

TABLE 15  
PN 200-110 STUDY NO. 308

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE  
ENDPOINT OF PLATEAU PERIOD (WEEKS 5-6) - VALID AND PARTIALLY VALID PATIENTS

Variable	Randomized Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted Mean Change*	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mm Hg)	PN 200-110	65	162.6	16.98	-14.97***	14.10	-14.91***	147.7	17.04
	Placebo	69	162.3	19.18	-3.36(*)	14.82	-3.41	149.0	18.04
Supine Diastolic B.P. (mm Hg)	PN 200-110	65	104.3	4.68	-10.62***	7.49		93.5	8.84
	Placebo	69	105.0	5.40	-5.43**	7.78		99.5	10.38
Supine Pulse (per min)	PN 200-110	65	74.7	8.40	-1.59	9.20	-1.40	73.1	9.48
	Placebo	69	73.9	7.63	0.19	7.04	0.01	74.0	7.53
Standing Systolic B.P. (mm Hg)	PN 200-110	65	158.9	20.33	-12.74***	18.23	-12.61***	146.2	19.55
	Placebo	69	158.3	21.66	-3.45	17.28	-3.58	154.9	18.95
Standing Diastolic B.P. (mm Hg)	PN 200-110	65	103.2	7.78	-8.86***	9.61	-8.94***	94.3	11.41
	Placebo	69	104.0	9.20	-2.74**	8.00	-2.67	101.3	10.96
Standing Pulse (per min)	PN 200-110	65	78.6	9.48	-0.67	9.35	-0.61	78.0	10.29
	Placebo	69	78.3	8.09	1.41	7.65	1.35	79.7	7.74

08-0032  
 ) p<.10, \* p<.05, \*\* p<.01, \*\*\* p<.001  
 presented only when analysis of covariance assumptions were met.

N 19546

ISRADIPINE - SAFETY UPDATE

DEC 9 1988 #1

Sponsor's Overall Summary

DATE OF REPORT: NOVEMBER 11, 1988

These data were submitted to me direct from Sandoz and permission was granted to me by Mr Warren Rumble, FDA CSO, to proceed with the summary and review.

INTRODUCTION

These data are obtained from 53 US clinical trials with a total of 2591 patients, of whom 1880 had received isradipine. The majority (1228) of isradipine patients had received the drug for the treatment of hypertension. Of these, 934 were in double blind studies of 3 -12 week duration. There were 374 normal volunteers, 137 angina patients, 72 CHF and 69 "other". The 1880 isradipine patients were treated for varying time periods as shown:

2 weeks	=	1338
10 weeks	=	765
6 months	=	455
12 months	=	336
24 months	=	96

The 542 "missing" patients are presumed to have been treated for less than 2 weeks.

The report is divided into two sections, short and long term trials. The short term studies are divided into NDA and post NDA studies in order "to provide a comparison of the newer studies post-NDA submission vs the experience summarized in the NDA...". The two data bases were then pooled in order to provide an overall summary of experience. Comparative data vs placebo and a pool of active controlled groups are also supplied. In the case of the long term data, individual comparisons were not provided but data were pooled for overall experience.

RESULTS

A. Short Term Studies

Sponsor states that there was no evidence that isradipine resulted in any adverse effects or increased frequency of adverse effects on any ECG variable.

Sponsor analyzed clinical laboratory results, pooling all data from studies that had utilised Metpath as the central laboratory. There were over 600 active and 250 placebo patients involved. The only variables to show statistically significant differences from placebo were total protein (+1% mean change from baseline), albumin (+0.8% change from baseline), sodium (-0.3% from baseline), potassium (-0.9% from baseline) and alkaline phosphatase (+5.4% change from baseline).

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Sponsor states that, in evaluating occurrence of newly occurring abnormalities, there was no indication that isradipine resulted in a higher frequency of abnormalities compared to placebo and/or active controls involving any laboratory variable. A comparison is given for increase (mg/dl) in mean serum glucose as follows:

Patients	Isradipine	Placebo	Active Controls
Non Diabetics	4.4	0.5	5.0
Diabetics	6.7	10.3	19.8

The most frequent adverse reactions reported in double blind studies in hypertension were:

<u>Adverse Reaction</u>	% Patients	
	<u>Isradipine</u> N = 934	<u>Placebo</u> N = 297
Headache	13.7	14.1
Edema	7.2	3.0
Dizziness	7.3	4.4
Palpitations	4.0	1.4
Fatigue	1.9	0.3
Flushing	2.6	0

Sponsor states that majority of the events were mild to moderate in severity and appeared to be transient in nature. Dose related events were edema, palpitations and fatigue. All vasodilation events were also dose related especially at a dose > 10 mg/ day isradipine.

In the hypertension studies, 49/934 (5.2%) were discontinued due to adverse reactions. In most cases, those patients who discontinued experienced more than one complaint.

#### B. Long Term Studies

Long term data were compiled from two sources: Study 351, one year, double blind, randomized, parallel group, placebo controlled study that allowed concomitant antihypertensives, and open label, long term extension trials to the short term studies. The long term results were from 558 isradipine patients; 503 hypertensives, 42 angina and 13 CHF. Mean daily dose was approximately 12 mg/day, range 5 - 22.5 mg/day. Mean duration in long term trial was 60 weeks.

Analysis of laboratory data had 218/558 with results from a central laboratory. Descriptive statistics calculated mean change from baseline averaged over each 3 month interval and averaged over the entire long term period for all laboratory variables. When averaged over entire trial, the greatest mean changes were a 10% increase in alkaline phosphatase, 5% increase in SGOT, 7% increase in SGPT and 6% increase in glucose. The following newly-occurring abnormalities were observed in more than 5% of patients and >1% of total determinations. All other abnormalities were seen in < 5% patients.

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<u>Variable</u>	<u>Number Patients</u>	<u>%</u>	<u>No Determinations</u>	<u>%</u>
Glucose (High)	113/539	21.0	277/3607	7.7
Creatinine	35/533	6.6	63/3517	1.8
BUN	45/507	8.9	84/3315	2.5
Uric Acid	31/531	5.8	51/3353	1.5
Alkaline Phos	86/535	16.1	366/6485	5.6
LDH	43/523	8.2	61/6183	1.0
SGOT	76/541	14.0	158/6541	2.4
SGPT	79/523	15.1	212/6284	3.4

Adverse reactions were collected at each visit and analyzed according to three month intervals of the trial. The most frequent events considered possibly/probably drug related were headaches (18.5% patients), peripheral edema (18.5%), dizziness (13.3%), palpitations (8.4%), fatigue (8.1%), flushing (5.4%) and abdominal discomfort (5.4%). Sponsor feels that adverse events were transient in nature.

A total of 228 patients were discontinued from the long term trials, of whom 34 were randomized to placebo in study 351. A total of 50 (9%) isradipine patients withdrew due to adverse events, mainly due to the vasodilating effects eg headache and edema. Five patients died and 5 experienced a non fatal MI during these trials.

#### C. Deaths

A total of 12 patients, 7 isradipine, died during the studies. Three other patients died for non drug related causes a few weeks after completing the trials. Of the 12 deaths, 10 were cardiovascular related. Of the 7 isradipine patients, 4 were being treated for hypertension, 1 angina and 2 CHF. Four additional patients died in a long term phase of CHF study. These data are not included in overall data-base.

Sponsor concludes that isradipine is safe and well tolerated.

## ISRADIPINE - SAFETY UPDATE.

### Introduction

This report is an update on the safety of isradipine and includes the total number people exposed to the drug, duration of treatment, clinical laboratory tests, ECG data, adverse reactions, dropouts, deaths and serious non fatal events.

### A. U.S. Studies

The data in this section are based on NDA database and safety update database. Except for the long term data, results are presented separately for each individual database, as well as for the pool of the two databases. Data were derived from clinical trials performed in U.S. and include all data from third quarter 1988, a total of 53 trials.

The total number of patients includes those who received the drug in crossover studies (n = 159) plus those who were originally randomized to placebo or active control and later received isradipine in long term, open label studies (n = 179). The total number of patients and duration of treatment are shown below:

Total number isradipine patients	= 1880
Duration of treatment:	
2 weeks	= 1338
10 weeks	= 765
6 months	= 455
12 months	= 336
24 months	= 96
> 24 months	= 82

The total population randomized into NDA trials and safety update are listed below, by treatment.

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<u>Treatment</u>	<u>NDA</u>	<u>Safety Update</u> <u>All New Patients</u>	<u>Total</u>
Isradipine	811	731	1542
Placebo	151	311	462
Active Control*	185	241	426
Crossover Angina or Migraine Studies**	<u>116</u>	<u>45</u>	<u>161</u>
Total	1263	1528	2591

\* Propranolol, prazosin, HCT, captopril, enalapril

\*\* Not included in totals listed above. Comparative agents placebo and nifedipine.

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## B. Foreign Studies

The safety update includes 1321 isradipine patients treated overseas and data were prepared for overseas registration. These data are provided as an appendix to present worldwide clinical experience. There are no data for post-marketing experience as isradipine is not approved in any country to date.

### Materials and Methods

A complete list of studies reported in the NDA and Safety Update are listed in Tables 1 (biopharmacology) and 2 (Phase I, Phase II, angina and CHF studies), 3 (Phase III hypertension). The total number of patients randomized, number completing, number discontinued and reasons for discontinuation are listed by study. (In this report all Table numbers refer to the Tables in the Sandoz submission.)

(The numbers in Tables 1, 2 and 3 add up to 2591, which was the figure originally given as the total number of patients/subjects evaluated. The total of isradipine patients was given as 1880. In addition, the number of isradipine patients in above Table was 1542 + 161 angina/migraine. This equals 1703, not 1880. Dr Gonasun at Sandoz was contacted to resolve this issue. He stated that, in addition to the 1703 patients, there were 179 patients who were on active or placebo controls and subsequently entered into open label long term studies. These numbers were cited earlier on. This total now reaches 1882. Dr Gonasun said that two patients were entered twice and this should reduce the total to 1880. He was not able to identify these two patients. Tables 1, 2 and 3 include all patients in the studies and not only isradipine group. In addition, the Table above is also incorrect in that the isradipine patients do not total 1542 but 1542 + 179. This database is very confusing.)

### A. Randomized Double-Blind Studies

Descriptive statistics were used to summarize the demographic information of Phase III hypertensive trials.

Patients who withdrew from the studies due to ECG abnormalities are discussed in the Dropout Section. Patients with newly occurring abnormal PR-intervals, QRS duration, or QT intervals were determined for each randomized group. A newly occurring abnormality was one where all, pre-randomization values were within normal limits and at least one occurrence after randomization fell outside established upper limits of normal. The upper limits were set as follows:

PR-Interval	0.20 sec
QRS Duration	0.08 sec
QT-Interval	0.44 sec

In most of the studies, clinical laboratory analyses were conducted by a central laboratory, Metpath. An endpoint analysis of variance pooled across all studies was used to evaluate changes observed in the post-treatment lab evaluation compared to baseline pre-treatment evaluation. Serum glucose was evaluated for diabetics and non-diabetics separately. Newly occurring abnormalities were identified after making the following adjustments to the normal ranges:

Hematologic variables adjusted  $\pm$  15%  
 Urinalysis: SG and pH  $\pm$  15%  
 Normal range for all variables adjusted + 15%; sodium, potassium, chloride, calcium, inorganic phosphorous, albumin and glucose were also adjusted - 15%. BUN, creatine, glucose, and liver function tests were also determined based on values exceeding the following upper limits:

BUN	50 mg/dl
Creatinine	2.0 mg/dl
Glucose	150 mg/dl
SGOT & SGPT	100 IU/L
LDH	300 IU/L
Total Bilirubin	2.0 mg/dl
Alkaline Phosphatase	200 IU/L

A newly occurring abnormality was one that was not present at baseline or one that deteriorated by + 15% over baseline abnormality.

Adverse reaction frequencies were displayed. The displays were prepared separately for NDA and Safety Update and also pooled across databases according to treatment. The incidences of the most commonly occurring events in the isracipine group are shown by week of double-blind studies. A newly occurring adverse reaction was defined as one occurring for the first time during the double-blind period, or an adverse reaction (ADR) whose severity had increased over that reported during the single-blind period. Attempts were also made to determine dose response relationships.

