TABLE 33
ISRADIPINE LONG TERM PATIENTS
ALL ADVERSE REACTIONS SAFETY UPDATE - 6-89
PATIENTS COUNT BY AR & TSRADIPINE-INTERVAL
NEW=NEWLY REPORTED (FIRST TIME DURING IS), RECU=RECURRENCES DURING IS
PER ADVERS REACTION
NOTE: TOTAL RECU=NO. PTS WITH AT LEAST ONE RECU.

	IS TREATMENT DURATION (MONTHS)			
	MONTHS 25 -27		TOTAL	
	RECU/NEW		RECU/NEW	
	RECU	NEW	RECU	NEW
ADVERSE REACTION	N	N	N	N
COUGHING			1	3
NASAL CONGESTION				1
SINUSITIS/SINUS INFLAM				1
ANGINA				2
CHEST PAIN				4
ECG/EKG ABNORMAL			1	1
EDEMA	1		3	6
HEART BLOCK				1
HEART FAILURE				1
HYPOTENSION(BL PRES LOW)				2
LEG/FEET CRAMPS				1
EPISTAXIS (NOSE BLEED)				1
PALPITATIONS			2	2
TACHYCARDIA				1

(CONTINUED)

* New adverse reaction since last safety update.

Table 33

TABLE 33
ISRADIPINE LONG TERM PATIENTS
ALL ADVERSE REACTIONS - SAFETY UPDATE - 8-89
PATIENTS COUNT BY AR BY ISRADIPINE-INTERVAL
NEW-NEWLY REPORTED (FIRST TIME DURING IS), RECU-RECURRENCES DURING IS
PER ADVERSE REACTION
NOTE: TOTAL RECU-NO PTS WITH AT LEAST ONE RECU.

	IS TREATMENT DURATION (MONTHS)			
	MONTHS 25 -27		TOTAL	
	RECURREW		RECURREW	
	RECU	NEW	RECU	NEW
	N	N	N	N
ADVERSE REACTION				
ABDOMINAL DISCOMFORT			1	1
DIARRHEA				2
* HEPATOMEGALY				1
CANKER SORE				1
NAUSEA				3
STOOL LOOSE				1
CYSTITIS (INFLAM BLADDER)				1
PROSTATITIS(INFLAMED PROSTATE				1
URINARY STREAM FORCE OF			1	1
URINARY TUFECTED				1
WEAKNESS				1
DIZZINESS				5
EQUILIBRIUM LOSS			1	1

(CONTINUED)

* New adverse reaction since the last safety update.

Table 33

TABL 33
ISRADIPINE LONG TERM PATIENTS
ALL ADVERSE REACTIONS - SAFETY UPDATE - 6-89
PATIENTS COUNT BY AR BY ISRADIPINE-INTERVAL
NEW=NEWLY REPORTED (FIRST TIME DURING IS), RECU=RECURRENCES DURING IS
PER ADVERSE REACTION
NOTE: TOTAL RECU=NO. PTS WITH AT LEAST ONE RECU.

	IS TREATMENT DURATION (MONTHS)			
	MONTHS 25 -271		TOTAL	
	RECU NEW		RECU NEW	
	RECU	NEW	RECU	NEW
	N	N	N	N
ADVERSE REACTION				
FATIGUE				2
HEADACHE				1
SYNCOPE				1
TREMOR				1
DRY MOUTH				1
TINGLING				1

CO-00427

Table 3

[illegible] last safety update.

Table 36 lists newly occurring ADRs for the 31 patients from SU-1 continuing in the database. This list is only of ADRs not previously reported. New ADRs were reported by 11 patients and, in the case of angina and CHF studies, the new ADRS occurred 3-4 years after study initiation.

Three patients from Table 36 were discontinued, two due to deterioration of their condition and one due to ADR (edema lower extremities).

Dropouts

Table 37 lists patients who were withdrawn since last update (47 new and 31 continuing patients). A total of 4/78 isradipine patients were withdrawn due to ADRs compared to 3% in SU-1. The next Table summarizes data for the entire long term experience in SU-2 plus SU-1 for isradipine treated group.

Isradipine Patients Withdrawn

Reason	SU-2	SU-2	Total
ADR	4	50	54
Ineffectiveness	3	18	21
Lost to Follow Up	0	63	63
Uncooperative	1	18	19
Non Related Drug Illness	2	21	23
Death	4	5	9
MI	0	4	4
Myocarditis	0	1	1
Miscellaneous	2	17	19
Study Termination	8	0	8
Total	24	197	221

Deaths and Serious Non Fatal Events-

During the long term studies, a total of 18 patients died. Sixteen were reported in SU-1. The two additional cases were an angina patient receiving propranolol who was hospitalized for respiratory failure and diagnosed ~~as~~ HIV positive. The final dose of medication was taken at least a couple of weeks prior to death. The second case was CHF and the patient died in an automobile accident; final dose taken a few weeks before the event. See attached Table.

Serious, non fatal ADRs were all reported in SU-1.

Conclusion

A total of 2039 patients received isradipine with 1510 receiving it for at least 2 weeks. Sponsor concludes that isradipine is a safe and well tolerated drug.

TABLE 36

ISRADIPINE LONG-TERM DATA

SAFETY UPDATE - 8/89

NEWLY-OCCURRING ADVERSE REACTIONS
FOR PATIENTS WITH ADDITIONAL LONG-TERM DATA

Study	Patient	Week(s)	Adverse Reaction	Due to Drug
10	111	196, 220	Shortness of Breath	Uncertain
		204, 217, 232	Intermittent CHF	Uncertain
		217, 220	Heart Pounding	Uncertain
	112	223	Dry Ears	Uncertain
		216, 223	Nasal Rash	Uncertain
		180, 196	Chest Pain	Uncertain
		216, 223	Dry Cough	Uncertain
		196	Pneumonia	No
		216, 223	Poor Balance	Uncertain
	124	224	Angina-like Pain	Uncertain
206	58	156	Mid-epigastric Pain	No
	102	165	Hand Cramps	Uncertain
	152	202, 206	Diarrhea	Uncertain
		210	Chest Pain	No
		216	Transient Ischemic Attack	No
350	335	48	Difficulty Focusing Eyes	Uncertain
	336	43, 47	Back Pain	No
	339	57	Edema-Lower Extremities	Yes
	378	53	Right Flank Pain	No
	781	38, 43, 48, 52	Lower Back Pain	No

Table 37
Isradipine Safety Update - 8-89
Listing of All Patients Discontinued
From the Long Term Phase Since the Last Update

