to include in the Precaution:Drug Interactions section of the package insert should be replaced by the following:

Recommendations:

Comment 2 and 3 should be taken into consideration and the package insert for Sular should be amended accordingly.

/S/ 4/6/1998

Patrick J Marroum Ph.D.

RD/FT initialed by Ameeta Parekh Ph.D. /S/ 4/6/98

cc: NDA 20-356, HFD 110, FOI (HFD 19), HFD 340 (Vishwanathan), CDER central document room (attention Mrs Barbara Murphy).

APPENDIX I

A study to compare the relative bioavailability of nisoldipine C.C. in epileptic patients undergoing long term phenytoin therapy in comparison to a group of healthy volunteers matched with respect to age and gender.

STUDY #: 795

INVESTIGATORS:

OBJECTIVES:

To investigate the effect of phenytoin on the nisoldipine bioavailability as regards to AUC and CMAX. The effect on other nisoldipine kinetic variables and the possible influence on phenytoin were secondary objectives.

FORMULATION:

-Nisoldipine 20 mg C.C. tablets (batch #: 527793), expiration date 3/31/1995.
-100 mg Phenytoin trade name DintoinA Recordati batch # MO14, expiration date 12/31, 1997.

STUDY DESIGN:

12 healthy volunteers (11 males and 1 female) and 15 epileptic patients (12 males and three females) between the ages of between the ages of 18 to 65 years participated in this study.
This study was a stratified, non-blinded trial in two centers, the center of Pavia treated the healthy volunteers whereas the center of Bologna treated epileptic patients.
There was 2 phases for the study, a screening and phenytoin intake phase which lasted for at least three weeks. The epileptic patients should have phenytoin levels within 10-30 mcg/ml and not varying by more than 25 %. The phenytoin levels should have been measured at least twice during the three months preceding enrollment. The morning dose of nisoldipine or phenytoin was taken after a standardized breakfast (tea and three biscuits) following an overnight fast from 10 pm.
On day -1, patients had 2 ml blood samples taken for the determination of phenytoin concentrations at 0, 2 and 4 hours after administration. On the morning of day 1, epileptic patients received a single dose of nisoldipine C.C. of 40 mg together with phenytoin followed by pharmacokinetic evaluation for nisoldipine for 48 hours. Phenytoin levels were measured at all times as for day -1. Healthy volunteers received a single dose of nisoldipine C.C. 20 mg followed by pharmacokinetic evaluation for 48 hours. Plasma levels for the measurement of nisoldipine were collected at the following times post dose administration: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36 and 48 hours.

ASSAY:

DATA ANALYSIS:

Pharmacokinetic parameters were calculated using model-independent techniques. The primary evaluation was carried out considering the 90 % CI of the intra-matched pairs (epileptic/healthy) ratio of AUC and CMAX.

RESULTS:

Figure 1 shows the geometric mean plasma concentration for nisoldipine in the healthy volunteers and in the epileptic patients on steady state phenytoin while Table I summarizes the corresponding pharmacokinetic parameters. Table 2 shows that the plasma levels for phenytoin were not affected by nisoldipine. However, the same could not be said for nisoldipine. Plasma levels on 4 sampling time points could be detected namely at 10, 12, 14 and 24 hours. At all other time points, the plasma concentrations were below the detection limits.

Conclusion:

In epileptic patients on chronic phenytoin administration, the plasma concentrations of nisoldipine C.C. were greatly reduced and were below the detection limits for most plasma time points. This great decrease in nisoldipine plasma levels is due to the well known enzyme inducing properties of phenytoin. Therefore patients that are on phenytoin or any other known CYP450 3A4 inducers should not be given nisoldipine C.C. Alternative antihypertensive therapy should be instituted in these patients.