Dropouts are identified as well as reasons for withdrawal.

#### B. Open-Label, Long-Term Studies

Descriptive statistics, as described, were used for long term studies as well.

### RESULTS

#### A. Randomized Short Term Studies

Tables 1, 2 and 3 list all the U.S. trials for this report. The total number of clinical trials were:

<u>Population</u>	<u>NDA</u>	<u>Safety Update</u>	<u>Total No Studies</u>
Biopharmacology Phases I, II, Angina, and CHF	14	2	16
<u>Hypertension</u>	17	10	24
<u>Total</u>	<u>6</u>	<u>7</u>	<u>13</u>
	<u>37</u>	<u>19</u>	<u>53</u>

Tables 4, 5, 6 and 7 summarize the study designs, objectives, population, patient numbers, investigators etc for all trials.

#### Demography

The demographic characteristics of all patients in the safety update for the hypertension studies are presented in Table 8. Table 9 presents the same data for all patients pooled. Reviewing the pooled data, there were 1645 patients in all the studies, of whom 934 received isradipine, 297 placebo and 414 active control. The mean age of the isradipine group was 54 years, range 22 - 91 years; the mean ages for placebo and active controls were 53 and 56 years respectively. The active controls were propranolol, HCT, prazosin, captopril and enalapril. About 65% were male and the race distribution was:

<u>Treatment</u>	<u>N</u>	<u>White</u>	<u>Black</u>	<u>Oriental</u>	<u>Other</u>
Isradipine	934	431 (46%)	457 (48%)	5 (5%)	41 (4%)
Placebo	297	131 (44%)	145 (48%)	0	21 (7%)
<u>Active</u>	<u>414</u>	<u>219 (52%)</u>	<u>194 (46%)</u>	<u>0</u>	<u>1(0.2%)</u>
<u>Total</u>	<u>1645</u>	<u>781 (47%)</u>	<u>796 (48%)</u>	<u>5 (0.3%)</u>	<u>63 (3%)</u>

Table 10 summarizes demographics of all patients discontinued from the studies due to ADRs. There are no apparent differences for each of the treatment groups compared to the total. (A few differences noted in the data for discontinued patients include duration of hypertension being 9 years for isradipine, 11 for active and 17 for placebo. The sex differences showed 56% of isradipine dropouts were male but only 1% placebo and 64% active control were male; 60% isradipine were white dropouts compared to 28% placebo and 57% actives.)

#### Doses Isradipine

Tables 4 - 7 present dose by study. In hypertension, dose range was 6.625 mg bid - 20 mg per day. Maximum daily dose used was 7.5 mg tid in angina and CHF studies. Dosage schedule was usually bid except for an once-a-day schedule in study 308 and tid with angina and CHF patients.

#### ECGs

Two types of analyses were done. The first listed patients discontinued due to an abnormal ECG and these are identified under "Dropout" section. The second method determined frequency on newly-occurring abnormalities for PR-intervals, QRS duration, and corrected QT-intervals above normal limits previously defined. Results are also summarized combining both databases of NDA and Safety Update. Results for these variables are found in Tables 11A, 11B, 11C through 13A, B and C. For hypertension studies, the incidence of PR-interval prolongations are similar to placebo (1.9% isradipine vs 2.6% placebo). In the angina and CHF studies, the incidence with isradipine is higher than with placebo.

Tables 12A - 12C summarize results of QRS duration. With the pooled database, there is a higher frequency of new abnormalities with isradipine compared to placebo, but the highest incidence was seen with HCT, prazosin and propranolol. Tables 13A - 13C present corrected QT-intervals. These results are similar to QRS duration.

#### Clinical Laboratory Tests

For the majority of studies, a central lab (MetPath) was used and endpoint analysis of variance tests were performed. The overall results are presented in Tables 14 A - 16 C for hematology, urinalysis and chemistry respectively.

For hematology, the only statistically significant change from baseline for isradipine was a 3-4% mean increase in total WBC count. This is borderline significant from placebo. There was a borderline significant change from baseline (-5.0%) for eosinophils. Tables 15A-C summarize data for urinalysis. No statistically significant changes were seen.

Blood chemistry results are presented in Tables 16 A-C. The statistically significant changes from baseline are presented in the attached Table. Sponsor states that none of the changes were regarded as clinically significant. However, there were statistically significant differences from placebo for a number of variables, especially BUN, SGOT and SGPT, alkaline phosphatase, sodium and potassium.

The frequency of newly occurring abnormalities are summarized in Tables 17 & 18 for hematology and urinalysis. Blood chemistry variables are presented in Table 19, except for certain parameters which are presented separately.

There are no major differences from placebo for any hematological variable, except WBC (2.6% vs 0.9% frequency; neutrophils 3.8% vs 0%; lymphocytes 5.8% vs 1.9%). There were no differences in urinalysis. Table 19 presents frequency of new lab abnormalities for blood chemistry. There were no major differences from placebo in the variables in this Table, except BUN (4.5% vs 1.9%). The effects on renal function parameters, glucose and liver function tests are presented separately in Tables 20A - 27C.

In case of renal function tests, the incidence of new abnormalities for BUN (Tables 20 A-C) and creatinine (Tables 21 A-C) was non significant. Tables 22 A - C present data on serum glucose. There is a higher frequency of elevated glucose with isradipine than with placebo but this incidence was not as high as with HCT or enalapril. The patients were divided into diabetics and non-diabetics and these data are presented in Tables 23 A - C. In non-diabetics, there was an overall group mean increase of 4.4 mg/dl and a maximum mean increase of 11.0 mg/dl. These increases are greater than for placebo but less than the pooled data for active controls. In the diabetic group, no differences were seen from placebo for mean values but the maximum increase was larger with isradipine.

PS

NDA DATABASE

<u>VARIABLE</u>	<u>BASELINE MEAN</u>	<u>MEAN CHANGE</u>	<u>± CHANGE</u>	<u>PAIRWISE COMPARISON VS. PCB.</u>
BUN-mg/dl	13.33	+0.58**	+4.3	p < 0.05
Glucose-mg/dl	106.7	+4.1*	+3.8	NS
Total Protein gm/dl	7.29	+0.08**	+1.1	NS
Albumin-gm/dl	4.17	+0.067***	+1.6	NS
Cholesterol mg/dl	216.1	+2.79*	+1.3	NS
Sodium-mEq/l	139.02	-0.31(*)	-0.2	p < 0.05
Potassium- mEq/l	4.16	-0.086***	-2.1	p < 0.01
Chloride- mEq/l	102.2	-0.286	-0.3	p < 0.05
Creatinine mg/dl	1.04	+0.021(*)	+2.0	NS
SGOT-IU/L	26.59	+1.22(*)	+4.6	p < 0.10
SGPT-IU/L	24.16	+0.74	+3.1	p < 0.05
Alkaline Phosphatase -IU/L	27.34	+2.32***	+8.5	p < 0.01

NS = not significant; (\*) = p < 0.10; \* = p < 0.05; \*\* = p < 0.01.  
\*\*\* = p < 0.001

**SAFETY UPDATE DATABASE**

<u>VARIABLE</u>	<u>BASELINE MEAN</u>	<u>MEAN CHANGE</u>	<u>% CHANGE</u>	<u>PAIRWISE COMPARISON vs. PCB.</u>
Ca <sup>++</sup> -mg/dl	9.53	+0.046*	+0.5%	NS
BUN-mg/dl	15.60	+0.54**	+3.5%	NS
Creatinine mg/dl	1.12	+0.018(*)	+1.6%	NS
Total Protein gm/dl	7.33	+0.064**	+0.9%	p < 0.10
Total Choles- terol mg/dl	225.2	+3.76**	+1.7%	NS
Sodium mEq/L	139.30	-0.40**	-0.3%	NS
Chloride mEq/L	101.5	-0.3(*)	-0.3%	NS
Alkaline Phosphatase IU/L	29.7	+1.54***	+5.2%	NS

NS = not significant; (\*) = p < 0.10; \* = p < 0.05; \*\* = p < 0.01  
\*\*\* = p < 0.001

Tables 24 a - C present data on alkaline phosphatase. There were no significant changes in this parameter. SGOT values are found in Tables 25 A - C and SGPT in 26 A - C. In the NDA studies, the incidence on new SGOT abnormalities with isradipine compared to placebo was 2.4% vs 1.1%; in safety update it was 1.5% vs 0.6% and overall 1.9% vs 0.8%. The incidence with propranolol was 2.5%. The corresponding numbers for SGPT were 2.6% vs 1.1% (NDA), 1.5 vs 0.6 (Safety) and 2.0 vs 0.8 (All); the propranolol incidence was 3.8%.

Incidence of newly occurring abnormalities in any of the liver function tests are shown in Tables 27 A - C. The overall incidence was 5.1% vs 2.6% for placebo and 10.0% propranolol. This group includes SGOT, SGPT, LDH, bilirubin, alkaline phosphatase.

Sponsor concludes that the results of the clinical laboratory tests for the new studies were similar to those in the NDA with one exception. The abnormal liver function tests seen in study 310 were not observed in later trials.

#### ADVERSE REACTIONS

Sponsor has tabulated all ADRs that were considered possibly or probably drug related. Those considered definitely not drug related are not listed. The ADRs are listed in sponsor's Tables as follows:

<u>Treatment Group</u>	<u>All Newly Occurring ADRs</u>	<u>All Newly Occurring Possibly/Probably Drug Related ADRs.</u>
Isradipine	28 A	28 B
Placebo	29 A	29 B
Active Controls	30 A	30 B

These Tables present frequency of ADR for NDA studies and Safety Update separately as well as pooled across studies. These ADRs included those volunteered by the patients as well as those elicited by inquiry. In most cases, the frequencies of ADRs are the same in NDA and Safety Update except for the following.

<u>ADR</u>	<u>NDA</u> <u>N = 410</u>	<u>Safety Update</u> <u>N = 524</u>	<u>Pooled Database</u> <u>N = 934</u>
Rash	2.2	1.0	1.5
Chest Pain	2.9	0.0	1.7
Edema	10.0	5.0	7.2
Palpitations	4.6	3.4	4.0
Tachycardia	2.7	0.6	1.5
Abdominal Discomfort	2.7	1.0	1.7
Fatigue	5.4	2.7	3.9
Headache	15.9	12.0	13.7
Flushing	4.9	0.8	2.6
<b>Total No Patients with at least one ADR</b>	<b>48</b>	<b>36</b>	<b>41</b>

(It was difficult reviewing these Tables as the same term appears under different headings in different places e.g chest pain is found under Musculo-Skeletal, Cardiovascular and Gastro-Intestinal. Fever is seen under Miscellaneous and CNS etc. Dr Gonesun at Sandoz was contacted and he was to investigate and send an explanation. In addition, similar conditions are reported using different terminology e.g ache generalized, arm/leg pain, backache/pain, feet/hand pain, flank pain, joint pain, leg pains etc. It is strongly recommended that these terms be condensed and presented to give a better idea of actual incidence of events.)

Sponsor feels that the lower incidence of events seen in Safety Update is due to lower dose used, slower titration and decrease in events as patients continue using the drug in long term studies. The NDA studies revealed that a dose of 2.5 - 5.0 mg bid was effective and that 2 - 3 weeks treatment was required for full effect, indicating a titration interval of 2 - 3 weeks. The most frequently reported ADRs are listed below. These data are for pooled results. (As mentioned, similar conditions were reported under different categories and using different terminology. This may lead to underestimation of events.)

Percentage of Patients with ADRs

<u>ADR</u>	<u>Isradipine</u> N = 934	<u>Placebo</u> N = 297
Rash	1.5	0.3
Chest Pain	1.7	2.4
Edema	7.2	3.0
Palpitations	4.0	1.4
Tachycardia	1.5	0.3
Abd. Discomfort	1.7	1.7
Diarrhea	1.1	2.0
Nausea	1.8	1.7
Vomiting	1.1	0.3
Pollakiuria	1.5	0
Dizziness	7.3	4.4
Fatigue	3.9	0.3
Headache	13.7	14.1
Weakness	1.2	0
Flushing	2.6	0

These data are presented by the sponsor, using Table 28 B. However, if same and similar terms from different categories are combined, the numbers will change, eg chest pain reported in 5 different places would be 0.54 + 0.21 + 1.71 + 0.11 + 0.21 = 2.78 instead of 1.7 as stated above. Similarly, dyspnea is cited as 0.21% but it is found in three places, adding up to 1.3. It is not, however, clear whether these are the same patients and whether it is an acceptable procedure to simply add the cases together. Sponsor should be requested to condense terms, categorise under one body system and then present the actual incidence.