Study No.	Patient No.	Total Daily Dose (mg)+	Weeks in Study	Reason
10	*112	20	223	not responding - worsening CHF
	*124	20	224	not responding - increasing angina
12	6	5	15	study ended
204	154	22.5	42	catheterization for unstable angina
222	151	22.5	69	illness not drug related - coronary bypass for unstable angina
253	101	22.5	62	patient died of a cardiac event probably not drug related
	110	15	15	adverse reaction - exacerbation of CHF
254	101	10	1	suicide
	103	22.5	35	died of a sudden cardiac event
	105	20	11	patient died
255	1001	22.5	15	study terminated
	1002	22.5	17	study terminated
	1026	7.5	13	adverse reaction - severe, progressive, symptomatic edema
	1028	22.5	41	study terminated
	1032	7.5	18	study terminated
	1033	7.5	19	study terminated
	1034	7.5	7	study terminated
	1078	7.5	23	study terminated
	7027	22.5	11	study drug ineffective
	7029	10	3	can't make appointments due to chemotherapy treatments
350	301	20	25	uncooperative
	309	5	3	adverse reaction - GI upset
	313	20	12	patient moved
	*339	10	57	adverse reaction - edema of lower extremities

\+ Prescribed daily dose at time of discontinuation from the study

* Patients included in the last update that have additional data

PATIENT DEATHS

STUDY NO. INDICATION	PAT. NO.	TREATMENT	REPORTED PREVIOUSLY IN NDA AND/ OR SU-1	CAUSE OF DEATH
[redacted]	111	Isradipine	Yes	myocardial infarction
301 LT Hypertension	415	Isradipine	Yes	Acute pulmonary edema, and cardiopulmonary arrest
303 LT Hypertension	236	Isradipine	Yes	Suicide
302 Hypertension	308	Isradipine	Yes	Myocardial Infarction
304 Hypertension	203	Propranolol	Yes	Cardiac Arrest Secondary to Arrhythmia or myocardial infarction
[redacted]	10	Placebo	Yes	Sudden Death
[redacted]	108	Isradipine	Yes	Severe Cardiomyopathy ventricular arrhythmia or embolic myocardial infarction
Emergency Use Protocol Heart Failure	150	Isradipine	Yes	Sudden Cardiac Death, History of Class IV CHF
252 [redacted]	104	Placebo	Yes	Cardiac & Respiratory Arrest

LT = long-term protocol

PATIENT DEATHS

STUDY NO. INDICATION	PAT. NO.	TREATMENT	REPORTED PREVIOUSLY IN NDA AND/ OR SU-1	CAUSE OF DEATH
252 [redacted]	304	Placebo	Yes	End Stage Ischemic Heart Disease with CHF and Ventricular fibrillation
301 LT Hypertension	408	Isradipine	Yes	Cardiac Arrest
351 Ctr. 1 Hypertension	106	Placebo	Yes	Automobile Accident
221 [redacted] the final dose was taken at least a couple of weeks before the patient expired	102	Propranolol	No	Hospitalize for Respiratory failure and diagnosed as HIV positive
255 [redacted] the final dose was taken at least a couple of weeks before the patient expired	36	Isradipine	No	Automobile Accident
253 LT [redacted]	101	Isradipine	Yes	Cardiac Event, probably ventriular fibrilation
254 LT [redacted]	101	Isradipine	Yes	Suicide
254 LT [redacted]	103	Isradipine	Yes	Cardiac Event Atherosclerotic heart disease w/ CHF
254 LT [redacted]	105	Isradipine	Yes	Ventricular Arrhythmia

[redacted]

IND No[redacted]
IND No[redacted]

No [redacted] isradipine studies have been completed at this time. Presently five (5) isradipine clinical trials are ongoing at [redacted]

* ISR-300: The Effects of Isradipine, Enalapril and Atenolol on the Quality of Life in the Elderly Female Hypertensive

* ISR-301 A Placebo Controlled Dose-Ranging Study to Evaluate the Safety and Efficacy of Isradipine Administered Once Daily for the Treatment of Hypertension

* ISR-325 A Placebo Controlled Comparative Evaluation of the Effects of Isradipine and Diltiazem on Antipyrine and Indocyanine Green Clearance in Elderly Volunteers

Table 1 lists the objectives, study design and treatments, and expected and actual enrollment numbers for each of the five studies.

TABLE 1

[redacted] ISRADIPINE STUDIES

DESIGN, OBJECTIVES AND ENROLLMENT

STUDY NO	OBJECTIVE	DESIGN	TREATMENTS	PATIENTS PLANNED	PATIENTS ENROLLED*	PATIENTS RANDOMIZED	PATIENTS COMPLETED	PATIENTS DROPOUTS**	IND SAFETY REPORTS	STUDY COMPLETION DATE ***
ISR-300	QUALITY OF LIFE	RANDOMIZED, D.B. PARALLEL TITRATION	ISRADIPINE ATENOLOL ENALAPRIL (ADD ON HCTZ)	480	258	150	7	13 (9)	8	JUNE 90
ISR-301	EFFICACY, SAFETY OF QD DOSING IN MILD TO MODERATE HYPERTENSION	RANDOMIZED D.B. PARALLEL FORCED PLACEBO CONTROL FORCED TITRATION	PLACEBO 5,10,15,20MG ISRADIPINE	350	384	239	198	27 (18)	0	SEPT 89
ISR-325	DRUG-INTERACTION HEPATIC CLEARANCE AND BLOOD FLOW	RANDOMIZED D.B. CROSSOVER	ISRADIPINE DILTIAZEM PLACEBO	18	18	18	0	0	0	AUG 89
		RANDOMIZED D.B. PLACEBO CONTROL PARALLEL	PLACEBO ISRADIPINE 10MG BID	60	68	61	50	2 (2)	0	AUG 89
		OPEN LABEL	ISRADIPINE 0.01MG/KG IV OVER 5 MIN	12	1	1	1	0	0	DEC 89

* As of July 15, 1989

** for any reason after randomization

( ) Number of patients dropped due to adverse events after randomization
Available information on adverse events of these patients are listed on the next page.

*** patient participation

PATIENTS DROPPED DUE TO ADVERSE EVENTS POST RANDOMIZATION

PROTOCOL ISR-300

PT. T050 - Sinus tachycardia
T098, T170 - Dizziness
T112 - Right arm fracture, leg cramps
T126 - Atrial fibrillation, hypothroidism
T135 - Ankle swelling, anxiety
T169 - Nausea, dizziness, rash
T181 - Facial tingling/warmth, nausea, lightheaded, mental confusion
T218 - Broken hip

PROTOCOL ISR-301

PT. T36 - Palpitations, flushing, weakness
T40, T43, T64, T68, T103, T156, T158, T160, T185 - Headache
T50 - Hot flushing, blurred vision, palpitations
T75 - Prostate biopsy
T82 - Dizziness, fluxhing, sleepiness
T85 - Flushing, headache, tachycardia
T154 - Headache, flushing, shakiness
T182 - Headache, weakness, decreased libido
T221 - Insomnia, left leg pain
T241 - Dizziness

PROTOCOL ISR-330

PT. T41 - Anxiety due to chest pain
T58 - Diagnosis of chololithiasis

B FOREIGN STUDIES

This is a review of the safety data of a multicenter and single group study ICR 1007 evaluating 590 angina patients. A total of 517 (88%) completed the study, which consisted of a 1-2 week placebo run in and a 12 week treatment period. Dose of isradipine started at 2.5 mg tid and was increased by 2.5 mg tid every two weeks to a maximum of 7.5 mg tid. The mean dose at the end of the study was 5.9 mg tid with a daily distribution of 19% 2.5 mg, 28% 5 mg and 53% 7.5 mg tid.

