NDA 19-546

DEC 2?

Sandoz Pharmaceuticals Corporation
Sandoz Research Institute
Attention: Mr. Douglas W. Bitz
Route 10
East Hanover, NJ 07936

Dear Mr. Bitz:

Please refer to your April 24, 1986 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dynacirc (isradipine) Capsules.

We also acknowledge receipt of your amendments dated November 29 and December 12 and 13(2), 1990, and correspondence dated September 24, and December 7, 10, and 13, 1990.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on December 13, 1990. Accordingly, the application is approved effective on the date of this letter.

At the time of your next printing, please make the editorial changes that are illustrated in the enclosed marked-up draft of your package insert.

In addition to these editorial changes, please add drug substance solubility information to the DESCRIPTION section.

Please submit one market package of the drug when it is available.

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

If you have any questions, please contact:

Mr. David Roeder
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

D.R

NDA 19-546

Sandoz Pharmaceuticals Corporation
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Attention: Mr. Douglas W. Bitz
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Dear Mr. Bitz:

Please refer to your April 24, 1986 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dynacirc (isradipine) Capsules.

We also acknowledge receipt of your December 27, 1985 presubmission of manufacturing and controls information and of your amendments and correspondence dated May 30, June 20, August 22, October 24, November 21 and 25, and December 17, 1986; January 15 and 21, July 20 and December 17, 1987; March 30, June 15, July 6, October 28 (2), November 22 and 23, and December 7, 20 and 21, 1988; January 24, February 23, March 7, April 3, September 13, November 17 and 21, 1989; January 22, February 16, April 20, May 11, and July 16, 1990.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit final printed labeling for the drug. The labeling should be identical in content to the enclosed marked-up draft. 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.

Please submit twelve copies of the printed labels and other labeling, seven of which are individually mounted on heavy weight paper or similar material.

Please submit a limited safety update that contains the following information:

1. All deaths in clinical trials, including the case report forms.

2. All adverse drop-outs other than those related to recognized side effects of the drug (headache, dizziness, edema, palpitations, etc.), including events possibly representing intercurrent illness.

3. All foreign post-marketing reports that would represent a serious unlabeled adverse event or a suggestion of increased rate of a known serious event.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Cardio-Renal Drug Products and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Labeling, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

We should point out at this time that we believe the comparative studies submitted to the application, none of which measured blood pressure at trough, do not constitute a basis for comparative claims, as they are comparing the peak effect of a drug with fairly large peak-trough difference (isradipine) to drugs with relatively constant effects over 24 hours (beta-blockers, diuretics).

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) is required before this application may be approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Mr. David Roeder
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

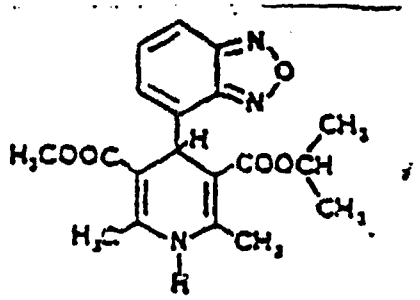
Marked up draft labeling RT 1/30

DYNACIRC® (isradipine) CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

DynaCirc® (isradipine) is a calcium antagonist available for oral administration in capsules containing 2.5 mg or 5 mg. The structural formula of isradipine is given below:



Chemically, isradipine is 3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester. It has a molecular weight of 371.39. Isradipine is a yellow, fine crystalline powder which is odorless or has a faint characteristic odor.

Active Ingredient: isradipine

Inactive ingredients: colloidal silicon dioxide, D&C Red No. 7 Calcium Lake, FD&C Red No. 40 (5 mg capsule only), FD&C Yellow No. 6 Aluminum Lake, gelatin, lactose, starch, titanium dioxide and other ingredients.

The 2.5 mg and 5 mg capsules may also contain: benzyl alcohol, butyl paraben, edetate calcium disodium, methyl paraben, propyl paraben, sodium propionate.