## DROPOUTS

A total of 2591 patients were randomized into all studies. A total of 446 (17%) were discontinued prior to completion. Reasons for withdrawals were:

<u>REASON</u>	<u>NUMBER</u>	<u>% TOTAL</u>
Adverse Reaction	131	5.1
Non Drug Related Illness	35	1.4
Uncooperative	52	2.0
Protocol Violation	37	1.4
Ineffectiveness	92	3.5
Other Reasons	99	3.8

There were 82 (5%) of all hypertensive patients withdrawn due to ADRs of whom 49/934 (5.2%) were receiving isradipine. The patients withdrawn for ADRs are listed in Tables 40 A and B. Most patients apparently withdrew for a variety of complaints occurring simultaneously. The most common events causing withdrawal were:

<u>ADR</u>	<u>Number of Patients Reporting Complaints</u>
Headache	18
Edema	8
Tachycardia	3
GI Complaints	4
Dizziness	6
Palpitations	8
Fatigue	3
Vomiting	4
Nausea	4
Flushing	3

It was found that there was a dose relationship for patient withdrawal.

	<u>2.5 mg</u>	<u>5.0 mg</u>	<u>10 mg</u>	<u>15 mg</u>	<u>20 mg</u>
Total Symptoms	4	30	52	10	9
Total # Patients	2	14	23	5	5

Majority of patients withdraw at a dose up to 10 mg/day

Table 41 lists patients in the Safety Update who discontinued for reasons other than adverse reactions. (It seems to the reviewer that some of these patients withdrew due to events that could be classified as ADRs but possibly were recorded by the investigators as not drug related e.g headache, angina, asthma, GI upset with vomiting and diarrhea etc). In hypertension studies 10 isradipine patients were lost to follow up, 1 had high blood pressure (? therapy failure), 1 CHF and 8 non drug related reasons.

Sponsor states that the most common events eg edema, palpitations, headache are related to the vasodilatory properties of isradipine. Sponsor says that even for edema, palpitations, dizziness and fatigue, there are little differences from placebo. However, in all cases the incidence with active drug is at least twice that for placebo.

Table 31 lists the number of patients who experienced at least one ADR rated as severe. Approximately 8% of isradipine patients reported at least one severe ADR; 33 patients were discontinued due to ADRs. The most common of the severe reactions was headache (3%) followed by dizziness, pain or backache, fatigue, edema, nausea, leg cramps, chest pain, indigestion, palpitation and toothache.

Incidence of ADRs by week of study is found in Tables 32 A - 34 B. (It should be noted that edema incidence increases over time, headache decreases after 7th week and the other events remain constant. These data are not consistent across all protocols.)

Two studies employing a fixed dose, protocols 301 and 330. The doses used were 0.625 mg, 1.25, 2.5, 5.0, 7.5, and 10.0 mg bid. To assess a dose response relationship for adverse experiences, these protocols were reviewed (Table 35 - 39). After one week, the highest incidence of events was seen at the 5 mg bid dose; week 2 there was a dose response relationship to 7.5 mg bid especially for edema and fatigue. Similar results are seen at week 3 for 10 mg bid. For weeks 5 & 6, the incidence of ADRs is higher at doses > 10 mg/day.

Sponsor next looks at the incidence of ADRs after the first week at each dose level. The most frequent ADRs show a dose response after the first week at each dose level, especially for doses > 10 mg/day. These results, using sponsor's Table, are shown below:

ADR	% Patients						
	Dose Per Day Isradipine						
	1.25 mg	2.5 mg	5 mg	10 mg	15 mg	20 mg	Placebo
Chest Pain	0	0	1.2	4.9	0	0	0
Edema	0	1.9	1.8	0	8.3	8.6	1.0
Palpitations	0	0	0.6	2.4	5.6	5.7	0
Tachycardia	0	0	0	2.4	2.8	0	1.0
Fatigue	0	1.9	1.2	0	8.3	8.6	1.0
Dizziness	1.9	0	4.1	0	0	0	2.0
Headache	7.7	1.9	4.1	7.3	8.3	2.9	4.0
Flushing	0	0	1.8	2.4	2.8	2.9	0
<b>Any Vasodilating ADR</b>							
	9.6	3.8	10.5	14.6	19.4	14.3	7.1

There appears to be a dose response relationship for edema, palpitations, fatigue etc. Sponsor maintains that the incidence of ADRs decreases over time for 5 mg and 10 mg/day groups. As efficacy may be achieved with 10 mg/day, it is possible that the overall incidence of ADRs would be reduced.

### LONG TERM STUDIES.

Table 42 A summarizes those studies included in the assessment of long term safety. These data were obtained from the open label, long term extension studies following the short term efficacy studies and study 351, a one year, double-blind, placebo controlled trial. The isradipine patients from the short term studies had their short and long term data combined to supply continuous safety information. At the time of this report, patients were still continuing in the long term studies.

Demographic characteristics may be found in Table 42 B. There were a total of 558 patients in the long term trials, with a mean age of 57 years (range 19 - 82). About 80% were male, 64% were white and 33% black. The dose administered ranged from 5 - 22.5 mg per day; hypertension dose was 2.5 - 10 mg bid but some angina patients received 7.5 mg tid. The mean daily doses of isradipine administered for each three month interval was:

<u>Months of Study</u>	<u>N</u>	<u>Mg/Day</u>
< 1 - 3	553	10.3
4 - 6	486	12.1
7 - 9	452	12.2
10 - 12	407	12.2
13 - 15	300	12.4
16 - 18	176	12.9
19 - 21	154	12.9
22 - 24	142	13.1
25 - 27	77	14.1
28 - 30	23	18.5
31 - 33	18	19.1
34 - 36	14	19.6
> 36	<u>10</u>	<u>19.8</u>
Overall Mean	554	11.6

Sponsor states that the mean daily doses are higher after two years because most of the patients were in angina protocols which required a higher dose. (It would be interesting to obtain a breakdown of how many were angina and how many hypertension patients; also, were the hypertension patients intentionally discontinued after two years and why were the angina patients continued past this period.)

Cumulative daily dose is shown graphically in Figure 1 and number of patients by month in Figure 2. The mean duration of treatment during long term trials was 60.8 weeks. A total of 455 patients completed 6 months, 336 completed 12 months and 96 completed 24 months.

### Clinical Laboratory Tests

A central lab, MetPath, performed analyses of 218/558 (39%) of patients. Descriptive statistics describe for MetPath data both mean changes from baseline averaged over each 13 week period and mean changes

averaged over the entire treatment period. Due to the small number of patients per center, similar analyses were not done of those centers using other labs. In addition to mean changes, frequency of newly occurring abnormalities was determined.

Data are presented in the following Tables: hematology (Table 43), urinalysis (Table 44) and blood chemistries (Table 45). There were no relevant changes noted in the hematology or urinalysis data. In the chemistry analyses, the following variables demonstrated changes from baseline.

<u>Variable</u>	<u>Baseline Mean</u>	<u>Mean Change From Baseline Averaged over Entire Trial</u>	<u>Range of Mean Change Averaged over 3 Month Interval</u>	
			<u>Min</u>	<u>Max</u>
BUN mg/dl	13.7	+ 0.6	+ 0.5	+ 3.5
Glucose mg/dl	106.2	+ 6.2	+ 5.9	+ 28.6
Cholesterol	212.0	+ 5.6	+ 2.9	+ 24.5
Alk Phosph	27.9	+ 2.8	+ 2.0	+ 5.4
SGOT IU/L	26.1	+ 1.4	- 1.2	+ 2.5
SGPT IU/L	23.7	+ 1.7	- 0.2	+ 5.0

(In addition to this Table, supplied by sponsor, it may be seen from Table 45 that LDH had changes of 7.3 IU at 24 months and 15.8 IU at 27 months but mean change over entire study was only 0.7. Similarly, the early changes seen for BUN were small but at 24 months the mean change was 2.6 mg/dl and at 30 months it was 3.5 mg/dl. Over entire study it was only 0.6 mg/dl. It seems obvious, therefore, that averaging changes over the entire study is not the ideal way of evaluating change especially if the changes occur with long term therapy.)

Newly Occurring abnormalities were defined as previously: hematology  $\pm 15\%$ , urinalysis  $\pm 15\%$  and chemistry  $\pm 15\%$  except calcium, inorganic phosphorous, glucose, albumin, sodium, potassium and chloride where adjustments were also  $- 15\%$ . Results are found in Tables 46 (hematology), 47 (urinalysis) and 48 (chemistries). The newly occurring abnormalities in the first two groups were in the range of 4% of patients.

Chemistry changes were seen in  $< 5\%$  of patients for majority of variables. Those variables with an incidence of  $> 5\%$  of patients and  $< 1\%$  determinations were:

<u>Variable</u>	<u>Number Patients</u>	<u>%</u>	<u>No. Determinations</u>	<u>%</u>
Glucose	113/539	21.0	227/3607	7.7
Creatinine	35/533	6.6	63/3517	1.8
BUN	45/507	8.9	84/3315	2.5
Uric Acid	31/531	5.8	51/3353	1.5
Alkal Phos	86/535	16.1	366/6485	5.6
LDH	43/523	8.2	61/6183	1.0
SGOT	76/541	14.0	158/6541	2.4
SGPT	79/523	15.1	212/6284	3.4

Sponsor states that, with the exception of BUN, the results are similar to those presented in the NDA. The number of patients with an elevated BUN increased from 4.2% to 8.9%. Values in excess of 100 IU/L for S<sub>CR</sub> and SGPT were seen in 20 and 23 patients respectively.

#### ADVERSE REACTIONS-

Tables 49 and 50 present number of patients with ADRs. Table 49 presents data by body system, Table 50 by event. Similar data are found in Tables 51 and 52 for those events considered possibly or probably drug related. Data are presented in 3 month intervals as the number of new patients reporting at least one ADR each 3 month period. Sponsor discusses only those patients considered possibly or probably drug related.

A total of 378/558 (68%) patients reported at least one ADR with 269, (48%), reporting at least one reaction during first 12 weeks. About 41% report ADRs on a recurring basis. The most frequent reports, in decreasing order, were found in the following body systems: CNS, cardiovascular, GI, autonomic, urogenital, musculoskeletal, skin, miscellaneous, respiratory, hematological and endocrine. ADRs reported at least once by at least 5% of patients were:

Edema 18.5%, headaches 18.5%, dizziness 13.3%, palpitations 8.4%, fatigue 8.1%, abdominal discomfort 5.4% and flushing 5.4%. Majority of patients report their event within first 3 months and the recurring basis decreases with time. Sponsor suggests that the events are transient but it could also be that patients become "used" to the event and no longer report it. As mentioned in the summary on short term studies, similar events are reported using different terminology and it is possible that the overall incidence of certain events would be higher if these terms were consolidated. This is especially the case in musculoskeletal system. It is also noted that there is an increased number of events in respiratory system especially cough, chest congestion, rales, dyspnea and pulmonary edema. This is not mentioned in sponsor's summary. If the various skin conditions were combined, the incidence would increase here as well.

Protocol 351 was a placebo controlled, one year study and these data were analyzed separately in Tables 53 - 56 for the placebo patients only. About 36% of placebo patients reported at least one ADR with 17% reporting on a recurring basis.

Sponsor states that the ADRs reported here are similar to those reported in NDA submission. Sponsor concludes that isradipine is well tolerated over long-term administration.

#### DROPOUTS

Table 57 lists all patients who were discontinued from the long term studies due to ADRs. Most complaints were related to vasodilating properties and usually more than one symptom was reported at time of withdrawal.

A total of 50/558 (9%) were withdrawn due to ADRs. Five placebo patients, 5.8%, withdrew from protocol 351. Majority of these withdrawals have been previously submitted.