Adverse Reactions

A total of 73 (12.4%) patients discontinued treatment for various reasons, including 43 (7.3%) for ADRs.

Reasons for Discontinuation of Treatment

Reason	N	%
Non Study Drug Related	11	1.9
Protocol Violation	10	1.7
Ineffectiveness	6	1.0
Coronary Artery Bypass	3	0.5
ADRs/ Non Serious	32	5.4
ADRs Serious	11	1.9
Total	73	12.4

Newly occurring ADRs were reported by 338 (57%) patients. ADRs with an incidence > 1% are listed in Table II. Sponsor has classified the events into three groups: those due to vasodilatory action of the drug, those involving the GI system and CNS and those of cardiovascular or respiratory systems. Table III lists the ADR reasons for discontinuation from the study. A total of 9 coronary events, including one death, were reported as well as 2 sudden deaths. There was one case of silent myocardial infarction.

There was no evidence indicating a dose response relationship with ADR incidence. There was a low incidence of hypotension peaking at Week 8 in 2% of patients.

ECG Changes

There were no consistent changes in ECGs. The changes that were seen were those expected in the population group.

Laboratory Data

Sponsor states that there were no clinically relevant changes during treatment. There was an increase in cholesterol in 3 patients, increased alkaline phosphatase in 6 and increased serum glucose in 4.

Foreign ADRs- not previously reported are attached in the next Table.

TABLE II:
Newly Occurring Adverse Events
(Incidence >1%)

Event	Dose When Event Occurred				Total	
	2.5 mg t.i.d.	5.0 mg t.i.d.	7.5 mg t.i.d.	un-known	n	%*
Related to vasodilatatic						
Oedema	35	53	40		128	21.7
Headache	53	25	17		95	16.1
Dizziness/faintness/hypotension	35	19	19	1	74	12.5
Flush/rubor	27	24	9		60	10.2
Palpitation/tachycardia/awareness of heart	30	10	11		57	9.7
Cardiovascular						
Chest pain/angina pectoris	5	8	5		18	3.1
Respiratory						
Cough	6		2		9	1.5
Dyspnea	4		3		14	2.4
Neurological/CNS						
Tiredness	15	7	2		24	4.1
Disturbed skin sensation	9	6	8		23	3.9
Visual disturbance	1	4	4		9	1.5
Gastrointestinal						
Nausea/vomiting	11	7	4		22	3.7
Indigestion/diarrhea	10	2	7		19	3.2
Stomach pain/epigastric pain	3	4	3		10	1.7
Miscellaneous						
Leg pain		3	3	1	7	1.2
Asthenia	2	2	2		6	1.0

* n = 590

TABLE III:
Adverse Events Resulting in Discontinuation of LOMIR

3a Serious Events	n	%*
Myocardial infarction	3	0.5
Severe angina attack/chest pain	2	0.3
Deterioration of angina (inc. ECG changes in 1 patient)	2	0.3
Sudden death	2	0.3
Death due to heart failure	1	0.1
Acute coronary insufficiency	1	0.1
Total	11	1.6

3b Other Events	n	%*
Lomir-induced vasodilation (inc. oedema)	29	4.9
Nausea/vomiting	2	0.5
Epistaxis	1	0.2
Total	32	5.6

ISRADIPINE (LOMIR®, PRESCAL®) FOREIGN ADVERSE EXPERIENCES: JANUARY 1988 - JULY 1989

SERIOUS AND UNEXPECTED ADVERSE EVENTS NOT DEEMED REPORTABLE UNDER 21 CFR 312.32

Study No.	Patient I.D.	Age/Sex	Indication	Isradipine mg/day	Time of Occurrence Post-Drug Administration	Adverse Event	Outcome	Relation to Isradipine Therapy
Foreign Clinical Studies								
1007 LT	345	73 M	Angina Pectoris	7.5	14 Weeks	Myocardial Infarction	Died	Disease Related[a,b]
1007 LT	307	51 M	Angina Pectoris	15-22.5	17 Weeks	Sudden Death	Died	Non-Drug Related[a]
505	440	52 M	Hypertension	5-10	9.5 Months	Myocardial Infarction	Recovered	Disease Related[a]
551	643	58 F	Hypertension	2.5	66 Days	Myocardial Infarction	Died	Non-Drug Related[a]
551	88	74 F	Hypertension	10	10.5 Months	Death	Died	Unlikely[a]
1502	507	42 M	Hemodynamic Study/ Chronic CHF	22.5	7 Months	Cardiac Failure	Died	Disease Related[a]
552	77	65 F	Hypertension	10	7 Weeks	Hypotension/CVA	Recovered	Unlikely[a,f]
Belgian General Practitioner Field Study								
Belgium	89/0028	68 M	Hypertension	5	42 Days	Cardiopulmonary Arrest	Died	Unlikely[a]
Belgium	89/0104	69 M	Hypertension	5	6 Days	Myocardial Infarction	Unknown	Non-Drug Related[a]
Belgium	89/0107	48 F	Hypertension	2.5	24 Days	Endometrial Hyperplasia	Not Recovered	Non-Drug Related[a]
Belgium	89/0137	63 M	Hypertension	2.5	28 Days	Sudden Death	Died	Non-Drug Related[a]
Belgium	89/0138	52 M	Hypertension	2.5	18 Days	Acute Arterial Insufficiency Due to Occlusion of Femoral Bypass	Recovered	Non-Drug Related[a]
Belgium	89/0126	61 F	Hypertension	5	3 Days	Transient Ischemic Attack Due to Carotid Stenosis	Recovered	Questionable[a,f]
Post-Marketing Surveillance								
Great Britain	89741	74 M	Hypertension	2.5	---	Right-Sided CVA	Unknown	Under Investigation[f]

[a]Evaluation by the Investigator.
[b]Evaluation by the European Medical Expert, Sandoz Ltd. No evaluation provided by the investigator.
[f]Evaluation by Sandoz U.S., subsequent to review of documentation provided by Sandoz Ltd.

SANDOZ S.A.

CH-4002 BALE/SUISSE

DEPARTEMENT PHARMACEUTIQUE
RECHERCHE ET DEVELOPPEMENT

PN 200-110: HYPOTENSION (PN 87/180/F/65/GB)

Study No. 552, PT. #77

Please see next page for evaluation by Sandoz U.S.

Epicrisis

A 65-year old hypertensive overweight female participated in a PN-study evaluating the safety of this drug in hypertension.