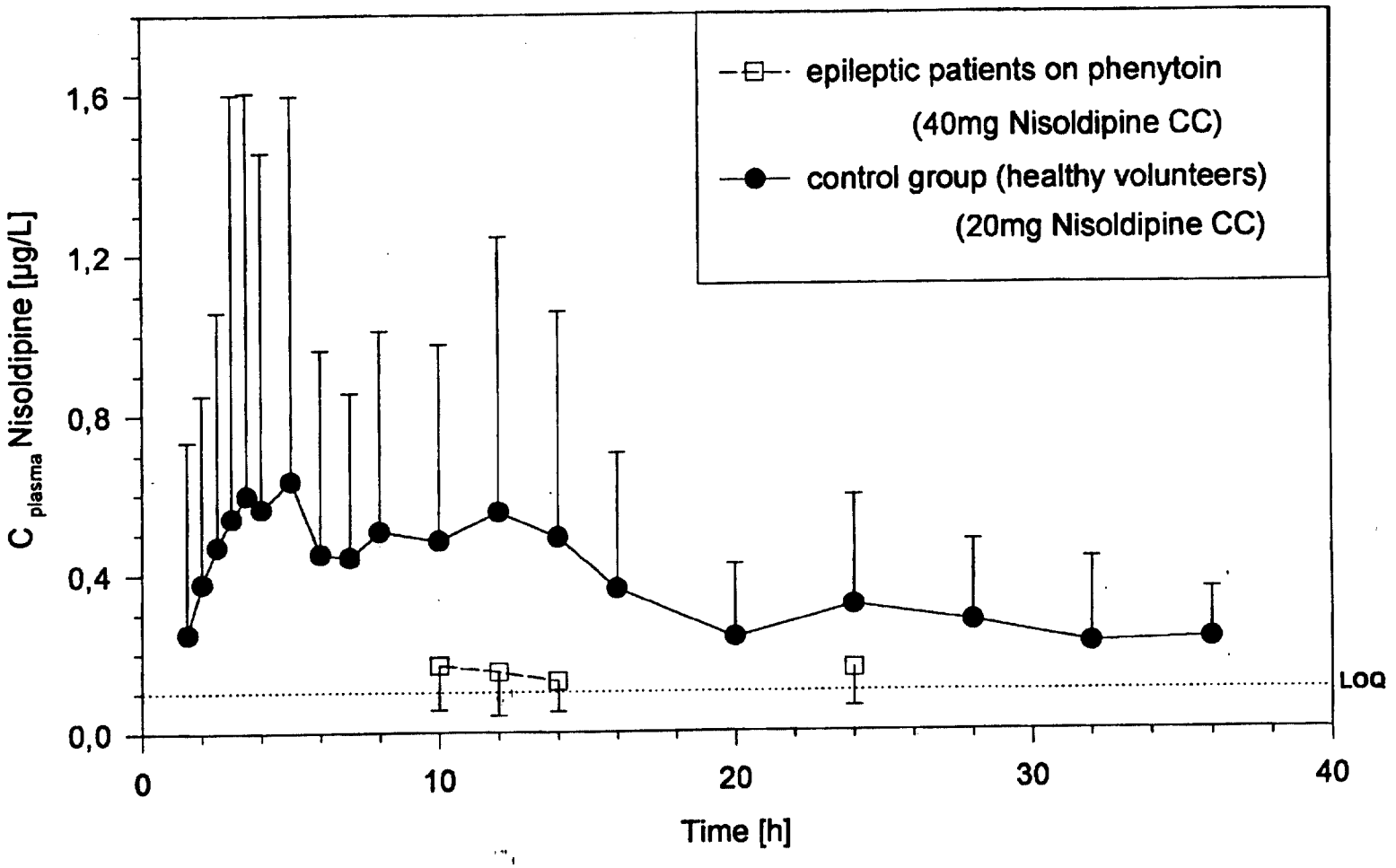

Figure I : Geometric means with 1S-range for plasma concentrations of nisoldipine (µg/L); limit of quantification (LOQ) : 0.1 µg/L

Table IV - Derived pharmacokinetic parameters of nisoldipine, geometric mean and standard deviation (SD) and minimum (min), median and maximum (max) value (n = 12)