One patient withdrew due to breast pain and gynecomastia. The symptoms were present during most of the study but as the reactions got worse, he was withdrawn after 21 weeks. Another patient developed abnormal lab values after 16 weeks (elevated GGTP, SGOT and SGPT). Values returned to normal one month after withdrawal. One patient was admitted to hospital after 14 - 15 weeks in the study with ataxia, diplopia and leg weakness, which may have been related to a lesion in the right brain and infection of CSF. Patient died but no autopsy was performed.

Table 58 lists all patients who were discontinued from the studies since submission of NDA for reasons other than ADRs. The table below summarizes this information for the entire long term experience included in the Safety Update for isradipine patients.

<u>REASON</u>	<u>NDA DATA</u>	<u>NEW DATA</u>	<u>TOTAL</u>
Ineffectiveness	12	6	18
Lost to Follow Up	27	36	63
Uncooperative	11	7	18
Non Drug Related			
Illness	9	12	21
Death	3	2	5
MI	2	2	4
Myocarditis	1	0	1
Miscellaneous	7	10	<u>17</u>
Total			147

#### Deaths and Serious Non-Fatal Events

There were a total of 12 deaths during the program. An additional three patients died a few weeks after completing the studies. One patient was found dead of unknown causes two weeks after completing hypertension protocol; a second died 2 months after withdrawal due to a malignant lymphoma and the third case was described previously (ataxia, weakness and brain lesion.).

The causes of the 12 deaths are summarized below:

<u>Treatment</u>	<u>Cause of Death</u>
Isradipine	Myocardial infarction
Isradipine	Acute pulmonary edema; cardio-pulmonary arrest
Isradipine	Suicide
Isradipine	Myocardial Infarction
Propranolol	Cardiac arrest secondary to arrhythmia
Placebo	Sudden Death

Isradipine	Severe cardiomyopathy, ventricular arrhythmia or embolic MI
Isradipine	Sudden Death
Placebo	Cardiac & Respiratory Arrest
Placebo	End stage ischemic heart disease with CHF and ventricular fibrillation
Isradipine	Cardiac Arrest
Placebo	Automobile accident

Non fatal serious events included 7 patients who experienced a MI, 1 pulmonary edema, 1 respiratory arrest, 1 myocarditis, 3 surgery for aortic aneurysms.

### CONCLUSIONS

Sponsor concludes that isradipine is a safe and well tolerated drug.

### COMMENTS

1. The sponsor should be requested to condense the terms used in the adverse experience data. A number of terms are so similar that they are probably the same clinical entity. Combination of these terms might change the overall incidence of adverse events.
2. Incidence of laboratory abnormalities is given over the length of the study. This confuses the issue in that a low initial value with gradual increase would not show the possible increasing trend of the abnormality. Examples of this are LDH and BUN
3. There appears to be a relatively high incidence of respiratory events. This is not alarming but a closer look should be given to possible drug relationship, especially when terms are condensed.
4. No ECG data are available for long term study.
5. There appears to be a definite effect on serum glucose both in diabetics and non-diabetics.
6. No mention is made in the long term studies as to which ADRs, if any, were reported as severe.

THE MULTICENTER EVALUATION OF THE SAFETY AND EFFICACY OF PN 200-110  
ADMINISTERED ONCE DAILY IN THE TREATMENT OF HYPERTENSION COMPARED TO  
PLACEBO.

PROTOCOL NUMBER 308

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DATES OF STUDY June 1986 to July 1987

OBJECTIVE

To determine the safety and efficacy of PN 200-110 administered once daily in doses 5 - 20 mg/day in treatment of patients with mild to moderate hypertension.

DESIGN

Double-blind, parallel group, placebo controlled, randomized, multicenter study.

POPULATION

Outpatients, 18 years and over, with a diagnosis of essential hypertension were enrolled. For randomization into double-blind period, patients were required to have a supine diastolic blood pressure (SDBP) of > 100 mm Hg and < 120 mm Hg at end of placebo washout period.

Exclusion criteria included secondary hypertension, malignant hypertension, angina pectoris, MI in previous 6 months, arrhythmias, investigational drug in previous 4 weeks, medication that could interfere with evaluation of test product, CHF, bradycardia, AV block > 1st degree, alcohol or drug abuse, pregnant or lactating females, any concurrent illness that could obscure evaluation of test drug and certain specified medications.

## MEDICATIONS

PN 200-110 5 mg or placebo capsules.

## STUDY PLAN

During a three week placebo washout period, all anti-hypertensives were discontinued. Patients with a SDBP 100 - 120 mm Hg were double-blind randomized into a six week active medication period. The single blind washout period could be extended by an additional two weeks if necessary. A decreasing trend in blood pressure during the washout period disqualified the patient. This was defined as an average SDBP for each visit of washout which was less than that of the previous visit and a baseline SDBP than was decreased by more than 10 mm Hg when compared to first visit.

During placebo period, all patients received 1 placebo capsule per day, before 12.00 noon. Following this washout period, patients were randomized, after being stratified according to their SDBP: 100 - 105 mm Hg and > 105 mm Hg. Patients entering the six week double-blind phase received either placebo or PN 200-110 5 mg/day, to be taken before noon, except on day of clinic visit when medication was taken after blood pressures had been recorded. Each visit was scheduled prior to 1.00 pm, and was to be within 23 to 25 hours following previous dose. Dosing was adjusted for each patient so that they were able to visit the clinic 23 - 25 hours post dose.

Initial dose of drug was 5 mg/day for 1 week. If at end of this period, SDBP was < 95 mm Hg with at least 10 mm Hg decrease from baseline, dose remained unchanged. If SDBP was < 95 mm Hg, dose was increased at week two to 2 x 5 mg capsules/day. If at end of second week, BP was not < 95 mm Hg, dose was increased to 3x 5mg once daily and, if necessary to 4 x 5 mg/day at week four. Dose remained unchanged for weeks 5 and 6, unless an adverse reaction necessitated a decrease in dose. At no time could dose be less than 5 mg or more than 20 mg/day.

## EVALUATIONS

Treatment schedule is shown in Table 2. On the day of visit, blood pressures were to be recorded approximately 24 hours after last dose. Laboratory evaluations were done at a central laboratory except for Dr Kirkendall's center.

## STATISTICAL METHODOLOGY

This is discussed in the report. In addition to evaluating actual decreases in blood pressures, categorical analyses were also performed. The definitions for the groups is the same as for previous studies.

## RESULTS

A total of 208 patients were entered into the study of whom 170 were randomized into double blind period. There were 84 in PN 200-110 group and 86 in placebo group. Table 4 gives number of patients randomized by center; the six centers each enrolled from 14% to 20% of total.

Of the 170 patients, 124 were considered valid for efficacy (60 active, 64 placebo); there were 37 partially valid (17 active, 20 placebo) and 9 invalid (7 active, 2 placebo). The reasons for declaring data partially valid or invalid are given in Table 5. The main reasons for declaring data partially valid were:

Reason	PN 200-110	Placebo
Study Drug Ineffective	4	11
Adverse Reactions	5	4
Protocol Violations	3	1
Other	5	4

Reasons for the 7 invalid PN patients were: noncompliant due to headaches and other reactions 4; lost to follow up 2; patient request 1. The two placebo reasons were elevated SGOT/SGPT; and blood pressure exclusion.

The number of valid patients by week were:

Treatment	n =	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
PN 200-110	84	77	75	71	69	65	60
Placebo	86	84	82	80	77	69	64
Total	170	161	157	151	146	134	124

Table 6 presents demographic data. The mean age was 55 years (27 - 90 years); 25% were white and 62% black; 45% were male. There were no statistical differences between groups at baseline. The mean once daily dose is shown in Table 7. For weeks 5 and 6, mean daily dose was 14.4 mg which was similar to dose at week 4 (14.2 mg). Prescribed average dose at weeks 5 and 6 for valid patients was:

Once Daily Dose	PN 200-110 (n=60)	Placebo (n=64)
1 capsule	7 (11.7%)	3 (4.7%)
2 capsules	11 (18.3%)	5 (7.8%)
3 capsules	21 (35%)	7 (10.9%)
4 capsules	21 (35%)	50 (78.1%)

For active group, 70% were titrated to 15 - 20 mg/day while 78% placebo received 4 capsules daily.

Of 893 visits recorded for 170 patients, mean post dose time for recording blood pressures was 24.9 hours (median 24.1). About 92% of visits were recorded between 23 and 25 hours post dose. Of 70 visits not meeting this time, 11 were invalid/partially valid due to reasons other than post dose considerations.

#### Efficacy Interactions

Table 9 presents results for treatment x investigator, treatment x time and treatment x time x investigator interactions. The only blood pressure variables to display significant interactions were supine and standing systolic pressure which had significant treatment x time

interaction. Sponsor states that this was due to an increase in systolic pressure in placebo group from weeks 5 to 6 and a decrease in PN 200-110 group. This was consistent in all centers and did not prevent pooling of results. There was also a significant interaction between treatment x investigator for supine and standing pulse rates.

#### EFFICACY - BLOOD PRESSURE AND PULSE RATE

Data from 170 patients were analyzed; only 124 completed the six weeks of double-blind treatment (valid patients); 37 were regarded as partially valid patients. Efficacy was analyzed by parametrically examining within group mean changes from baseline (Week - 1) for each treatment, and comparing the changes from baseline between the two groups. Second type of analysis was by categorizing blood pressure response into four groups as in previous studies.

##### Weeks 1 and 2

Tables 10 and 11 summarize results of first two weeks titration period. Results for change from baseline for SDBP were:

Treatment	n =	Week 1	n =	Week 2
PN 200-110	77	- 5.3***	75	- 8.7***
Placebo	84	- 5.0***	82	- 4.8***

The differences between the groups at week 2 were \*\*\*. After one week both groups produced equivalent and statistically significant reductions in supine and standing blood pressures, 24 hours after dosing. At week 2, there was a greater decrease with active drug than with placebo for all blood pressure variables.

##### Weeks 3 and 4

Tables 12 and 13 present results for these two weeks. The SDBP results, 24 hours post dose, are shown below:

##### Mean Change from Baseline

Treatment	n =	Week 3	n =	Week 4
PN 200-110	71	- 8.4***	69	- 11.0***
Placebo	80	- 3.9***	76	- 4.6***

The between group differences were \*\*\*. There were statistically significant between group differences for all blood pressure variables with the greatest difference being found in supine diastolic blood pressure at week 4. The decreases in standing position were less than in supine position.

## Weeks 5 and 6

These results are found in Table 14. PN 200-110 produced a statistically significantly greater reduction in blood pressure than did placebo, 9/5 mm Hg supine and 7/7 mm Hg standing. Decrease in SDBP was 11.4 mm Hg active drug and 6.4 mm Hg placebo. Table 15 presents data at endpoint for valid and partially valid patients during weeks 5 and 6. These results are similar to those for valid patients only. The between group differences were clinically and statistically significant for all blood pressure variables.

Categorical responses for these two weeks were:

Treatment	n =	1	2	3	4
PN 200-110	60	19 (32%)	14 (23%)	16 (27%)	11 (18%)
Placebo	64	10 (16%)	10 (16%)	18 (28%)	26 (41%)

Fifty five percent of active group had at least 10 mm Hg reduction in blood pressure compared to 32% placebo.

## All Patients - Endpoint Analysis

Table 16 summarizes endpoint analyses for all patients. SDBP was decreased by 10.3 mm Hg active group and 3.8 mm Hg placebo.

## Graphic Displays

Figures 1 - 6 display mean changes from baseline for each week of study. Maximum reduction in blood pressure occurred at week 4.

## **SAFETY**

Table 18 list changes in physical examination. There were 11 active patients (16.7%) with newly reported changes in their physical examinations compared with 11 (13.4%) placebo. Five active group had mild edema of extremities as well as two placebos. Cardiovascular findings are reported in Table 20. There were 13 (16.5%) active and 5 (5.9%) placebo patients with new abnormalities. In active group, there was a higher incidence of murmurs and edema. Chest x-ray abnormalities at baseline are found in Table 21.