The patient's initial blood pressure was 190/115, the HR being 78 bpm. The patient was given 2.5 mg PN b.i.d. and his blood pressure was 160/105, heart rate 60 bpm.

The PN dose was increased to 5 mg b.i.d. The patient experienced two episodes of facial paresthesia and slurred speech lasting 15 minutes each after she had taken 3 doses of this increased regimen. The blood pressure was 160/60 mm Hg, she was in sinus rhythm and ECG was normal with no recent changes.

PN 200-110 was stopped and the patient recovered over the next 12 hours. She had had nothing similar before and there was no past history of cerebrovascular disease.

The patient suffered a right-sided cerebrovascular accident with aphasia and hemiplegia about 7 weeks after having been discontinued form the PN-study. The patient is still recovering from this incident.

Comment

Please note that the cerebrovascular accident occurred only 7 weeks after study discontinuation.

When transient ischemic attacks precede a stroke, they almost always stamp the process as thrombotic. Fully 60 percent of cases of atherothrombic strokes are preceded by transient ischemic attack, the risk of stroke in the population of cases experiencing transient ischemic attack is 6 to 7 percent the first year.

It cannot be excluded that drug-induced mild hypotension may have been a concomitant factor in the development of this patient's transient neurological symptoms.

E. Fröding, MD
Drug Monitoring Centre

C.D. Sundstedt, MD
PN/PY Task Force

European Study No. 552, Patient No. 77

Evaluation by Sandoz U.S.

The patient discussed obviously had a cerebral vascular accident preceded by an episode of transient cerebral ischemia. A direct relationship to isradipine is highly unlikely. Based on the data given in the circular letter, the patient was not hypotensive. Direct relationship is even more remote when one recognizes that isradipine had been stopped approximately seven weeks prior to the cerebral vascular accident.

This particular adverse drug experience occurred in August, 1987. All other foreign ADEs on the table occurred Jan. 1988 - July 1989, as indicated on the table.

SANDOZ LTD.

CH-4002 BASLE / SWITZERLAND

PHARMACEUTICAL DIVISION
RESEARCH AND DEVELOPMENT
DRUG MONITORING CENTRE

Lomir® 89/0126

Case History : This 71-year-old hypertensive woman was treated with Lomir® in the "Belgian General Practitioner Field Study". Three days after Lomir® therapy with 5 mg/day was started she suffered from dizziness, paresis of the left arm and leg and the left side of the mouth and a transient ischemic attack was diagnosed. Four days later the daily dose of Lomir® was reduced and one week later the drug was discontinued. The patient made a complete recovery. Subsequently, the patient moved elsewhere and a stenosis of the carotid artery was diagnosed. A consulted neurosurgeon recommended a surgical intervention.

Comment : The reporting physician judged the causal relationship between the event and the drug administration as questionable. However, he reasoned that a drop in blood pressure in this elderly patient with a carotid stenosis may have produced the described symptoms.

Prof. P. Krupp, M.D.

3109/PK/Old
August 18, 1989

SANDOZ LTD.

CH-4002 BASLE / SWITZERLAND

PHARMACEUTICAL DIVISION
RESEARCH AND DEVELOPMENT
DRUG MONITORING CENTRE

Prescal® (Dynacirc®/Lomir®)

Case Report : 89741

This 74-year-old patient participated in the UK PMS of Prescal® in hypertensive patients, which is conducted by [redacted] the licence holder of Prescal in UK. The patient suffered a CVA while receiving 2.5 mg Prescal® b.i.d. for hypertension. Since the patient has moved area and is now treated by an another general practitioner, the collection of follow-up information was difficult and delay has occurred.

Further information on this case will be provided as soon as it becomes available.

Prof. P. Krupp, M.D.

3109/PK/Old
August 21, 1989

LOMIR/DYNACIRC (isradipine)

Worldwide Regulatory Actions as of 8/89

PRODUCT LAUNCHED		APPROVAL OBTAINED		SUBMISSIONS PENDING		SUBMISSIONS PLANNED	
Great Britain	2/89	Great Britain*	1/89	Canada	9/87	India	7/89
Ireland	9/89	Belgium	1/89	Argentina	3/88	Korea	8/89
		Columbia	2/89	Denmark	4/88¶	Peru	8/89
		Ireland*@	3/89	Norway	4/88	Thailand	8/89
		Switzerland	6/89	Netherlands	5/88¶¶	Italy	10/89
		Chile	7/89	Portugal	5/88	Turkey	9/90
		Uruguay	7/89	Finland	6/88		
		Egypt	8/89	Swedon	6/88		
		Czechoslovakia	8/89	New Zealand	6/88		
				Austria	7/88		
				Mexico	8/88		
				Australia	9/88		
				Brazil	9/88		
				Luxembourg	9/88		
				Spain	11/88		
				South Africa	11/88		
				Venezuela	12/88		
				Israel	1/89		
				Pakistan	3/89		
				France	7/89		
				Germany	7/89		
				Greece	7/89		

@ Hypertension and angina pectoris

* To be marketed by [redacted]

¶ Initial application not accepted due to toxicological & clinical safety reasons (see p.165). Appeal submitted 6/21/89.

¶¶ Initial application not accepted due to pharmacological, toxicological, & clinical design reasons (see pp.166-168). Hearing took place 5/11/89; Additional data submitted 6/10/89.

FOREIGN REGISTRATION

As indicated on the table on the previous page, isradipine has been approved in nine (9) countries for the indication of hypertension. In Ireland, the drug has also been approved in angina pectoris.

In Denmark and The Netherlands, the application was not accepted by the regulatory authorities, as originally submitted. Additional data and analyses were requested, and subsequently submitted, in both cases. Data generated in U.S. studies, not included in the original foreign applications, was oftentimes used to address the issues identified on the following pages.

Sandoz Pharmaceuticals Corporation in the U.S. is in receipt of the responses sent to the Danish and Dutch authorities by our affiliates, and this information is available to the FDA upon request.

translation

NATIONAL BOARD OF HEALTH
Medicines Department

Date:01.March 1989
ref.no. 2810-13269/70
1988 AK/bj

Sandoz A/S
Titangade 9 A
2200 København N. DENMARK

Reference to the company's previous communications, latest of Jan 27th 1989 regarding LOMIR, Sandoz, tablets of 2.5 mg and 5 mg isradipin.

Following the recommandation from the Advisory Committee on Registration (Registreringsnævnet) the National Board of Health has decided that the application does not fulfil the requirements for issuing a marketing authoritation as laid down in § 15, 4 in the Medicines Act.

(The grounds given)
The toxicological documentation is insufficient as the carcinogenicity study in mice - in light of the results - should be repeated.

The clinical documentation is insufficient as supplementary studies to elucidate the products action on the liver function as well as studies in patients with impaired liver function are needed.

The pharmaceutical documentation is accepted.

