APPLICATION NUMBER: NDA 20356/S7

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

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:

Gynecomastia 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,

[Signature]  
[Date]

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
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,

[Signature]

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
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. Cmax and AUC increase by factors of approximately 1.5 and 2.5, respectively, from first dose to steady state. After oral administration, the concentration of total 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% bound over the plasma concentration range of 10 to 60 mg/ml.

Nisoldipine is highly metabolized. 5 major primary 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 cyclopropyl ester. A hydroxylated derivative of the side chain is 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 P450 isoenzymes are believed to play a major role in the metabolism of nisoldipine. The particular cytochrome P450 system responsible for its metabolism has not been identified, but other dihydropyridines are metabolized by cytochrome P450 1A2. 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 Cmax 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 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. Determinations 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 (Cmax and AUC) than young subjects. This should be reflected in more cautious dosing (See DOSAGE AND ADMINISTRATION).

Hypersensitivity: 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. Further studies 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.

Dose Adjustment: Hyperuricemia does not significantly alter the pharmacokinetics of nisoldipine.

Pharmacodynamics
- Hemodynamic Effects
  - Administration of a single dose of nisoldipine leads to decreases in 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 non-angiotensin system or plasma noradrenaline concentration or plasma renin activity. 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 effect on cardiac function, and did not result in 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.

- Electrocardiographic Effects
  - Nisoldipine has no clinically important electrophysiologic effects. Except for mild shortening of QRS cycle, SA conduction with an ARI interval, 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 dose of which could be limited 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 doses in one study, the phenomenon has not been a cause of concern in clinical trials.

Clinical Studies in Hypertension
- The antihypertensive efficacy of SULAR was studied in 5 double-blind, placebo-controlled, randomized studies, in which over 400 patients treated with SULAR as monotherapy and about 300 with placebo; 4 of the five studies compared 2 or 3 fixed doses while the fifth showed titration from 10 - 40 mg. Once daily administration of SULAR projected sustained reductions in systolic and diastolic blood pressure for more than 24 hours in both supine and standing positions. The most 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:

<table>
<thead>
<tr>
<th>SULAR Dose</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/20 mg</td>
<td>20 mg/30 mg</td>
<td>40 mg/60 mg</td>
</tr>
<tr>
<td>10-10 mg</td>
<td>8-11 mmHg</td>
<td>3-5 mmHg</td>
</tr>
<tr>
<td>11-14 mmHg</td>
<td>7-10 mmHg</td>
<td>8-10 mmHg</td>
</tr>
</tbody>
</table>
In patients receiving atenolol, supine blood pressure reductions with SULAR at 20, 40, and 80 mg once daily were 12%, 15%, and 22% for 10 mg, respectively. The sustained antihypertensive effect of SULAR was demonstrated by 24-hour blood pressure monitoring and examination of diastolic and trough effects. The trough/pulse 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.

For further studies, in patients with normal or decreased baseline blood pressure, careful monitoring of blood pressure during the initial administration and titration of SULAR is recommended. Careful observation is especially important for patients already taking medications that are known to lower blood pressure. Although in most patients the antihypertensive effect of SULAR is modest and well tolerated, occasional patients have had an excessive and poorly tolerated hypotensive response. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment.

Cautions: Because nisoldipine, like other vasodilators, could cause peripheral vasodilation, 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 antihypertensive effect of SULAR is modest and well tolerated, occasional patients have had an excessive and poorly tolerated hypotensive response. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment.

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>10 mg</th>
<th>20 mg</th>
<th>30 mg</th>
<th>40 mg</th>
<th>60 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Edema</td>
<td>10</td>
<td>7</td>
<td>15</td>
<td>20</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

The common adverse events occurred at about the same rate as 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 C% of all patients treated for hypertension in U.S. and foreign clinical trials, or with unspecified incidence in other studies. Although a causative relationship of SULAR to these events cannot be established, they are listed to alert the physician to a possible relationship with SULAR treatment.