CLINICAL PHARMACOLOGY

Mechanism of Action

Isradipine is a dihydropyridine calcium channel blocker. It binds to calcium channels with high affinity and specificity and inhibits calcium flux into cardiac and smooth muscle. The effects observed in mechanistic experiments in vitro and studied in intact animals and man are compatible with this mechanism of action and are typical of the class.

Except for ~~the~~ diuretic activity, the mechanism of which is not clearly understood, the pharmacodynamic effects of isradipine

observed in whole animals can also be explained by calcium channel blocking activity, especially dilating effects in arterioles which reduce systemic resistance and lower blood pressure, with a small increase in resting heart rate. Although like other dihydropyridine calcium channel blockers, isradipine has negative inotropic effects in vitro, studies conducted in intact anesthetized animals have shown that the vasodilating effect occurs at doses lower than those which affect contractility. In patients with normal ventricular function, isradipine's afterload reducing properties lead to some increase in cardiac output.

Effects in patients with impaired ventricular function have not been fully studied.

Clinical Effects

Dose-related reductions in supine and standing blood pressure are achieved within 2-3 hours following single oral doses of 2.5 mg, 5 mg, 10 mg, and 20 mg DynaCirc® (isradipine), with a duration of action (at least 50% of peak response) of more than 12 hours following administration of the highest dose.

DynaCirc® has been shown in controlled, double-blind clinical trials to be an effective antihypertensive agent when used as monotherapy, or when added to therapy with thiazide-type diuretics. During chronic administration, divided doses (bid) in the range of 5 mg - 20 mg daily have been shown to be effective, with response at trough (prior to next dose) over 50% of the peak blood pressure effect. The response is dose-related between 5-10 mg daily. DynaCirc® is equally effective in reducing supine, sitting, and standing blood pressure.

On chronic administration, increases in resting pulse rate averaged about 3-5 beats/min. These increases were not dose-related.

Hemodynamics

In man, peripheral vasodilation produced by DynaCirc® is reflected by decreased systemic vascular resistance and increased cardiac output. Hemodynamic studies conducted in patients with normal left ventricular function produced, following intravenous isradipine administration, increases in cardiac index, stroke volume index, coronary sinus blood flow, heart rate, and peak positive left ventricular dP/dt. Systemic, coronary, and pulmonary vascular resistance were decreased. These studies were conducted with doses of isradipine which produced clinically significant decreases in blood pressure. The clinical consequences of these hemodynamic effects, if any, have not been evaluated. Effects on heart rate are variable, dependent upon rate of administration and presence of underlying cardiac condition. While increases in both peak positive dP/dt and LV ejection fraction are seen when intravenous isradipine is given, it is

impossible to conclude that these represent a positive inotropic effect due to simultaneous changes in preload and afterload. In patients with coronary artery disease undergoing atrial pacing during cardiac catheterization, intravenous isradipine diminished abnormalities of systolic performance. In patients with moderate left ventricular dysfunction, oral and intravenous isradipine in doses which reduce blood pressure by 12 to 30 percent, resulted in improvement in cardiac index without increase in heart rate, and with no change or reduction in pulmonary capillary wedge pressure. Combination of isradipine and propranolol did not significantly effect left ventricular dP/dt max. The clinical consequences of these effects have not been evaluated.

Electrophysiologic Effects

In general, no detrimental effects on the cardiac conduction system were seen with the use of DynaCirc®. Electrophysiologic studies were conducted on patients with normal sinus and atrioventricular node function. Intravenous isradipine in doses which reduce systolic blood pressure did not effect PR, QRS, AH* or HV* intervals.

No changes were seen in Wenckebach cycle length, atrial, and ventricular refractory periods. Slight prolongation of QTc interval of 3% was seen in one study. Effects on sinus node recovery time (CSNRT) were mild or not seen.

In patients with sick sinus syndrome, at doses which significantly reduced blood pressure, intravenous isradipine resulted in no depressant effect on sinus and atrioventricular node function.

*AH = conduction time from low right atrium to His bundle deflection, or AV nodal conduction time; HV = conduction time through the His bundle and the bundle branch-Purkinje system.