Yours sincerely

Agnete Kjærvig

SANDOZ B.V.
Holland

Annex 1 to letter of 14.4.1989 re Lomir / Registration

OBJECTIONS OF THE DUTCH AUTHORITIES RE THE PHARMACOLOGICAL, TOXICOLOGICAL AND CLINICAL DATA

1. Isradipine is advised to be given twice daily. There are however doubts if the duration of control of blood pressure covers the interval between two dosage administrations (i.e. 12 hours). The moment of blood pressure measurement was not mentioned in a majority of the clinical studies. It was only mentioned that measurements were done on the same moment each day and on the same arm. The moment of measurement however, in relation to the medication, is of extreme importance. Therefore more insight is necessary into the effectiveness of isradipine during the last part of the dosage interval.
At the moment, there are only one uncontrolled pharmacodynamic study (McMahon, US study #9, study #5 in Vol II Lomir Clinical Data, Doc 603-362) and two clinical studies (Strozzi, Basle study #514, study #54 in Vol XXIV Lomir Clinical Data, Doc 0603-442; Adams, Basle study #519, study #56 in Vol XXIV Lomir Clinical Data, Doc 0603-448) available in this respect.
McMahon investigated negroid patients who usually respond better to treatment with a calcium antagonist than white patients.
Strozzi and Adams respectively investigated patients with an average age of 60 and 71 years. Older patients show different pharmacokinetics from younger patients. In these older patients, isradipine has a significantly longer half life and a significantly higher bioavailability (Schran/Lewis/Cohen, US study #321, study #17 in Lomir Clinical Data, Doc 0303-035). It is therefore not certain if in the patient population aimed

00-000166

at, which consists mostly of younger patients, blood pressure control will be obtained during the entire dosage interval.
The study by D. Nelson et al. (Multicenter evaluation of the safety in out-patients with essential hypertension, Lomir Clinical Data Vol XXXI, Final Report, Doc 045927) is, because of poor design (single blind and uncontrolled), purpose (safety study), patient selection and the high percentage of patients receiving concomitant medication (32%), not suitable for illustration of blood pressure control during the dosage interval.
Evenmore, in the submitted clinical data, during dose titration in monotherapy, in order to obtain adequate blood pressure control more than once a dose had to be used which was higher than 5 mg twice daily.
Also because of the adverse effects, it is therefore necessary to use the following text in the section "Indications":
"Essential hypertension. Isradipine can be given as monotherapy but it is preferred to combine this drug with a beta-antagonist and, if necessary, a diuretic."

2. There are doubts concerning the pharmacological activity of the metabolites of isradipine. The influence of renal insufficiency on the pharmacokinetic parameters is not clear.

3. Hardly any attention has been given to the pharmacological effects of isradipine in general, such as central effects.

4. No studies have been submitted showing that there is no interaction between isradipine and other receptors as well (e.g. α- and ß-adrenergic, 5-HT and dopaminergic receptors).

5. The effect of (sub)chronic treatment with isradipine on

plasma renin and aldosteron has not been reported. It is known that derivatives of dihydropyridine can raise PRA and aldosteron. This can be of importance in the interaction with ACE-inhibitors during the treatment of hypertension.

6. On basis of the submitted experiments regarding the possible preventive effect of isradipine against atherosclerotic processes and ischemia, it can not be said without doubt that this drug has anti-ischemic, cholesterol lowering or vascular wall protecting properties in humans. As a consequence, the statement that Lomir has an anti-atherogenic effect, is not adequately supported.

7. The effect on hemodynamics have not been investigated in the awake dog. This is important in order to obtain more insight in reflectory mechanisms in not-anesthetised conditions.

8. It is known that other calcium-antagonists can lead to a rise in CPK. Also abnormal LE-serolcgy (ANF- and ANA-serology) has been reported. The Board would like to receive data concerning these effects with isradipine.

9. With nifedipine menorrhagia or metrorrhagia sometimes is reported and gingival hyperplasia sometimes is seen during the use of other calcium antagonists. The Board would like to receive data on the occurence of these side effects with the use of isradipine.

Remark: In view of the seriousness of the above mentioned objections, part IB (Basic text) and the insert leaflet have not been reviewed yet.

Isradipine (LOMIR®, PRESCAL®)

Marketing History

As of July 31, 1989, sales of isradipine have taken place only in Great Britain (where the product is marketed as PRESCAL, by Ciba-Geigy).

The amount of PRESCAL sold in Great Britain as of July 31, 1989 is approximately 12,000 packs, where each pack contains sixty (60) 2.5 mg tablets.

The U.S. is the only country which will market a capsule formulation, DYNACIRC®. All other countries will be marketing a tablet, LOMIR® or PRESCAL® (Great Britain and Ireland only).

Product launch in Ireland is scheduled for September, 1989.

Other countries in which approval has been received are expected to launch in the fourth-quarter 1989 or first-quarter 1990.

11-22-88
Safety Update

FEB - 1 1989

CLINICAL DATA SUMMARY - OVERSEAS EXPERIENCE

All data used in this report are found in Sandoz report, volume 3 of 16. The drug is discussed by Sandoz, using the European name LOMIR. The report is dated November 13, 1987.

Sponsor states that this clinical data summary results were obtained in a total of 525 normal subjects and 2569 patients. Of these, 445 normal subjects and 1745 patients received LOMIR. The studies reviewed are listed in Tables I - VI. The numbers quoted by the sponsor do not balance with the numbers in the tables. These tables are:

Table #	Indication	# Active Patients
I	Clinical Pharmacodynamics	123
II	Pharmacokinetics	458
III	Hypertension	1275
IV	Angina	239
V	Pilot Studies in Other Conditions	55
VI	Safety Studies	

1. REVIEW OF SAFETY DATA FROM NORMAL VOLUNTEER STUDIES

This review includes normal volunteer safety, bioavailability and pharmacokinetic studies conducted both in the US and Europe. A total of 433 volunteers received single or multiple doses of LOMIR, 1.25 mg - 22.5 mg/day. Summary data for all ADRs are presented in Table I. (This is a different Table I than the one mentioned above. Apparently the sponsor is using a new series. This Table I is found on page 09-00399 of the summary). All results are adjusted for occurrences during the placebo washout periods.

The 1231 administered doses were divided into four groups to try to analyze data by dose effect. The four groups were: < 5mg/day (406 doses); 7.5 - 10 mg/day (643 doses), 15 mg/day (71 doses) and > 20 mg/day (111 doses). There was no dose-event relationship seen. The most common events reported were headache (50%), dizziness (11%), fatigue (10%), flushing (9%) and GI complaints (10%).

In most of the studies there was no placebo control group. In only about a third did the investigator indicate whether the event was drug related or not. Most of the events were classified as mild.

In about a third of normal volunteer studies, there was a mean increase in pulse rate of 5-15 bpm and this occurred mainly at 10-20 mg/day dose. One volunteer experienced hypotension (98/50 mm Hg) and a tachycardia of 112 bpm about two hours after a 5 mg dose. He recovered without treatment. The overall incidence of tachycardia was 4%.