- Body Ache: Cellulitis, chills, local edema, fever, flu syndrome, malaise
- Cardiovascular: atrial fibrillation, cerebrovascular accident, congestive heart failure, first degree AV block, hypotension, hypertension, jugular venous distention, migraine, myocardial infarction, posterior hypermotility, ventricular arrhythmias, supraventricular tachycardia, syncope, systolic ejection murmur
- Digestive: abnormal liver function tests, anorexia, colitis, diarrhea, dry mouth, dyspepsia, dysphagia, flatulence, gastritis, gastrointestinal hemorrhage, gingival hyperplasia, glossitis, hepatomegaly, increased appetite, mental, mouth ulceration
- Endocrine: diabetes mellitus, thyroiditis
- Hematologic: anemia, ecchymoses, leukopenia, petechiae
- Metabolic and Nutritional: gout, hypokalemia, increased serum creatinine, increased nonprotein nitrogen, weight gain, weight loss
- Musculoskeletal: arthritis, arthritis, leg cramps, myalgia, myopathy, myositis, tendinitis
- Neurologic: abnormal dreams, abnormal tremor and confusion, amnesia, anorexia, ataxia, central ischemia, decreased libido, depression, hypotension, hypnosis, enuresis, nervousness, paresthesia, somnolence, tremor, vertigo
- Respiratory: asthama, dyspnea, endotracheal wheezing and nose, epistaxis, increased cough, laryngitis, pharyngitis, pleural effusion, rhinitis, sinusitis
- Skin and Appendages: acne, alopecia, dry skin, exfoliative dermatitis, fungal dermatitis, herpes simplex, lichen planus, maculopapular rash, pruritus, purpuric rash, skin discoloration, skin ulcer, sweating, urticaria
- Special Senses: abnormal vision, amblyopia, blepharitis, conjunctivitis, ear pain, glaucoma, itchy eyes, keratoconjunctivitis, otitis media, retinal detachment, trachoma, watery eyes, taste disturbance, temporary unilateral loss of vision, visual fluctuation, watery eyes

The following postmarketing event has been reported very rarely in patients receiving SULAR: systemic hypertension reaction which may include one or more of the following: angioneurism, 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 niophilide but not observed with SULAR was one case of photosensitivity. Gynecomastia has been associated with the use of calcium channel blockers.

OVERDOSE

There is no experience with niophilide overdose. Generally, overdose with other hydrazides 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 niophilide would be expected to be slowed in patients with impaired liver function. Since niophilide is highly protein bound, dialysis is not likely to be of any benefit, however, pancreatitis may be beneficial.

DOSAGE AND ADMINISTRATION

The dosage of SULAR must be adjusted to each patient’s needs. Therapy usually should be initiated with mg orally once daily, then increased by mg weekly or biweekly intervals, to attain adequate control of blood pressure. Usual maintenance dosage is mg to mg daily. The blood pressure response increases over the 10 - 60 mg daily dose range but adverse event rates also increase. Doses over 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 niophilide. Their blood pressures 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.
<table>
<thead>
<tr>
<th>CHEMIST’S REVIEW</th>
<th>ORGANIZATION</th>
<th>NDA Number</th>
</tr>
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<tbody>
<tr>
<td>Name and Address of Applicant (City &amp; State)</td>
<td>Zeneca Limited - Macclesfield, England</td>
<td>20-356</td>
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<tr>
<td></td>
<td>US Agent - Zeneca Pharmaceuticals</td>
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<td></td>
<td>1800 Concord Pike, P.O. Box 15437</td>
<td></td>
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<td></td>
<td>Wilmington, DE 19850-5437</td>
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<td>Supplement Provides For:</td>
<td>Draft labeling information - gynecomastia.</td>
<td></td>
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<tr>
<td>Pharmacological Category</td>
<td>Hypertension</td>
<td></td>
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<td>How Dispensed</td>
<td>Rx</td>
<td></td>
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<tr>
<td>Dosage Form(s)</td>
<td>Tablets</td>
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<td>Coat core (extended release)</td>
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<tr>
<td>Potency(ies)</td>
<td>10, 20, 30 and 40 mg</td>
<td></td>
</tr>
<tr>
<td>Chemical Name and Structure</td>
<td></td>
<td></td>
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<tr>
<td>Comments:</td>
<td>Zeneca proposed to revise the Adverse Experiences section of the labeling to include the information on gynecomastia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Labeling is satisfactory for DESCRIPTION and HOW SUPPLIED sections.</td>
<td></td>
</tr>
<tr>
<td>Conclusions and Recommendations:</td>
<td>Satisfactory for DESCRIPTION and HOW SUPPLIED sections.</td>
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<tr>
<th>REVIEWER</th>
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<tbody>
<tr>
<td>Name</td>
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<td>Date Completed</td>
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Distribution: 
- Original Jacket
- Reviewer
- Division File
- CSO
- District
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</thead>
<tbody>
<tr>
<td></td>
<td>HFD-110</td>
<td>20-356</td>
</tr>
</tbody>
</table>