Pharmacokinetics and Metabolism

Isradipine is 90-95% absorbed and is subject to extensive first-pass metabolism, resulting in a bioavailability of about 15-24%. Isradipine is detectable in plasma within 20 minutes after administration of single oral doses of 2.5-20 mg, and peak concentrations of approximately 1 ng/ml/mg dosed occur about 1.5 hours after drug administration. Administration of DynaCirc® (isradipine) with food significantly increases the time to peak by about an hour, but has no effect on the total bioavailability (area under the curve) of the drug. Isradipine is 95% bound to plasma proteins. Both peak plasma concentration and AUC exhibit a linear relationship to dose over the 0-20 mg dose range. The elimination of isradipine is biphasic with an early half-life of 1½-2 hours, and a terminal half-life of about 8 hours. The total body clearance of isradipine is 1.4 L/min and the apparent volume of distribution is 3 L/kg.

Isradipine is completely metabolized prior to excretion and no unchanged drug is detected in the urine. Six metabolites have been characterized in blood and urine, with the mono acids of the pyridine derivative and a cyclic lactone product accounting for >75% of the material identified. Approximately 60-65% of an administered dose is excreted in the urine and 25-30% in the feces. Mild renal impairment (creatinine clearance 30-80 mL/min) increases the bioavailability (AUC) of isradipine by 45%. Progressive deterioration reverses this trend, and patients with severe renal failure (<10 mL/min) who have been on hemodialysis show a 20-50% lower AUC than healthy volunteers. No pharmacokinetic information is available on drug therapy during hemodialysis. In elderly patients, C_{max} and AUC are increased by 13% and 40%, respectively; in patients with hepatic impairment, C_{max} and AUC are increased by 32% and 52%, respectively (see Dosage and Administration).

INDICATION AND USAGE

Hypertension

DynaCirc® (isradipine) is indicated in the management of hypertension. It may be used alone or concurrently with thiazide type-diuretics.

CONTRAINDICATIONS

DynaCirc® is contraindicated in individuals who have shown hypersensitivity to any of the ingredients in the formulation.

WARNINGS

None

PRECAUTIONS

GENERAL

Blood Pressure: Because DynaCirc® decreases peripheral resistance, like other calcium blockers DynaCirc® may occasionally produce symptomatic hypotension. However, symptoms like syncope and severe dizziness have rarely been reported in hypertensive patients administered DynaCirc®, particularly at the initial recommended doses (see Dosage and Administration).

Use in Patients with Congestive Heart Failure: Although acute hemodynamic studies in patients with congestive heart failure have shown that DynaCirc® reduced afterload without impairing myocardial contractility, it has a negative inotropic effect at high doses in vitro, and possibly in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker.

DRUG INTERACTIONS

Nitroglycerin: DynaCirc® has been safely co-administered with nitroglycerin.

Hydrochlorothiazide: A study in normal healthy volunteers has shown that concomitant administration of DynaCirc® and hydrochlorothiazide does not result in altered pharmacokinetics of either drug. In a study in hypertensive patients, addition of isradipine to existing hydrochlorothiazide therapy did not result in any unexpected adverse effects, and isradipine had an additional antihypertensive effect.

Propranolol: In a single dose study in normal volunteers, coadministration of propranolol had a small effect on the rate but no effect on the extent of isradipine bioavailability. Coadministration of DynaCirc® resulted in significant increases in AUC (27%) and C_{max} (58%) and decreases in t_{max} (23%) of propranolol.

Digoxin: The concomitant administration of DynaCirc® and digoxin in a single-dose pharmacokinetic study did not affect renal, nonrenal and total body clearance of digoxin.