Twenty one volunteers discontinued the trials for the following reasons: Liver function abnormalities (10); headache (3); abdominal discomfort (1); positive urine screen for drugs (3); personal (3) and uncooperative (1).

2. REVIEW OF SAFETY DATA FROM HYPERTENSION TRIALS.

This section contains safety data from more than 1200 hypertensive patients, treated with LOMIR. Over 400 received long term therapy. Sponsor points out that the incidence of ADRs depends on the method of collecting the data e.g direct questioning as well as dose, length of therapy etc. All data from different trials were pooled and compared to other antihypertensives. Emphasis was placed on low dose (< 10 mg/day) since the optimal dose in hypertension was found to be lower than the doses usually used in the clinical studies. The review concentrates on 15 phase III comparative short term studies conducted in US and Europe.

The most frequent reported ADRs are listed system-wise in Table II, page 09-00403 and in Table III (09-00408) for those that were drug related. Once again, adjustment has been made for those events that occurred during the placebo periods. Table IV summarizes reasons for withdrawal of LOMIR therapy.

There were 1028 LOMIR patients analyzed and, of these 538 (52%) reported an adverse event. Approximatey 29% of these events were considered drug related; 60% were reported spontaneously, 30% were elicited and for 10% it was unknown how they were collected. Most events were mild to moderate in severity. Of the 11% of patients withdrawn from the studies, about 75% were due to an ADR. Approximately 59% of patients receiving an active control drug reported an ADR, 29% being drug related and 18% being withdrawn from the studies. About 31% of placebo patients had ADRs with less than a quarter being drug related.

The most common events reported with LOMIR were headache (17%), flushing (15%), edema (12%), palpitation (9%), dizziness (9%), fatigue (3%), abdominal discomfort (3%) and chest pain (3%).

The mean daily dose in free titration studies was 6.2 mg - 22.2 mg. The mean daily dose for some of the comparative agents were: atenolol 68.8 mg, diltiazem 292.6 mg, HCT 40.5 mg, nifedipine retard 55.1 mg, prazosin 9.5 mg and propranolol 332 mg. The mean duration of treatment was 5 weeks in the placebo controlled studies and 12 weeks in the active controlled trials. The mean duration of LOMIR exposure in the 15 comparative trials was 9.2 weeks.

Sponsor states that the incidence rates are similar to those seen with calcium antagonists in general. When an optimal dose of 2.5 - 10 mg/day was used, fewer events occurred. Only 18-48% of patients in the lower dose groups reported ADRs. When results were pooled, it was found that 28% in doses 2.5 mg bid and 26% placebo had ADRs.

Central Nervous System

The most common events were headache (17%) and dizziness (9%). Two percent of patients withdrew due to headache and 1% due to dizziness. Sponsor states that with a dose of 10 mg/day or less, the incidence of headache decreases within a few weeks of continued treatment. The percentage of patients in controlled trials reporting headache and dizziness were:

	Headache		Dizziness	
Control Drug	%	LOMIR %	Control %	Lomir %
Nifedipine	37	30	20	26
Nifedipine	26	13	9	9
Diltiazem	16	17	16	6
HCT	16	17	10	10
HCT	15	19	4	7
Atenolol	17	25	8	11
Atenolol	7	21	0	7
Propranolol	14	28	5	9
Prazosin	16	20	20	10

NB. Where a drug appears twice, results are taken from two different studies.

The incidence of fatigue was 3% compared to 6% with control drugs, mainly propranolol. The remaining CNS events (Tables II and III) were less frequent. However, if some of these terms were combined the incidences would increase eg fatigue, lethargy, weakness and malaise, and possibly drowsiness and energy decrease. If all these terms were combined, the overall incidence of fatigue would then be 7% instead of 3%.

Table IV presents the reasons for patients withdrawing from the study due to an ADR. Three patients had a serious CNS event causing withdrawal: cerebrovascular insult associated with pulmonary edema, tiny dot hemmorhages in the perimacular area and TIA with dizziness and headache in a patient receiving LOMIR plus atenolol. Another patient had a stroke on the day after receiving his final dose of LOMIR.

Sponsor concludes that when LOMIR is used in the elderly patient with risk factors for cerebrovascular disease, the dose should be carefully titrated.

Autonomic Nervous System

Flushing occurred in 15% of patients and hypergidrosis in 1%. Once again, sponsor states that the incidence of flushing decreases with continued use of the drug in a dose of 10 mg/day or less. Flushing was reported in more than 10% of patients withdrawn from treatment but was the only reason for wothdrawal in only three of them.

Gastrointestinal System

Abdominal discomfort was reported in 3% of patients. One patient was withdrawn due to acute cholycystitis, unrelated to treatment. Elevated liver enzymes without symptoms were found in some patients. Constipation was reported in 1%, diarrhea in 2% and nausea in 2%.

Cardiovascular System

Calcium antagonists produce negative inotropic, chromotropic and dromotropic effects. LOMIR, in animals, was found to have selective actions on the heart as well as on peripheral circulation.

Tachycardia and palpitation were reported in 1.4% and 9% respectively. The incidence rate for tachycardia is 3% when all patients are included who demonstrated this at one time period during treatment on ECG or cardiovascular examination. The mean increase in pulse rate was 2-5 bpm and this appeared to be dose related. About 1% discontinued therapy due to tachycardia. Bradycardia was seen on ECG in less than 1% of patients, with a higher incidence reported in the beta-blocker control groups.

Sponsor states that the "inhibitory action of LOMIR on the sinus node which was demonstrated in animal experiments was not seen in man, although the reflex homeostatic mechanisms which were induced by LOMIR through peripheral vasodilatation may have been attenuated by such an effect."

Six patients withdrew due to myocardial ischemia and/or signs and symptoms thereof (Table IV). Death (2 cases) and MI (1 case) were not considered to be drug related by the investigators. Relationship is uncertain in the other cases.

There were no negative dromotropic effects on the AV node during PES studies. There was no apparent negative inotropic effect in patients with normal LV function. Three patients developed and/or had worsening of CHF and had to be withdrawn from trials.

Three patients had atrial flutter/fibrillation with LOMIR and were withdrawn. Two withdrew due to angina increase and two experienced aortic dissection on treatment. Hypotension was reported in four patients and dose should be titrated in the elderly patient.

Peripheral edema was reported in 12% of patients but this incidence decreases with continued treatment and is less with a lower dose (< 10 mg/day). About 2% were withdrawn due to edema.

On examination of Table II, it is seen that chest pain occurred in 3% in addition to the 0.3% incidence of angina and 0.4% of retrosternum pain. (Chest pain was also reported under gastrointestinal system 0.2%, 0.4% under respiratory system, 0.3% under musculo-skeletal system). Sponsor should be requested to "collapse" terms better.

Respiratory System

There were no clinically relevant ADRs on respiratory function. A review of Table II shows that dyspnea, coughing and nasal congestion were all reported in 1% of patients.