## ECG Changes

These are presented in Tables 22 and 23. There were 17/79 active patients with changes compared to 17/82 placebo. The majority of changes included a variety of wave changes, sinus bradycardia, conduction defects and premature beats. Summary of comparative results using only completed patients showed no clinically significant differences between groups with regard to quantitative ECG variables (Table 24).

There were no significant changes in body weight, temperature or respiratory rate (Tables 25 - 27).

## Clinical Laboratories

Specimens were assayed at Metpath for 5 centers and Path Lab for Dr Kirkendall's center. Comparative data are found in Tables 28 - 30.

There were no major differences in hematology or urine analyses. Active group had a statistically significant reduction in WBCs from baseline. Blood chemistries (Table 30) show significant increases in alkaline phosphatase and SGOT for placebo. The values increased in active group as well. Tables 31 - 33 summarize newly occurring or worsening abnormalities. None of the changes appeared clinically relevant.

## DROPOUTS

The list of dropouts was presented in Table 5. A total of 44 (26%) patients discontinued following randomization; 23 were in PN group and 21 placebo group. Four active and 11 placebo withdrew due to ineffectiveness of treatment. Nine active and 4 placebo were due to adverse reactions, as previously discussed.

## ADVERSE REACTIONS

The number of newly occurring events by week is shown below:

Week of Study	PN 200-110	Placebo
1	17/84 (20%)	13/86 (15%)
2	21/75 (28%)	25/82 (31%)
3	21/71 (30%)	24/82 (29%)
4	24/69 (35%)	19/77 (25%)
5	18/67 (27%)	10/71 (14%)
6	17/59 (29%)	10/65 (15%)

A listing of all ADRs is found in Table 35. Table 36 compares the two groups, adjusted for baseline effects. Fifty seven percent of active group reported at least one new event compared to 47% placebo. The most frequently reported events in active vs placebo were:

Adverse Reaction	PN	Placebo
Headache	34.5%	17.4%
Weakness	7.1%	0%
Palpitations	8.3%	1.2%

Four patients in each group had edema; dizziness occurred in 6 active and 5 placebo patients and flushing in 3 active 0 placebo.

## DISCUSSION

Total 170 patients randomized. PN 200-110 was administered once daily in dose 5 - 20 mg daily. Blood pressure was significantly reduced compared to baseline and the differences from placebo were also significant.

## COMMENTS

1. This was a well designed, well reported study.
  2. PN 200-110 was effective in lowering elevated blood pressures when administered once daily. The incidence of side effects appears high (55%)
  3. Once again, no analyses were done with stratification of patients.
  4. Except for lack of peak/trough data, this study should be sufficient for approval of once a day claim. This also depends on whether the one study is sufficient for approval.
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## ISRADIPINE - SAFETY UPDATE 2

NDA # 19,546

### Introduction

This report updates the safety profile for isradipine, NDA 19,546, subsequent to the NDA submission of November 26, 1986 and safety update 1 (SU-1), November 22, 1988. Safety update 1 presented data from the NDA database plus new data to time of submission. The data in safety update 2 (SU-2) is minimal and has not been pooled with SU-1. Total exposure to isradipine is, however, calculated based on pooling the new data with those in SU-1. The items addressed in both updates include:

- Number of new patients exposed to isradipine and total exposure from SU-1 and SU-2
- Total number of patients by duration of treatment with isradipine
- Clinical laboratory tests
- ECG variables
- ADRs
- Dropouts
- Deaths and serious non fatal events

### A U.S. Studies

The cut-off date for this report is June 30, 1989 and data from 281 randomized patients were evaluated; this is an increase of 11% in the total number since SU-1. Of the 281 patients, 172 were randomized to receive isradipine; an additional 13 received drug for the first time during long term phase after receiving a control drug during the double blind phase. This, therefore, represents an increase of 9.8% in the total number randomized to receive isradipine, i.e. intent-to-treat. Some patients were entered into crossover trials and discontinued prior to receiving test drug in the second period of the crossover design, only 181/185 actually received isradipine.

New long term data were analyzed for this report, including data from 47 patients whose long term data were not included in SU-1 and 31 who had some data in SU-1 and additional data since the previous cut-off date.

Data in this analysis are only from US studies with the immediate release formulation and conducted by Sandoz. Data from studies conducted by [REDACTED] are not included as those studies are still ongoing. Except for data from 72 patients which were not ready for analysis, the analyses included all data from completed or nearly completed trials sponsored by Sandoz.

Patients currently receiving immediate release isradipine in ongoing trials include (1) 600 patients, half of whom are receiving isradipine, randomized to a 3 year, double blind, HCT controlled MIDAS trial, study 360 sponsored by Sandoz under IND [REDACTED] (2) 48 patients enrolled as of August 15, 1989 into study 340, an extensive clinical experience "Phase 3.5" trial in hypertension being conducted by a contract organization, [REDACTED] under IND [REDACTED] and (3) those in four studies ongoing under [REDACTED] sponsorship IND [REDACTED] in which 468 patients have been randomized into double blind [REDACTED]. No data are presented as all these trials are ongoing.

Clinical trials have been completed with other dosage forms of isradipine, including 4 studies with I.V. form and 18 studies with modified release forms of the drug. With IV (IND [REDACTED]), 88 subjects have received isradipine in doses up to 2.0 mg. For the various modified release forms (IND [REDACTED] and [REDACTED]) approximately 394 subjects have been randomized with about 281 receiving isradipine. All trials are completed but data not included as the immediate release formulation was not used. An additional study with IV is ongoing by [REDACTED] (IND [REDACTED]) with only one patient randomized.

In the case of the 72 patients whose data were excluded from analysis, 52 were randomized into hypertension trials, 9 into CHF trials and 11 angina. These case report forms were collected subsequent to June 30, 1989.

The total number of patients randomized and included in both safety reports and scheduled to receive isradipine (intent-to-treat) and number actually receiving drug, by duration are summarized below. The difference between intent-to-treat and actual is due to some patients being randomized into crossover trials and discontinuing prior to receiving test drug.

	<u>SU-1</u>	<u>SU-1 and SU-2</u>
Total No Randomized	1880	2065
Total Actually Treated		
< 2 Weeks	1358	2039
2 Weeks or More	1338	1510
10 Weeks	765	880
6 Months	455	485
12 Months	336	367
24 Months	96	98
> 24 Months	82	84

The total population randomized into the trials according to treatment group are listed below.

	<u>SU-1</u>	<u>SU-2</u>	<u>Total</u>
Isradipine (Parallel Studies)	1542	104	1646
Placebo, (Parallel Studies)	462	21	483
Active Controls (Parallel Studies)	425	98	514
Crossover Trials	161	68	229
<b>Total</b>	<b>2591</b>	<b>291</b>	<b>2872</b>

#### B-- Foreign Studies

A summary of data for 1321 patients from foreign studies was included in SU-1. Data from an additional 590 [REDACTED] patients are included in a separate section.

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### C Worldwide Approval/Marketing Experience

The results are minimal and are presented separately.

### Materials and Methods

These are similar to those discussed in the original NDA submission. Except where indicated, data from SU-2 are not pooled with those from SU-1.

A list of US studies involved in SU-2 (excluding long term studies) is presented in Table 1.

study 326 involved normal volunteers and 331, 352 and 354 were comparative trials assessing effects of isradipine vs enalapril, captopril and diltiazem in hypertension.

---

### Randomized Double Blind Studies

Descriptive statistics were used to summarize the demographic information of patients in Phase III hypertension studies. In addition to identifying patients discontinued due to ECG abnormalities, sponsor determined the number of patients with newly occurring abnormal PR intervals, QRS durations or QT intervals for each group. The upper limits of normal were set at:

PR-interval	0.20 sec
QRS Duration	0.08 sec
QTc Interval	0.44 sec (corrected for heart rate)

Clinical laboratory tests were conducted by a central lab (Metpath) for most Phase II hypertension studies in SU-1. An endpoint analysis of variance was used to evaluate mean changes from baseline to post treatment lab. Similar analyses were used in SU-2. Percent changes from baseline were calculated and included in the text for the variables demonstrated statistically significant or borderline significant. In addition, newly-occurring abnormalities were identified and incidences displayed after the following adjustments were made to the normal ranges. (See page 9, attached).

### Evaluation of ADRs

Frequency reporting of each newly occurring ADR was prepared. Separate displays list all ADRs as well as drug related ADRs. These were prepared by treatment group but SU-2 was not combined with SU-1 for this Table. The most frequent ADRs are listed as well as summary descriptive statistics assessing possible dose response relationships.

A list of all drop outs is presented.

For all quantitative variables involving comparative statistics, two-tailed tests were used to assess within group changes from baseline and between group differences. The following designations are used: (\*) p < 0.10; \* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001.

**TABLE 1**  
**ISRADIPINE SAFETY UPDATE - 8/89**  
**SUMMARY OF END OF STUDY INFORMATION**

Study Number	Completed Protocol	Adverse Reaction	Illness Not Due To Drug	Uncooperative	Protocol Violation	Study Drug Ineffective	Other	Total Number Entered
202	18							18
208	8	2						10
221	8		1					9
222	8						2	10
223	7	1			1		1	10
255	19 <sub>4</sub>	5	2	1			17	44
326	8			3				11
*331	27			1	1	1		30
*352	23			2		1		26
354	105	4				1	3	113
<b>Total</b>	<b>231</b>	<b>12</b>	<b>3</b>	<b>7</b>	<b>2</b>	<b>3</b>	<b>23</b>	<b>281</b>

\*Only includes patients since the last safety update.  
 Other patients' data from these studies reported in SU-1

03-00000

Table 1

### Open-Label Long Term Studies

Similar descriptive statistics were used in the long term trials. Data from this section were not pooled with SU-1 but separate analyses were performed. A determination of total number isradipine patients was presented graphically by month of exposure and this included SU-1.

SU-2 is comprised of two data sources, new patients (n=47) whose data were never previously analyzed and patients (n=31) who had some data previously analyzed and included in SU-1 but now have additional data.

### RESULTS

Table 1 lists US clinical trials included in SU-2. The total number of trials is shown below.

Population	SU-1	SU-2	Total*
Biopharmacology	16	0	16
<u>Phase I and II</u>			
Safety	5	0	5
Angina	6	5	11
CHF	6	1	7
Ventric Arrhythmias	1	0	1
Migraine	1	0	1
Bronchospasm	1	0	1
Hypertension	4	0	4
Sodium Handling	0	1	1
Sub Total	24	7	31
Phase III	13	3*	14*
.....			
TOTAL	53	10	61*

\* Totals are strictly additive since some data from studies 331 and 352 were included in SU-1.

Tables 2, 3 and 4 summarize study designs, objectives, patient population, patient numbers etc for each indication.

### Demographics

Background data for patients in well controlled Phase III hypertension studies are summarized in the following Table. All these Phase III studies utilized randomized, double blind, parallel design with a duration up to 10-12 weeks.

An additional 81 patients received isradipine in these studies making the total population of SU-1 and SU-2 together 1015 isradipine, 297 placebo and 502 active controls.

**TABLE 2**  
**CLINICAL PHARMACOLOGY (PHASE II)**  
**STUDIES INCLUDED IN SAFETY UPDATE -2**

Study No.	Investigator	No. of Subjects Revalued	No. of Subjects Completed	No. of Subjects Discontinued	No. of Deaths	Objectives	Dosage	Duration of Study Drug Administration/ Design	Remarks
26	Gordon Willis, M.D.	11	8	3	0	Assess the effects of lercadipine vs. nifedipine on determinants of sodium handling in normal male volunteers	lercadipine: 2.5 mg tid increased to 5 mg tid; nifedipine: 10 mg tid increased to 20 mg tid	Total duration of dosing of each treatment = 5 days, double-blind, randomized, crossover study design	Urinary sodium excretion after acute saline load enhanced by lercadipine but not by nifedipine.