Fentanyl Anesthesia: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta blocker and a calcium channel blocker. Even though such interactions have not been seen in clinical studies with DynaCirc®, an increased volume of circulating fluids might be required if such an interaction were to occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Treatment of male rats for 2 years with 2.5, 12.5, or 62.5 mg/kg/day isradipine admixed with the diet (approximately 6, 31, and 156 times the maximum recommended daily dose based on a 50 kg man) resulted in dose dependent increases in the incidence of benign Leydig cell tumors and testicular hyperplasia relative to untreated control animals. These findings, which were replicated in a subsequent experiment, may have been indirectly related to an effect of isradipine on circulating gonadotropin levels in the rats; a comparable endocrine effect was not evident in male patients receiving therapeutic doses of the drug on a chronic basis. Treatment of mice for two years with 2.5, 15, or 80 mg/kg/day isradipine in the diet (approximately 6, 38, and 200 times the maximum recommended daily dose based on a 50 kg man) showed no evidence of oncogenicity. There was no evidence of mutagenic potential based on the results of a battery of mutagenicity tests. No effect on fertility was observed in male and female rats treated with up to 60 mg/kg/day isradipine.

Pregnancy

PREGNANCY CATEGORY C. Isradipine was administered orally to rats and rabbits during organogenesis. Treatment of pregnant rats with doses of 6, 20, or 60 mg/kg/day produced a significant reduction in maternal weight gain during treatment with the highest dose (150 times the maximum recommended human daily dose) but with no lasting effects on the mother or the offspring. Treatment of pregnant rabbits with doses of 1, 3, or 10 mg/kg/day (2.5, 7.5, and 25 times the maximum recommended human daily dose) produced decrements in maternal body weight gain and increased fetal resorptions at the two higher doses. There was no evidence of embryotoxicity at doses which were not maternotoxic and no evidence of teratogenicity at any dose tested. In a peri/postnatal administration study in rats, reduced maternal body weight gain during late pregnancy at oral doses of 20 and 60 mg/kg/day isradipine was associated with reduced birth weights and decreased peri and postnatal pup survival.

Nursing Mothers

It is not known whether DynaCirc® is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for adverse effects of DynaCirc® on nursing infants, a decision should be made as to whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness have not been established in children.

ADVERSE REACTIONS

In multiple dose U.S. studies in hypertension, 1228 patients received DynaCirc® alone or in combination with other agents, principally a thiazide diuretic, 934 of them in controlled comparisons with placebo or active agents. An additional 652 patients (which includes 374 normal volunteers) received DynaCirc® in U.S. studies of conditions other than hypertension, and 1321 patients received DynaCirc® in non-U.S. studies. About 500 patients received DynaCirc® in long-term hypertension studies, 410 of them for at least 6 months. The adverse reaction rates given below are principally based on controlled hypertension studies, but rarer serious events are derived from all exposures to DynaCirc®, including foreign marketing experience.

Most adverse reactions were mild and related to the vasodilatory effects of DynaCirc® (dizziness, edema, palpitations, flushing, tachycardia) and many were transient. About 5% of isradipine patients left studies prematurely because of adverse reactions

(vs. 3% of placebo patients and 6% of active control patients), principally due to headache, edema, dizziness, palpitations and gastrointestinal disturbances.

The table below shows the most common adverse reactions, volunteered or elicited, considered by the investigator to be at least possibly drug related. The results for the DynaCirc® treated patients are presented for all doses pooled together (reported by 1% or greater of patients receiving any dose of isradipine), and also for the two treatment regimens most applicable to the treatment of hypertension with DynaCirc®: (1) initial and maintenance dose of 2.5 mg bid, and (2) initial dose of 2.5 mg bid followed by maintenance dose of 5.0 mg bid.