Muscullo-Skeletal System

Sponsor states that there were no ADRs occurring more than in the control groups. Table II lists backache/pain with an incidence of 1%, joint pain 2% plus pains in various limbs.

Integumentary System

Rash 2% was the most common event reported. Seven patients withdrew due to rash.

Urogenital System

The only important effects cited by the sponsor were increased diuresis/pollakisuria possibly due to the natriuretic effect of LOMIR. Certain abnormal lab results were seen which are discussed later.

Hemoporetic and Lymphatic System

No evidence of any consistent changes in any of these variables.

Miscellaneous

One patient was withdrawn due to relapsing mammary carcinoma. Gingival hypertrophy was seen in dogs but not reported in any study in man. As the event occurred only rarely in dogs, it is possible that there were not sufficient patients in these studies to detect a small incidence of this occcurrence.

Incidence of ADRs and Maximum Daily Dose.

The five most commonly reported ADRS were analyzed by grouping the patients of 15 phase III short term studies as follows: Each patient was classified in one of six dose groups (1, 2.5, 5, 10, 15 and 20 mg/day) according to the maximum daily dose received during the first 6 weeks of the study. All new and/or worsening occurrences of a particullar ADR occurring during the first 6 weeks were added for each patient and the incidence calculated for each dose group. The following observations were made by sponsor:

dizziness, flushing, headache, edema and palpitations allincreased with dose.

LONG TERM CLINICAL TRIALS

This review includes 420 patients from US and European long term studies. The mean dose of LOMIR ranged from 11.0 mg/day to 16.2 mg/day. The mean duration of treatment was 57 weeks (19-112). About one fifth of patients received a concomitant antihypertensive medication. ADRS from the long term studies are presented in Tables VI and VII. Baseline adjustments were made using following criteria:

the last visit during the placebo washout period before initial double-blind trial was used as baseline for those receiving LOMIR as monotherapy or in combination with HCT.

the last visit of the initial double-blind study for those who had received one of the control test drugs in the double-blind study.

There were 77% reporting an ADR during long term treatment. Table VII presents those cases resulting in withdrawal from the study (11.6%). Sponsor states that all 12 serious events resulting in withdrawal were not drug related; they had been on LOMIR for 3-15 months prior to the event. Three addutional patients had a MI but were not withdrawn for this reason. One TIA was also not withdrawn.

A comparison is made by the sponsor between the ADRs in the short term studies and those in long term trials. As the lengt of therapy obviously differs, sponsor has grouped those events of at least 1% occurrence. The groups are events occurring 2-5 times as often in long term studies and 6 times and more.

These listings are found on page 09-00371 but do not really tell anything. A review of Table VI shows the following events with an occurrence of more the 1% during long term treatment:

Central Nervous System

Dizziness (16%), headache (27%), fatigue (8%), insomnia, nervousness and syncope (3%); drowsiness, lethargy, tinnitus and weakness all 1%.

Autonomic Nervous System

Flushing (21%), dry mouth, hyperhidrosis, numbness, parasthesia all 1%

Gastrointestinal System

Abdominal discomfort 8%, nausea 5%, vomiting 2% and constipation 1%

Cardiovascular System

Edema (21%), palpitations (14%), chest pain (7%), angina, leg cramps 2%, tachycardia 3%, and dyspnea 1%

Respiratory System

Coughing (5%), dyspnea again 5%, nasal congestion 6%, chest pain again 2%, others 1%

Musculo-skeletal

Backache 5%, chest pain again (2%), pains in various limbs 1% each.

Other Systems

Rash 5%, pruritus 2%, impotence 2%, nocturia 2%, pain 2%

For a full list of events occurring more than 1%, refer to Table VI.

Placebo Crossover Trials

Table I presents the most common abnormalities seen on physical examination, cardiopulmonary examination and ECG.

ADR	Lomir n= 92 (%)		Placebo n= 92 (%)	
Atrial Gallop	8	(9%)	7	(8%)
Edema	22	(29%)	4	(4%)
Palpitation	11	(12%)	3	(3%)
Abdominal Discomfort	3	(3%)	5	(5%)
Nausea	4	(4%)	2	(2%)
Dizziness	3	(3%)	4	(4%)
Fatigue	9	(10%)	5	(5%)
Headache	16	(17%)	10	(11%)

In three US trials, increases in sitting heart rates (3-7 bpm) were noticed in the active group at the pre-crossover analysis. In the European trial, a mean decrease in heart rate (-2.2 bpm) was seen with LOMIR.

A total of 7 patients were discontinued due to ADRs: nausea + angina; headache; nervousness + angina; nausea; tachycardia; elevated LDH; palpitations + burning sensation in lower limbs.

Nifedipine Crossover Trials

~~The most frequent events were palpitation, tachycardia, dizziness,~~ headache, fatigue and shaking and these were more common with nifedipine.

ADR	LOMIR n= 71 (%)		Nifedipine n= 74 (%)	
Edema	8	(11%)	9	(12)
Palpitation	3	(4%)	6	(8%)
Tachycardia	2	(3%)	5	(7%)
Increased Angina	3	(4%)	1	(1%)
MI	2	(3%)	1	(1%)
Dizziness	10	(14%)	24	(32)
Headache	9	(13%)	19	(26%)
Fatigue	3	(4%)	8	(11%)
Shaking	0	(0%)	5	(7%)
Nausea	1	(1%)	3	(4%)
Vertigo	0	(0%)	3	(4%)
Flushing	6	(9%)	9	(12%)
Sudden Death	0	(0%)	1	(1%)

When added to a beta-blocker, there were no events that sponsor attributed to combination therapy. In most trials, there were elevations of glucose and liver enzymes which are discussed later.

Long Term Trials

There were 36 patients enrolled in long term [redacted] The mean age was 64 years, final LOMIR dose was 19.4 mg/day and mean duration of treatment was 51.8 weeks (3-126 weeks).

The most frequently reported events were chest pain and dyspnea. There were more patients with a deterioration in their NYHA class (5/36 compared to 8/225 hypertensives). In 3 of the 5, NYHA class returned to pre-LOMIR class during treatment; the remaining two were discontinued after 62 and 66 weeks therapy. There were more ADRs than in long term hypertension tests possibly because of the higher doses of drug used.

There were 56% patients with new or worsening abnormalities in their blood chemistries (hypertension was 58%). These are discussed later. There were 19 (53%) patients discontinued due to ADRs: Death; atrial fibrillation, chest pain + MI; increased angina/MI; MI; chest pain with ST depression; severe angina; unstable angina; angina, pedal edema; muscle cramps feet/hands; other 8. Except for two, all received drug for more than 23 weeks.

LOMIR was withdrawn due to ineffectiveness in 4 cases treated for 6 months and in one after 66 weeks.