TABLE 3  
 PHASE III  
 HYPERTENSION STUDIES INCLUDED IN SAFETY UPDATE -2

nr	No. of Subjects Randomized	No. of Subjects Completed	No. of Subjects Discontinued	No. of Deaths	Objectives	Dosage	Duration of Study Drug Administration/ Design	Remarks
.D. N.D. , N.D. .D.	30 <sup>00</sup> (129) <sup>+</sup>	27 <sup>00</sup> (113) <sup>+</sup>	3 <sup>00</sup> (16) <sup>+</sup>	0 <sup>00</sup> (0) <sup>+</sup>	Assess the <u>safety and efficacy</u> of lera- dipine in the treatment of <u>hyper-</u> <u>tension compared to</u> <u>enalapril</u>	leradipine: 1.25 mg - 5 mg bid; or Enalapril: 2.5 mg - 20 mg bid	10 weeks; double- blind, randomized, parallel group design	Study completed, data under analysis.
ger, .D. .D. by, .D. N.D.	26 <sup>00</sup> (94) <sup>+</sup>	23 <sup>00</sup> (78) <sup>+</sup>	3 <sup>00</sup> (16) <sup>+</sup>	0 <sup>00</sup> (0) <sup>+</sup>	Assess the <u>safety and efficacy</u> of leradipine in the treatment of black <u>hypertension</u> com- pared to <u>atenolol</u>	leradipine: 2.5 mg bid - 10 mg bid; or atenolol 25 mg bid - 50 mg tid	10 weeks; double- blind, randomized, parallel group design	Study completed, data under analysis.
.D. N.D. .D. tw, , N.D. N.D. .D. , N.D.	113	105	8	0	Assess the <u>safety and efficacy</u> of lera- dipine in the treatment of hyper- tension compared to diltiazem	leradipine: 1.25 mg - 5 mg bid; or dil- tiazem: 40 mg tid - 120 mg tid	12 weeks; double- blind, randomized, parallel group design	Study completed, data under analysis.

multicenter studies listed in this and other tables, only the total numbers of subjects across all centers are listed.

included in Safety Update -1.

Table 3

TABLE 4  
PAGE III

CLINICAL TRIALS IN PATIENTS WITH STABLE, EFFORT-INDUCED ANGINA PECTORIS INCLUDED IN SAFETY UPDATE -2

**TABL. 5**  
**PHASE III**

**STUDIES OF PATIENTS WITH CONGESTIVE HEART FAILURE INCLUDED IN SAFETY UPDATE -2**

Summary of Background Information - Phase III Hypertension Studies

<u>Variable</u>	<u>N</u>	<u>Mean</u>	<u>S.D.</u>	<u>Min</u>	<u>Max</u>
<u>Age (years)</u>					
Isradipine	81	54	11.9	26	74
Active Control	88	54	10.8	29	74
Total	169	54	11.3	26	74
<u>Weight (lbs)</u>					
Isradipine	81	186	37.8	110	313
Active Control	88	186	40.5	114	316
Total	169	186	39.1	110	316
<u>Duration Hypertension (yrs)</u>					
Isradipine	78	9	9.0	1	40
Active Controls	86	10	7.7	1	40
Total	164	10	8.3	1	40
<u>Sex</u>					
		<u>Male</u>		<u>Female</u>	
Isradipine	81	51	63%	30	37%
Active Controls	88	55	63%	33	38%
Total	169	106	63%	63	37%
<u>Race</u>					
		<u>White</u>		<u>Black</u>	
Isradipine	81	25	31%	43	53%
Active Controls	88	32	36%	41	47%
Total	169	57	34%	84	50%
		<u>Other</u>			
				13	16%
				15	17%
				28	17%

The total hypertension population was 1914 patients (includes 297 placebo). The active controls were HCT, cranosin, propranolol, captopril, enalapril or diltiazem.

Doses of Isradipine

Tables 2-5 present the doses used in each indication. In hypertension, doses ranged from 1.25 mg bid to 20 mg/day and the maximum dose in any trial was 7.5 mg tid for angina and CHF.

ECGs

Two types of analyses were performed. The first was listing patients discontinued due to ECG abnormalities and these patients are identified under "Dropout or Patient Discontinuations". The second method involved determining the frequency of newly occurring abnormalities for PR-intervals, QRS durations and QT-intervals. These results are summarized in Tables 7, 8 and 9.

The incidence of newly occurring PR-interval prolongations in Table 7 includes hypertension, phase I and II heart failure studies and angina patients. The frequency of abnormalities is similar to SU-1, 1.9% SU-1 vs 1.2% SU-2.

**TABLE 7**

**ISRADIPINE SAFETY UPDATE - 8/89**

**FREQUENCY OF ABNORMAL PR INTERVALS**

Treatment	Total Number of Subjects	Number of Evaluations		Number of Subjects with at Least One Newly-Occurring Abnormality or Increase from a Baseline Abnormality*	Frequency
		Pre-Study Drug	Post-Study Drug		
Phase I, Phase II, CHF**					
Isradipine	75	254	215	3	4.0
Placebo	13	24	19	1	7.7
Phase III - Hypertension					
Isradipine	81	161	146	1	1.2
Captopril	14	27	26	0	0.0
Enalapril	18	36	18	0	0.0
Diltiazem	54	108	102	2	3.7

\*Based upon maximum values for pre-study drug and post-study drug and a value of 0.2 sec.

\*\*Includes all congestive heart failure studies.

**TABLE 8**

**ISRADIPINE SAFETY UPDATE - 8/89**  
**FREQUENCY OF ABNORMAL QRS DURATIONS**

Treatment	Total Number of Subjects	Number of Evaluations		Number of Subjects with at Least One Newly-Occurring Abnormality or Increase from a Baseline Abnormality*	% Frequency
		Pre-Study Drug	Post-Study Drug		
Phase I, Phase II, CHF**					
Isradipine	75	255	216	16	21.3
Placebo	13	26	20	2	15.4
Phase III - Hypertension					
Isradipine	81	161	146	5	6.2
Captopril	14	27	26	1	7.1
Enalapril	18	36	18	0	0.0
Diltiazem	54	108	103	7	13.0

\*Based upon maximum values for pre-study drug and post-study drug and a value of 0.08 sec.

\*\*Includes all congestive heart failure studies.

000000

Table 8

**TABLE 9**

**ISRADIPINE SAFETY UPDATE - 6/89**

**FREQUENCY OF ABNORMAL CORRECTED QT INTERVALS**

Treatment	Total Number of Subjects	Number of Evaluations		Number of Subjects with at Least One Newly-Occurring Abnormality or Increase from a Baseline Abnormality*	% Frequency
		Pre-Study Drug	Post-Study Drug		
Phase I, Phase II, CHF**					
Isradipine	75	255	216	15	20.0
Placebo	13	25	21	5	38.5
Phase III - Hypertension					
Isradipine	81	161	146	16	19.8
Captopril	14	27	26	6	42.9
Enalapril	18	36	18	1	5.6
Diltiazem	54	108	103	5	9.3

\*Based upon maximum values for pre-study drug and post-study drug and a value of 0.44 sec.

\*\*Includes all congestive heart failure studies.

Similarly, QRS duration (Table 8) the comparative frequencies are 15.8% SU-1 and 6.2% SU-2. For QT the comparisons are 25.4% vs 19.8% respectively.

### Clinical Laboratory Tests

Tests were performed at a central lab, Metpath. Since this lab performed > 75% of the tests, an endpoint analysis of variance was performed on Metpath database for double blind studies. All patients were included in the analysis even if the tests were performed at another lab.

Results are summarized in the following Tables:

Table 10 Hematology. The only statistically significant change ( $p < 0.05$ ) from baseline for isradipine in SU-1 was a 3-4% increase in total WBC count. In SU-2 the significant changes are increases in hemoglobin (+1.4%), hematocrit (+2.2%), WBC (+5.3%), and basophils (+15.6%).

Table 11 Urinalysis. No statistically significant changes

Table 12 Chemistry. The following significant changes were noted for isradipine: Calcium, total protein, albumin, glucose, cholesterol, chloride, CO<sub>2</sub>, SGOT and alkaline phosphatase.

These changes are similar to SU-1.

### Newly Occurring Abnormalities

The frequency of newly occurring abnormalities is summarized in Tables 13 and 14 for hematology and urinalysis respectively. For hematology, there were no major differences between isradipine, placebo and active control. In the angina consover studies, there was a higher frequency in some variables, mainly lymphocytes, neutrophils, eosinophils, platelets and basophils. Sponsor does not postulate a cause for these abnormalities.

Table 15 summarizes blood chemistry abnormalities. Except for creatinine, there are no differences in isradipine group compared to placebo or active nor is there a difference from SU-1.

Creatinine values were higher with test drug than with placebo or active controls. These abnormalities were seen in 4 hypertension and one CHF patient. With hypertension, the highest end of trial value was 1.6 mg/dl (normal 1.3 mg/dl). In the CHF patient, a value of 3.0 mg/dl was noted mid-way in the study after a baseline of 2.5 mg/dl. By the end of the study, the value was 1.9 mg/dl.

Results for new abnormalities for BUN, creatinine are shown in Tables 16 and 17. No patient entered into Phase III hypertension studies developed a newly occurring abnormality in BUN greater than 50 mg/dl or creatinine > 2.0 mg/dl. When these abnormalities occurred, they were in CHF patients.

Serum glucose abnormalities were discussed in NDA and SU-1. Isradipine had a higher frequency of elevated glucose ( $\geq 150$  mg/dl) than did placebo group 8.8% vs 5.7% respectively. These results are summarized in Table 18 while Table 19 presents comparative statistics from baseline.

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3. Clinical Laboratory Tests (Cont'd)

- o Hematologic Variables - All variables were adjusted  $\pm 15\%$  with the exception of bands, monocytes, basophils and eosinophils which were adjusted  $+15\%$  only.
- o Urinalysis Variables - The normal ranges for specific gravity and pH were adjusted  $\pm 15\%$ . All other normal ranges remained standard.
- o Chemistry Variables - The normal ranges for all variables were adjusted  $+15\%$ . Sodium, potassium, chloride, calcium, inorganic phosphorus, albumin, and glucose were the only variables whose normal ranges were also adjusted  $-15\%$ .

Additionally for BUN, creatinine, glucose, and the liver function battery, the frequency of newly-occurring abnormalities was also determined based on values which exceeded the following upper limits considered to be of more clinical relevance than the  $15\%$  adjustments to the normal range described above:

* BUN:	50 mg/dL
* Creatinine:	2.0 mg/dL
* Glucose:	150 mg/dL
* SGOT & SGPT:	100 IU/L
* LDH:	300 IU/L
* Total Bilirubin:	2.0 mg/dL
* Alkaline Phosphatase:	200 IU/L

A patient was considered to have a newly-occurring laboratory abnormality if all pre-randomization or baseline evaluations for a particular variable were within the adjusted normal range and the patient had at least one post-randomization evaluation outside the adjusted normal range. For those variables whose normal ranges were only adjusted  $+15\%$ , evaluations falling below the normal range were considered to be normal.

In addition, if a patient had an evaluation falling outside the adjusted normal range during the baseline evaluations and the patient demonstrated a worsening during the treatment evaluations following randomization (i.e., a further increase or decrease of at least  $15\%$  from their pre-dose value), then this patient was also considered to have had a newly-occurring laboratory abnormality.