Add 2.5 mg (10 bid) column since it's a recd dose

Adverse Experience	DynaCirc® All Doses (N = 934) %	DynaCirc® 2.5 mg bid (N = 199) %	DynaCirc® 5 mg bid† (N = 150) %	Placebo (N = 297) %	Active Controls* (N = 414) %
Headache	13.7	12.6	10.7	14.1	9.4
Dizziness	7.3	8.0	5.3	4.4	8.2
Edema	7.2	3.5	8.7	1.0	2.9
Palpitations	4.0	1.0	4.7	1.4	1.5
Fatigue	3.9	2.5	2.0	0.3	6.3
Flushing	2.6	3.0	2.0	0.0	1.2
Chest Pain	2.4	2.5	2.7	2.4	2.9
Nausea	1.8	1.0	2.7	1.7	3.1
Dyspnea	1.8	0.5	2.7	1.0	2.2
Abdominal Discomfort	1.7	0.0	3.3	1.7	3.9
Tachycardia	1.5	1.0	1.3	0.3	0.5
Rash	1.5	1.5	2.0	0.3	0.7
Pollakiuria	1.5	2.0	1.3	0.0	<1.0
Weakness	1.2	0.0	0.7	0.0	1.2
Vomiting	1.1	1.0	1.3	0.3	0.2
Diarrhea	1.1	0.0	2.7	2.0	1.9

† Initial dose of 2.5 mg bid followed by maintenance dose of 5.0 mg bid.
* Propranolol, prazosin, hydrochlorothiazide, enalapril, captopril.

Except for headache, which is not clearly drug-related (see table above), the more frequent adverse reactions listed above show little change, or increase slightly, in frequency over time, as shown in the following table:

INCIDENCE RATES FOR DYNACIRC® (ALL DOSES) BY WEEK
(%)

Week	1	2	3	4	5	6	7	8	9	10	11	12
N	694	90%	649	847	432	494	153	377	261	362	107	105
Adverse Reaction												
Headache	6.5	6.1	5.2	5.2	5.8	4.5	2.0	2.7	1.9	2.8	2.8	3.8
Dizziness	1.6	1.9	1.7	2.2	2.3	2.0	2.0	1.9	2.3	3.9	4.7	3.8
Edema	1.2	2.5	3.2	3.2	5.3	5.5	5.9	5.0	4.6	4.7	3.8	3.8
Palpitations	1.2	1.3	1.4	1.9	2.1	1.4	1.3	0.8	0.8	1.7	1.9	2.9
Fatigue	0.4	1.0	1.4	1.2	1.2	1.6	2.0	2.7	1.5	1.4	0.9	1.9
Flushing	1.2	1.3	2.0	1.4	2.1	1.4	3.3	1.3	1.1	0.8	0.0	0.0

Edema, palpitations, fatigue, and flushing appear to be dose-related, especially at the higher doses of 15-20 mg/day.

In open-label, long-term studies of up to two years in duration, the adverse events reported were generally the same as those reported in the short-term controlled trials. The overall frequencies of these adverse events were slightly higher in the long-term than in the controlled studies, but as in the controlled trials most adverse reactions were mild and transient.

The following adverse events were reported in ~~less than 1%~~ 0.5 - 1.0% of the isradipine treated patients in hypertension studies, or are rarer but more serious events from ~~this and~~ other data sources, including post marketing exposure, are shown in italics. The relationship of these adverse events to isradipine administration is uncertain.

Skin: pruritus, *urticaria*

Musculoskeletal: chest pain, cramps of legs/feet

Respiratory: cough

Cardiovascular: shortness of breath, chest pain, hypotension, *atrial fibrillation, ventricular fibrillation, myocardial infarction, heart failure*

Gastrointestinal: abdominal discomfort, constipation, diarrhea

Urogenital: nocturia

Nervous System:	drowsiness, insomnia, lethargy, nervousness, impotence, decreased libido, depression, syncope, paresthesia (which includes numbness and tingling), transient ischemic attack, stroke
Autonomic:	hyperhidrosis, visual disturbance, dry mouth, numbness
Miscellaneous:	throat discomfort, leukopenia, elevated liver function tests

OVERDOSAGE

Although there is no well documented experience with DynaCirc® overdosage, available data suggest that, as with other dihydropyridines, gross overdosage would result in excessive peripheral vasodilation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension overdosage calls for active cardiovascular support including monitoring of cardiac and respiratory function, elevation of lower extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as epinephrine, norepinephrine or levarterenol) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Since isradipine is highly protein-bound, dialysis is not likely to be of benefit.