	I. Epileptic patients		II. Healthy volunteers	
Dose	40 mg nisoldipine CC		20 mg nisoldipine CC	
Comedication	indiv. dose phenytoin		-	
Variable	geo.mean (SD)	median/min-max	geo.mean (SD)	median/min-max
$AUC(0\text{-}tn)_{norm}$ (g*h/L)	5.70 (4.10)	5.59/0.61-118.89	55.03 (1.71)	52.02/22.64-172.93
$C_{max,norm}$ (g/L)	0.69 (2.71)	0.45/0.28-5.74	3.85 (1.88)	3.64/1.46-11.85
t_{max} (h)		10.0/2.08-24.30		4.50/2.00-32.00

TABLE VI: Phenytoin pharmacokinetic parameters

Patient number	AUC(0-4) (mg*h/l) with nisoldipine treatment	C_{max} (mg/l)	AUC(0-4) (mg*/l) without nisoldipine treatment	C_{max} (mg/l)
23				
24				
25				
27				
28				
29				
30				
31				
32				
33				
34				
35				
n-MEAN	12	12	12	12
MEAN-GEO	62.0959	16.465	65.0127	17.093
S.D.-GEO	1.35435	1.3514	1.40004	1.3314
MEAN-ARI	64.7687	17.168	68.1218	17.721
S.D.-ARI	19.8045	5.2581	20.0230	4.8256

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20356/S7

ADMINISTRATIVE DOCUMENTS

JUL 14 1998

RHPM Review of Draft Labeling

Applications: NDA 20-356/S-007
NDA 20-356/S-008

Applicant: Zeneca Pharmaceuticals

Supplement Dates: March 14, 1997 (S-007)
December 23, 1997 (S-008)

Review

These supplements provide for draft labeling revised as follows:

S-007

The following paragraph was added to **PRECAUTIONS: Drug Interactions:**

> In a pharmacokinetic study, plasma concentrations of nisoldipine were considerably lower in epileptic patients on phynytoin therapy than in healthy volunteers. Since clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

S-008

In accordance with our written request of September 24, 1996, the following sentence was added to the end of the **ADVERSE EXPERIENCES** section:

> Gynecomastia has been associated with the use of calcium channel blockers.

In reviewing supplement S-007, Dr. Patrick Marroum made the following recommendations:

The proposed paragraph under **PRECAUTIONS: Drug Interactions** should be replaced with the following:

- 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.

The following sentence should be added to the **DOSAGE AND ADMINISTRATION** section:

Recommendation

An approvable letter should be drafted with Dr. Marroum's recommendations.

/S/

David Roeder
Regulatory Health Project Manager

dr/6-29-98

cc: NDA 20-356
HFD-110
HFD-110/DRoeder/SBenton

JAN 10 2000

RHPM Review of Final Printed Labeling

Application: NDA 20-356/S-009
Sular (nisoldipine) Extended Release Tablets

Sponsor: Zeneca Limited

Letter Date: November 18, 1999

Receipt Date: November 19, 1999

Review

An approvable letter was issued for NDA 20-356/S-007 and S008 on July 14, 1998 asking that the sponsor submit final printed labeling with the following revisions:

Add the following paragraph to **PRECAUTIONS: Drug Interactions:**

> 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.

Add the following sentence to the end of the **ADVERSE REACTIONS** section:

> Gynocomastia has been associated with the use of calcium channel blockers.

Add the following sentence to the end of the **DOSAGE AND ADMINISTRATION** section:

The sponsor proposed in a submission dated August 4, 1999 that the recommended revised to the **DOSAGE AND ADMINISTRATION** section be deleted. The Division agreed with their proposal.

The final printed labeling was reviewed and found to be identical to the August 4, 1999 draft that was agreed upon.

Recommendation

I recommend that the application be approved. An approval letter will be drafted for Dr. Lipicky's signature.

/S/

David Roeder
Regulatory Health Project Manager

dr/1-7-00

cc: NDA 20-356
HFD-110
HFD-110/DRoeder/SBenton