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

7. Supplement Provides For:
   Final printed labeling.

8. Amendments & Other (reports, etc) Dates

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


17. Conclusions and Recommendations:

    Labeling is satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER

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

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

   20357S08.AM1
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

7. Supplement Provides For:
   Labeling changes.

9. Pharmacological Category
   Hypertension

10. How Dispensed
    □ 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

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
   Danute G. Cunningham

   Signature
   /S/

   Date Completed
   April 2, 1997

   Distribution:
   ☑ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO ☐ District

   20356807 SUP
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20356/S7

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)
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:

$S_\text{olar}^R$

Nisoldipine C.C. 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.

Patrick J Marroum Ph.D.

4/6/98

RD/FT initialed by Ameeta Parekh Ph.D. 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 1 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 1: Geometric means with 1S-range for plasma concentrations of nisoldipine (μg/L); limit of quantification (LOQ): 0.1 μg/L
### Table I
Derived pharmacokinetic parameters of nisoldipine, geometric mean and standard deviation (SD) and minimum (min), median and maximum (max) value (n = 12)

<table>
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<tr>
<th>Variable</th>
<th>I. Epileptic patients</th>
<th>II. Healthy volunteers</th>
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</thead>
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<tr>
<td>Dose</td>
<td>40 mg</td>
<td>20 mg</td>
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<tr>
<td>Comedication</td>
<td>nisoldipine CC</td>
<td>nisoldipine CC</td>
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<tr>
<td></td>
<td>indiv. dose</td>
<td>phenytoin</td>
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<tr>
<td>Variable</td>
<td>geo.mean (SD)</td>
<td>median/min-max</td>
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<tr>
<td>AUC(0-t)_{norm} (g*h/L)</td>
<td>5.70 (4.10)</td>
<td>5.59/0.61-118.89</td>
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<tr>
<td>C_{max,norm} (g/L)</td>
<td>0.69 (2.71)</td>
<td>0.45/0.28-5.74</td>
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<tr>
<td>t_{max} (h)</td>
<td>10.0/2.08-24.30</td>
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### Table II
Phenytoin pharmacokinetic parameters

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<tr>
<th>Patient number</th>
<th>AUC(0-4) (mg*h/L)</th>
<th>C_{max} (mg/l)</th>
<th>AUC(0-4) (mg*h/L)</th>
<th>C_{max} (mg/l)</th>
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<td>without nisoldipine treatment</td>
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<td>n-MEAN</td>
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<td>MEAN-GEO</td>
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20356/S7

ADMINISTRATIVE DOCUMENTS
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 phynytin 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 caffeine 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
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:

Gynecomastia 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.

David Roeder
Regulatory Health Project Manager

dr/1-7-00

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