~~In acute toxicity studies, one-half of the animals died when mice were~~ Significant Lethality was observed in mice given oral doses of over 200 mg/kg and rabbits given about 50 mg/kg of isradipine. Rats tolerated doses of over 2000 mg/kg without effects on survival.

DOSAGE AND ADMINISTRATION

The dosage of DynaCirc® (isradipine) should be individualized. The recommended initial dose of DynaCirc® is 2.5 mg bid alone or in combination with a thiazide diuretic. An antihypertensive response usually occurs within two to three hours. Maximal response may require 2-4 weeks. If a satisfactory reduction in blood pressure does not occur after this period, the dose may be adjusted in increments of 5 mg per day at 2-4 week intervals up to a maximum of 20 mg per day. Most patients, however, show no additional response to doses above 10 mg/day, and adverse effects are increased in frequency above 10 mg/day.

The bioavailability of DynaCirc® (increased AUC) is increased in elderly patients (above 65 years of age), patients with hepatic functional impairment, and patients with mild renal impairment. Ordinarily, the starting dose should still be 2.5 mg bid in these patients.

HOW SUPPLIED

DynaCirc® (isradipine) Capsules:

2.5 mg, white, imprinted twice with the DynaCirc® (isradipine) logo and "DynaCirc®" on one end, and "2.5" and a triangle (S) on the other. Bottles of 100 capsules (NDC 0078-0226-05); bottles of 60 capsules (NDC 0078-0226-44); and SandoPak® (unit-dose) packages of 100, 10 strips, 10 blisters (2x5) per strip (NDC 0078-0226-06).

5 mg, light pink, imprinted twice with the DynaCirc® (isradipine) logo and "DynaCirc®" on one end, and "5" and a triangle (S) on the other. Bottles of 100 capsules (NDC 0078-0227-05); bottles of 60 capsules (NDC 0078-0227-44); and SandoPak® (unit-dose) packages of 100, 10 strips, 10 blisters (2x5) per strip (NDC 0078-0227-06).

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

SANDOZ PHARMACEUTICALS CORPORATION
East Hanover, New Jersey 07936

November 28, 1990

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-546

FEB 9 1990

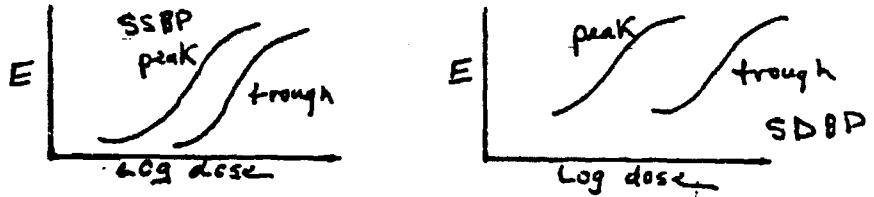
NZ 219190

Sandoz Pharmaceuticals Corporation
Sandoz Research Institute
Attn: Mr. Doug Bitz
Route 10
East Hanover, NJ 07936

Dear Doug,

As per our conversation this morning, Dr. Lipicky has reviewed the SBA for isradipine and would like you to make the following revisions.

1. On page 33, Fig. 2; Plasma concentration vs. time
   Change to a semi-log plot.
2. Page 34, Fig. 3:;Plasma concentration vs. time
   Do not break X-axis.
3. Page 37, Fig. 5; Plasma concentration vs. time
   Change to a semi-log plot.
4. Pages 38 & 46, Figs. 6 & 11;
   Do not break X-axis.
5. Page 52, Table 7;
   Make figure with variable plotted against log dose.
6. Pages 55-57, Figs. 13, 14, & 15;
   Plot drug-placebo difference.
7. Pages 67 & 68, Figure 16 & 17;
   Plot log Dose-Response for SSBP & SDBP for peak and trough on same graph. Dr. Lipicky suggests the following format.



8. Pages 128 & 129, Tables 28 & 29
   Plot dose vs adverse effect.

Dr. Lipicky said to call him if you have any questions or problems.

Warren Rumble, CSO

cc Orig
HFD-110
HFD-110 CSO