TAB. E 10  
ISRADIPINE SAFETY UPDATE - 8-88  
HEMATOLOGY - MEIPATH LAB DATA  
ANOVA - ENDPOINT

Normal Ranges		END POINT						
ITEM	TREATMENT N	MEAN PRE-RX	UNADJUSTED CHANGE	STD	ADJUSTED CHANGE	PAIRWISE PLAC	COMPARISONS (1) AC	
<b>HEMOGLOBIN</b>								
(11.9-17.6gms/dl)	ISRADIPINE107	14.132	0.193 *	0.972		0.63 *	0.13	
	PLACEBO 10	14.940	-0.440	1.059			-0.50	
	ACTIVE CON 99	14.037	0.062	0.887				
<b>HEMATOCRIT</b>								
(37-54%)	ISRADIPINE107	43.317	0.939 **	3.442	0.933	0.44	0.34	
	PLACEBO 10	44.870	0.250	2.848	0.486		-0.10	
	ACTIVE CON 99	43.254	0.613 (*)	3.208	0.595			
<b>WBC</b>								
(3.9-11.4x10 <sup>3</sup> CUBIC MM)	ISRADIPINE107	6.634	0.349 **	1.227	0.360	1.11 **	0.36 *	
	PLACEBO 10	8.120	-0.870 **	0.917	-0.747		-0.75 (*)	
	ACTIVE CON 99	6.305	0.037	1.279	0.002			
<b>BANDS</b>								
(0-5%)	ISRADIPINE 98	0.000	0.000	0.000		0.00	0.01	
	PLACEBO 10	0.000	0.000	0.000			0.01	
	ACTIVE CON 90	0.011	-0.011	0.105				
<b>NEUTROPHILS</b>								
(42-81%)	ISRADIPINE107	57.112	0.168	7.583	0.098	-2.42	0.18	
	PLACEBO 10	68.400	-0.600	8.682	2.511		2.80	
	ACTIVE CON 97	58.618	0.155	8.198	-0.087			
<b>LYMPHOCYTES</b>								
(10-47%)	ISRADIPINE107	33.000	0.262	7.312	0.247	1.62	0.43	
	PLACEBO 10	23.400	1.400	6.022	-1.373		-1.18	
	ACTIVE CON 96	34.115	-0.498	8.084	-0.184			
<b>MONOCYTES</b>								
(0-10%)	ISRADIPINE107	6.804	-0.374 (*)	2.247	-0.258	-0.35	-0.19	
	PLACEBO 10	8.000	-0.800	2.440	0.089		0.25	
	ACTIVE CON 96	6.281	0.063	2.275	-0.159			
<b>EOSINOPHILS</b>								
(0-8%)	ISRADIPINE108	2.623	-0.038	1.640	-0.009	0.18	-0.08	
	PLACEBO 10	1.400	0.100	0.568	-0.171		-0.24	
	ACTIVE CON 96	2.480	0.073	1.630	0.069			

(1) - UNADJUSTED MEANS USED WHEN ASSUMPTIONS FOR ANALYSIS OF COVARIANCE NOT MET

(2) - CHANGE IS POST - PRE

\*\*\* P<.001, \*\* P<.01, \* P<.05, (\*) P<.10

+ Includes data for Study No. 352 which was not available for the last Safety Update.

TABLE 10 (Cont'd)  
 ISRADIPINE SAFETY UPDATE - 8-89  
 HEMATOLOGY - MLTPATH LAB DATA+  
 ANOVA - ENDPOINT

Normal Ranges

ITEM	TREATMENT	N	MEAN PRE-RX	UNADJUSTED		ADJUSTED CHANGE	PAIRWISE COMPARISONS (1)	
				CHANGE	STD		PLAC	AC
BASOPHILS								
(0-2%)	ISRADIPINE	108	0.728	0.113 *	0.304	0.120	-0.30	
	PLACEBO	10	0.600	0.500	0.872	0.420		-0.08
	ACTIVE CON	98	0.710	0.177 *	0.768	0.178		0.24

(1) - UNADJUSTED MEANS USED WHEN ASSUMPTIONS FOR  
 ANALYSIS OF COVARIANCE NOT MET  
 (2) - CHANGE IS POST - PRE  
 \*\*\* P<.001, \*\* P<.01, \* P<.05, (\*) P<0.10

+ Includes data for Study No. 352 which was not available  
 for the last Safety Update.

03-00072

Table 10

TABLE 11  
 ISRADIPINE SAFETY UPDATE - 8-88  
 URINALYSIS - METPATH LAB DATA\*  
 ANOVA - ENDPOINT

END POINT

Normal Ranges ITEM	TREATMENT N	MEAN PRE-RX	UNADJUSTED		ADJUSTED CHANGE	PAIRWISE COMPARISONS (1)	
			CHANGE	STD		PLAC	AC
-----							
SPECIFIC GRAVITY							
(1.001-1.035)	ISRADIPINE105	1.018	-0.001 (*)	0.008		0.00	-0.00
	PLACEBO 0	1.018	-0.002	0.011			-0.00
	ACTIVE CON 98	1.019	-0.001 (*)	0.007			
PH							
(5-7)	ISRADIPINE105	5.219	0.081	0.801	0.077	-0.10	-0.01
	PLACEBO 0	5.333	0.111	0.828	0.175		0.10
	ACTIVE CON 98	5.240	0.073	0.700	0.077		

(1) - UNADJUSTED MEANS USED WHEN ASSUMPTIONS FOR  
 ANALYSIS OF COVARIANCE NOT MET

(2) - CHANGE IS POST - PRE

\*\*\* P<.001, \*\* P<.01, \* P<.05, (\*) P<.10

\* Includes data for Study No. 352 which was not available  
 for the last Safety Update.

TABLE 12  
 ISRADIPINE SAFETY UPDATE - 8-89  
 CHEMISTRY - METPATH LAB DATA +  
 ANOVA - ENDPOINT

Normal Ranges		END POINT					
ITEM	TREATMENT N	MEAN PRE-RX	UNADJUSTED CHANGE	TD	ADJUSTED CHANGE	PAIRWISE COMPARISONS (1) PLAC AC	
(8.8-10.5mg/dl)	ISRADIPINE107	8.525	0.117 *	0.509	0.122	0.28 *	0.07
	PLACEBO	8.518	-0.164 (*)	0.298	-0.162		-0.21 (*)
	ACTIVE CON101	8.503	0.056	0.368	0.051		
(2.2-4.6mg/dl)	ISRADIPINE107	3.312	-0.013	1.030	0.014	0.05	-0.08
	PLACEBO	3.073	0.084	0.413	-0.033		-0.14
	ACTIVE CON101	3.224	0.121 (*)	0.631	0.102		
(6-23mg/dl)	ISRADIPINE107	14.818	0.075	3.143	0.113	-0.80	0.28
	PLACEBO	18.364	-0.364	2.420	0.710		0.88
	ACTIVE CON101	14.078	0.010	3.207	-0.147		
(2.2-8.3mg/dl)	ISRADIPINE107	5.767	-0.088	0.830	-0.076	-0.38	-0.05
	PLACEBO	7.327	-0.027	0.388	0.288		0.31
	ACTIVE CON101	5.485	0.023	0.911	-0.024		
(65-130mg/dl)	ISRADIPINE107	110.832	0.794	38.815	1.357	-28.2 **	3.52
	PLACEBO	159.818	10.455	38.680	30.541		32.70 ***
	ACTIVE CON101	102.436	0.624	21.540	-2.160		
(6.4-8.1mg/dl)	ISRADIPINE107	7.430	0.108 **	0.407		0.34 **	0.08
	PLACEBO	7.336	-0.227 (*)	0.408			-0.27 *
	ACTIVE CON101	7.445	0.047	0.398			
(3.7-5.0gm/dl)	ISRADIPINE107	4.030	0.056 **	0.216	0.055	0.20 ***	0.08 *
	PLACEBO	4.008	-0.227 *	0.332	-0.238		-0.23 ***
	ACTIVE CON101	4.042	-0.004	0.209	-0.002		
(120-240mg/dl)	ISRADIPINE107	227.187	4.178	28.375	4.831	17.67 *	7.85 *
	PLACEBO	217.455	-11.455 *	15.807	-12.738		-9.82
	ACTIVE CON101	220.448	-2.257	27.548	-2.818		

(1) - UNADJUSTED MEANS USED WHEN ASSUMPTIONS FOR ANALYSIS OF COVARIANCE NOT MET

(2) - CHANGE IS POST - PRE

\*\*\* P<.001, \*\* P<.01, \* P<.05, (\*) P<.10

+Includes data for Study No. 352 which was not available for the last Safety Update.

TABLE 12  
ISRADIPINE SAFETY UPDATE - 8-89  
CHEMISTRY - MEIPATH LAB DATA +  
ANOVA - ENDPOINT

END POINT

Normal Ranges		MEAN PRE-RX	UNADJUSTED		ADJUSTED		PAIRWISE COMPARISONS (1)	
ITEM	TREATMENT N		CHANGE	STD	CHANGE	PLAC	AC	
<b>SODIUM</b>								
(134-143mEq/l)	ISRADIPINE107	139.188	-0.093	3 248	-0.254	-0.07	0.17	
	PLACEBO	11 139.909	0.384	2 014	0.712		1.13	
	ACTIVE CON101	139.594	-0.554 *	2 825	-0.472			
<b>POTASSIUM</b>								
(3.5-5.3mEq/l)	ISRADIPINE107	4.379	-0.107	0 880		0.04	-0.14	
	PLACEBO	11 4.509	-0.145	3 372			-0.18	
	ACTIVE CON101	4.274	0.032	0 582				
<b>CHLORIDE</b>								
(25.32mEq/l)	ISRADIPINE107	101.374	-0.589 (*)	3 388	-0.612	0.83	-0.18	
	PLACEBO	11 97.727	0.636	3 202	-1.442		-0.84	
	ACTIVE CON101	101.861	-1.050 **	3 336	-0.798			
<b>CO2</b>								
(0.6-1.3mg/dl)	ISRADIPINE 41	28.854	-1.073 *	3 304		-1.71	-0.89	
	PLACEBO	11 28.182	0.636	1 748			0.82	
	ACTIVE CON 32	25.750	-0.188	3 207				
<b>CREATININE</b>								
(10-50 U/L)	ISRADIPINE107	1.083	-0.013	0.183	-0.012	-0.08	-0.01	
	PLACEBO	11 1.173	0.055	0 181	0.070		0.07	
	ACTIVE CON101	1.061	0.061	0 270	-0.002			
<b>SGOT</b>								
(5-55 U/L)	ISRADIPINE107	27.121	2.308 (*)	14.147	2.438	7.48	1.82	
	PLACEBO	11 31.273	-0.838	12.699	-5.040		-5.68	
	ACTIVE CON101	25.871	0.931	15 826	0.618			
<b>SGPT</b>								
(10-50 U/L)	ISRADIPINE107	24.850	1.336	12.405		4.52	2.08	
	PLACEBO	11 22.364	-3.182	10.265			-2.44	
	ACTIVE CON101	22.465	-0.743	12.852				
<b>ALKALINE PHOS.</b>								
	ISRADIPINE107	27.514	1.243 (*)	8.885		3.15	0.55	
	PLACEBO	11 28.909	-1.909	5.770			-2.68	
	ACTIVE CON101	28.782	0.693	8.822				

(1) - UNADJUSTED MEANS USED WHEN ASSUMPTIONS FOR ANALYSIS OF COVARIANCE NOT MET

(2) - CHANGE IS POST - PRE

\*\*\* P<.001, \*\* P<.01, \* P<.05, (\*) P<.10

+ Includes data for Study No. 952 which was not available for the last Safety Update.

TABLE 12  
 ISRADIPINE SAFETY UPDATE - 8-88  
 CHEMISTRY - METPATH LAB DATA +  
 ANOVA - ENDPOINT

Normal Ranges		MEAN PRE-RX	UNADJUSTED		ADJUSTED CHANGE	PAIRWISE COMPARISONS (1)	
ITEM	TREATMENT N		CHANGE	STD		PLAC	AC
TOT. BILIRUBIN							
0.2-1.6mg/dl)	ISRADIPINE107	0.588	-0.028	0.177	-0.028	-0.00	-0.05 *
	PLACEBO 11	0.753	-0.072 {*}	0.128	-0.028		-0.05
	ACTIVE CON101	0.558	0.027	0.201	0.024		
LDH							
110-250 U/L)	ISRADIPINE107	188.187	9.697	45.819	0.848	1.88	2.97
	PLACEBO 11	201.000	-7.099	26.142	-1.248		1.07
	ACTIVE CON101	188.610	-1.870	36.747	-2.321		

(1) - UNADJUSTED MEANS USE, WHEN ASSUMPTIONS FOR ANALYSIS OF COVARIANCE NOT MET

(2) - CHANGE IS POST - PRE

\*\*\* P<.001, \*\* P<.01, \* P<.05, {\*} P<0.10

+ Includes data for Study No. 352 which was not available for the last Safety Update.

**Table 13**  
**Isradipine Safety Update - 8/89**  
**Frequency of New Lab Abnormalities\***  
**Short Term**

**Hematology**

	Isradipine n=110(‡)	Placebo n=11(‡)	Active Control n=105(‡)	Cross- over+ n=66(‡)
Hemoglobin gm/dl	0 (0.0)	0 (0.0)	3 (2.9)	0 (0.0)
Hematocrit %	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
WBC 10*3 cu.mm.	2 (1.8)	0 (0.0)	5 (4.8)	4 (6.1)
Bands ‡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophils ‡	3 (2.7)	0 (0.0)	1 (1.0)	6 (9.1)
Lymphocytes ‡	2 (2.7)	0 (0.0)	1 (1.0)	12 (18.2)
Monocytes ‡	4 (3.6)	1 (9.1)	0 (0.0)	5 (7.6)
Eosinophils ‡	0 (0.0)	0 (0.0)	1 (1.0)	9 (13.6)
Basophils ‡	0 (0.0)	1 (9.1)	2 (1.9)	9 (13.6)
Platelet Estimate	0 (0.0)	0 (0.0)	0 (0.0)	7 (10.6)

\* Includes data for study no. 352 which was not available for the last safety update.

+ Includes all patients in studies with crossover designs. All other columns are for patients in parallel group studies.

**Table 14**  
**Isradipine Safety Update - 8/89**  
**Frequency of New Lab Abnormalities\***  
**Short Term**

**Urinalysis**

	Isradipine n=110(†)	Placebo n=11(‡)	Active Control n=105(‡)	Cross- over+ n=66(‡)
Specific Gravity	0 (0.0)	0 (0.0)	0 (0.0)	14 (21.2)
Acetone	2 (1.8)	0 (0.0)	5 (4.8)	2 (3.0)
Albumin	6 (5.5)	0 (0.0)	7 (6.7)	8 (12.1)
Glucose	5 (4.5)	1 (9.1)	1 (1.0)	5 (7.6)
Bile	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
pH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cast/HPF	4 (3.6)	0 (0.0)	2 (1.9)	5 (7.6)
RBC/HPF	7 (6.4)	0 (0.0)	12 (11.4)	1 (1.5)
WBC/HPF	6 (5.5)	0 (0.0)	5 (4.8)	3 (4.5)

\* Includes data for study no. 352 which was not available for the last safety update.

+ Includes all patients in studies with crossover designs. All other columns are for patients in parallel group studies.

**Table 15**  
**Isradipine Safety Update - 8/89**  
**Frequency of New Lab Abnormalities\***  
**Short Term**

**Chemistry**

	<b>Isradipine n=110(†)</b>	<b>Placebo n=11(‡)</b>	<b>Active Control n=105(‡)</b>	<b>Cross- over+ n=66(‡)</b>
Calcium mg/dl	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Inorganic Phosphorus mg/dl	4 (3.6)	0 (0.0)	7 (6.7)	2 (3.0)
BUN mg/dl	4 (3.6)	1 (9.1)	0 (0.0)	3 (4.5)
Glucose mg/dl	11 (10.0)	2 (18.2)	6 (5.7)	13 (19.7)
Uric Acid mg/dl	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Total Protein mg/dl	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Albumin gm/dl	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Total Bilirubin mg/dl	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.5)
Cholesterol mg/dl	2 (1.8)	1 (9.1)	1 (1.0)	1 (1.5)
Alkaline Phosphatase Units	4 (3.6)	0 (0.0)	1 (1.0)	5 (7.6)
LDH Units	4 (3.6)	0 (0.0)	3 (2.9)	2 (3.0)
SCOT Units	5 (4.5)	0 (0.0)	7 (6.8)	2 (3.0)
SGPT Units	2 (1.8)	0 (0.0)	3 (2.9)	12 (18.2)
Sodium mEq/l	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Potassium mEq/l	2 (1.8)	0 (0.0)	3 (2.9)	0 (0.0)
Chloride mEq/l	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CO2 mEq/l	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine mg/dl	5 (4.5)	0 (0.0)	1 (1.0)	4 (6.1)

\* Includes data for study no. 352 which was not available for the last safety update.

+ Includes all patients in studies with crossover designs. All other columns are for patients in parallel group studies.

TABLE 16

ISRADIPINE SAFETY UPDATE - 8/89

FREQUENCY OF ABNORMAL BUN TESTS

Treatment	Total Number of Subjects	Number of Evaluations		Number of Subjects with at Least One Newly-Occurring Abnormality or Increase from a Baseline Abnormality*	% Frequency
		Pre-Study Drug	Post-Study Drug		
Phase I, Phase II, CHF**					
isradipine	72	142	169	1	1.4
placebo	11	22	20	0	0.0
Phase III - Hypertension***					
isradipine	101	231	214	0	0.0
lisinopril	33	64	62	0	0.0
enalapril	18	36	52	0	0.0
clonidine	54	131	110	0	0.0

\*Based upon maximum values for pre-study drug and post-study drug and a value of 50 mg/dl.

\*\*Includes all congestive heart failure studies.

\*\*\*Includes data for Study No. 352 which was not available for the last safety update.

TABLE 17

ISRADIPINE SAFETY: UPDATE - 8/89

FREQUENCY OF ABNORMAL CREATININE TESTS

Treatment	Total Number of Subjects	Number of Evaluations		Number of Subjects with at Least One Newly-Occurring Abnormality or Increase from a Baseline Abnormality*	% Frequency
		Pre-Study Drug	Post-Study Drug		
Phase I, Phase II, CHF**					
Isradipine	72	142	170	2	2.8
placebo	11	22	20	0	0.0
Phase III - Hypertension***					
Isradipine	101	231	214	0	0.0
lisinopril	33	64	62	1	3.0
enalapril	18	36	52	0	0.0
diltiazem	54	131	110	0	0.0

\*Based upon maximum values for pre-study drug and post-study drug and a value of 2.0 mg/dl.

\*\*Includes all congestive heart failure studies.

\*\*\*Includes data for Study No. 352 which was not available for the last safety update.

**TABLE 18**

**ISRADIPINE SAFETY UPDATE - 8/89**

**FREQUENCY OF ABNORMAL SERUM GLUCOSE TESTS**

Treatment	Total Number of Subjects	Number of Evaluations		Number of Subjects with at Least One Newly-Occurring Abnormality or Increase from a Baseline Abnormality*	% Frequency
		Pre-Study Drug	Post-Study Drug		
<b>Phase I, Phase II, CHF**</b>					
Isradipine	72	142	168	11	15.3
Placebo	11	22	20	4	36.4
<b>Phase III - Hypertension***</b>					
Isradipine	101	231	198	4	4.0
Lisina	33	64	62	0	0.0
Enalapril	18	36	26	0	0.0
Diltiazem	54	131	110	0	0.0

\*Based upon maximum values for pre-study drug and post-study drug and a value of 150 mg/dl.

\*\*Includes all congestive heart failure studies.

\*\*\*Includes data for Study No. 352 which was not available for the last safety update.

TABLE 19

ISRADIPINE SAFE T UPDATE - 8/89

ALL SUBJECTS IN PARALLEL DESIGN STUDIES - CHANGES TO SERUM  
GLUCOSE FROM BASELINE TO ACTIVE TREATMENT PERIOD BY  
TREATMENT GROUP AND DIABETIC STATUS\*

Variable	Treatment Group	Diabetic?	N	Baseline		Active Treatment		Treatment Group	Diabetic?	Placebo	Active Control	Iradipine	Placebo	Active Control	
				Mean	S.D.	Mean	S.D.								No
Mean Change from Baseline	Iradipine	No	103	100.7	27.4	3.8	26.4			(*)					..
	Placebo	No	7	112.5	44.4	23.9 (*)	28.5								..
	Active Control	No	103	99.5	13.6	8.4	17.0								.
	Iradipine	Yes	7	218.1	101.0	-6.8	107.6								(*)
	Placebo	Yes	4	232.9	105.1	5.3	52.8								.
	Active Control	Yes	2	230.5	146.4	-51.5	27.6								
Maximum Increase from Baseline	Iradipine	No	103	100.7	27.4	10.7**	29.8								..
	Placebo	No	7	112.5	44.4	40.1(*)	43.6								...
	Active Control	No	103	99.5	13.6	6.8**	15.9								.
	Iradipine	Yes	7	218.1	101.0	25.5	117.7								..
	Placebo	Yes	4	232.9	105.1	21.1	73.8								.
	Active Control	Yes	2	230.5	146.4	-51.8	26.9								

(\*)p<.10, \*\*p<.05, \*\*\*p<.01, \*\*\*\*p<.001

Although the subjects in the above analyses were not randomized into treatment groups by diabetic status, the analyses do give an indication of the differential effects on serum glucose between treatment groups and subjects with or without diabetes.

\*Includes data for Study No. 352 which was not available for the last safety update.

02-00000

Table 19

There were statistically significant mean increases in alkaline phosphatase in hypertension studies. Table 20 summarizes frequency of newly occurring elevations  $\geq 200$  U/L. No patient in Phase III hypertension studies developed this abnormality; ~~one angina patient was~~ involved. Leave in. JB

Tables 21 and 22 summarize SGOT and SGPT abnormalities (100 U/L). Results are similar to SU-1 and to active controls. Table 23 summarizes incidence of new abnormalities in any liver function test. Incidence with test drug was slightly lower than for control groups.

Overall, results from these tests are similar to SU-1.

#### Adverse Reactions

Tables 24 and 25 summarize ADRs reported during the double blind, hypertension studies with treatment durations up to 10-12 weeks. All newly occurring ADRs are identified as "A" and those considered possibly drug related as "B". These Tables also identify ADRs not previously reported in SU-1.

The most common ADRs are listed below with a comparison with SU-1. These ADRs were compiled from double blind studies of 3-12 weeks. There are very few patients in SU-2 database resulting in a potential bias in percentage incidence.

#### ADR Frequency, Comparison of SU-1 and SU-2 Percentage of Patients

ADR	SU-2 (N=81)	SU-1 (N=934)
Headache	8.6	13.7
Fatigue	6.2	3.9
Dizziness	3.7	7.3
Impotence	3.7	1.0
Decreased Libido	3.7	0.5
Pollakiuria	3.7	1.5
Edema	2.5	7.2
Palpitations	2.5	4.0
Total No with at least one new ADR possibly/probably drug related	36	41

Only two new ADRs were considered drug related by the investigators, bruise and depression. There were two cases of bruising in SU-1 but they were not considered drug related. In addition, there were two other new ADRs reported but not considered drug related, flatulence and an epileptic seizure. In the case of the seizure, 2-3 days after initiating treatment, the patient was found unconscious. Dose of isradipine was 1.25 mg bid. All tests on the patient were negative and the patient completed the 12 week study with Dilantin and Traxodone as concomitant drugs. The latter drug was later discontinued due to a feeling of confusion by the patient.

TABLE 20

ISRADIPINE SAFETY UPDATE - 8/89

FREQUENCY OF ABNORMAL ALKALINE PHOSPHATASE TESTS

Treatment	Total Number of Subjects	Number of Evaluations		Number of Subjects with at Least One Newly-Occurring Abnormality or Increase from a Baseline Abnormality*	% Frequency
		Pre-Study Drug	Post-Study Drug		
	72	160	250	1	1.4
	11	22	20	0	0.0
Phase III - Hypertension***					
Isradipine	101	231	241	0	0.0
Captopril	33	64	85	0	0.0
Enalapril	18	35	52	0	0.0
Diltiazem	54	131	110	0	0.0

\*Based upon maximum values for pre-study drug and post-study drug and a value of 200 U/L.

\*\*Includes all congestive heart failure studies.

\*\*\*Includes data for Study No. 352 which was not available for the last safety update.

03-00054

Table 20

TABLE 21

ISRADIPINE SAFETY UPDATE - 8/89

FREQUENCY OF ABNORMAL SGOT

Treatment	Total Number of Subjects	Number of Evaluations		Number of Subjects with at Least One Newly-Occurring Abnormality or Increase from a Baseline Abnormality*	% Frequency
		Pre-Study Drug	Post-Study Drug		
	72	160	251	0	0.0
	11	22	20	0	0.0
<b>Phase III - Hypertension***</b>					
Isradipine	101	231	241	1	1.0
Captopril	33	64	85	0	0.0
Enalapril	18	36	52	0	0.0
Diltiazem	54	131	110	2	3.7

\*Based upon maximum values for pre-study drug and post-study drug and a value of 100 U/L.

\*\*Includes all congestive heart failure studies.

\*\*\*Includes data for Study No. 352 which was not available for the last safety update.

03-00055

Table 21