SAFETY IN PATIENTS WITH BRONCHIAL ASTHMA/ IMPAIRED PULMONARY FUNCTION

In a placebo controlled crossover study of 12 asthmatics with exercise inducible bronchospasm, LOMIR was given in a fixed dose for 3 days. LOMIR decreased exercise induced bronchospasm as assessed by post-exercise FEF 25-75%. There were no statistically significant differences between drug and placebo with regard to FEV1, FVC, PEF. No clinically relevant abnormalities were seen in the safety data except one patient with a history of premature atrial contractions who had atrial fibrillation with LOMIR.

SAFETY IN CONGESTIVE HEART FAILURE

A total of 18 CHF patients (NYHA class II-IV) received single oral doses of 2.5-15 mg/day. Two patients with a significant degree of CHF developed hypotension after single doses of 5 and 10 mg. Another 10 patients received LOMIR iv 0.1 g/kg/min x 30 min followed by 0.3 g/kg/min x 30 min. Mild abnormalities in ECG changes and liver enzyme increases were seen. An additional 10 patients entered a long term trial and 6 discontinued due to non-compliance; death; moved out of state; leukopenia; noncompliance; death. In no case, according to sponsor, was there a drug relationship.

ELECTROPHYSIOLOGICAL AND ANTIARRHYTHMIC EFFECTS.

In an 11 patient study with diagnostic routine electrophysiological evaluation, iv LOMIR 0.3 micrograms/kg/min x 30 minutes was infused. There was no depressant effect on the normal sinus and AV node. Shortening of cycle length by 8%, atrial to His interval 4%, intraarterial conduction time 6%, AV nodal function refaractory period 6% were all seen, possibly due to an indirect effect of the drug.

A total of 15 patients entered a two period, single-blind, placebo controlled study evaluating oral LOMIR in patients with chronic PVCs. Of 12 receiving drug, one had increases in total frequency PVCs and in single PVCs; another had increases in total frequency PVCs and in the number of beats occurring during ventricukat tachycardia. The rest had little or no change.

EFFECTS ON ENDOCRINE FUNCTION

LOMIR has been reported to inhibit insulin release from isolated pancreatic islets in response to glucose. When administered to 6 normal males in single doses of 5 or 10 mg, basal secretion of insulin [illegible] influenced. In addition, insulin secretion stimulated by lunch was inhibited by LOMIR.

In 12 diabetics, one had a deterioration in his diabetic state but the rest did not change but only 6 completed the study so data are limited. In 10 obese hypertensives who received either drug or placebo for 4 weeks and then crossed over, 6 had normal and 4 impaired glucose tolerance tests. 21 patients with stable type II diabetes were enrolled in a double blind, randomised crossover trial with nifedipine retard. LOMIR showed favorable effects on fasting blood sugar etc. Sponsor concludes that LOMIR has no effect on glucose homeostasis.

There were both increases and decreases in serum glucose in some diabetics. Overall incidence of new or worsening laboratory abnormalities for serum glucose was 7% with LOMIR, 8.7% with control drugs and 5% placebo.

OTHER HORMONES

It had been found that, in rats, there was a significant increase of Leydig cell hyperplasia and a benign tumor incidence was found in the testes. It is believed by the sponsor that these cases are directly caused by a LOMIR induced chronic elevation of circulating LH and/or FSH level, which is specific to the Sprague-Dawley Charles River CD rats.

In man it was found, in four studies, that LOMIR did not influence total or pulsatile secretion of GH, TSH, LH, prolactin and insulin. There was no impairment of insulin secretion following food stimulation nor were sleep-stimulated secretion of prolactin, GH, ACTH, LH, TSH and cortisol affected. There were no clinically significant between differences from placebo for FSH, LH, testosterone or prolactin. In another study, LOMIR given as a single dose, 10 mg, to 9 male volunteers did not modify the release of GH induced by 20 minutes bicycle ergometer stress.

LIVER FUNCTION ABNORMALITIES

Liver function abnormalities were found in 11 volunteers 4-6 weeks after the conclusion a bioavailability study. There were 7 subjects with elevated serum transaminases ranging from 200 to 1600 units (upper normal range 50-55 units) and of these 4 had positive hepatitis B core antibodies with negative hepatitis b surface antigen. Four complained of tiredness and one had slight anorexia; two reportes periods of dark urine and light stools before repeat liver function tests were done 4-6 weeks after the study. The cause of the elevated enzymes remains unknown. Nine have been rechallenged with LOMIR, single dose 10 mg, and only two of these nine developed SGOT and SGPT elevations 4-6 days after rechallenge.

The sponsor has reviewed all data on liver function tests with LOMIR. Sponsor states that no case with clinical symptoms of hepatotoxicity nas been reported. Equal frequencies of liver functionabnormalities compared to LOMIR were found with diltiazem and nifedipine in short term studies. The incidence of new or worsening liver function abnormalities in 14 phase III comparative short term studies is shown below.

Elevated Value Under:	LOMIR (%) n = 956	Comparative Drug (%) n=547	Placebo n=161
Alk Phosph	5.2	5.8	5.6
Total bilirubin	1.5	2.7	1.9
LDH	2.8	5.3	1.9
SGOT	5.0	3.6	5.6
SGPT	5.6	6.4	8.1

In addition to previous reports, slight but statistically significant increases in mean serum alkaline phoshphatase have been seen.

Sponsor concludes by quoting the 1986 report that this type of hepatic reaction may be due to an idiosyncratic reaction and that there was no evidence that LOMIR had a greater potential for causing hepatic reactions than other calcium channel blocking agents.

DIGOXIN

A study evaluating influence of LOMIR on single dose pharmacokinetics of digoxin showed that there ws no clinically relevant interaction with digoxin.

BETA-BLOCKERS

Concomitant administration of 10 mg LOMIR and 80 mg propranolol as a single dose in 18 volunteers resulted in a statistically significant increase of propranolol bioavailability. Sponsor reviews some studies were LOMIR was administered with a beta-blocker and concludes that the pharmacokinetic interaction with propranolol was unlikely to be clinically relevant and that hemodynamic ill effects cased by the concomitant use of the drugs were expected to be rare.

OTHER DRUGS

Concomitant use of LOMIR and HCT did not result in altered pharmacokinetics of either drug. No dose adjustments are required and the combination is well tolerated.

There are not sufficient data to allow a recommendation for the combined use of coumarin or of cimetidine.

IMPAIRED RENAL FUNCTION

The variable pharmacokinetic results in patients with impaired renal function show that individual dosing regimen is required.

PREGNANCY AND LACTATION

No studies were performed in these patient groups.

IMPAIRED LIVER FUNCTION

The bioavailability of LOMIR was greater in subjects with impaired liver function and lower doses should be used in this population and careful individual dosing is required.

CONCLUSIONS

Sponsor concludes that LOMIR in doses up to 22.5 mg/day was associated with ADRs similar to those seen with current dihydropyridine calcium antagonists. The frequency of ADRs is highest in the first three months of treatment.

Basel Friedman, M.D.
reviewer

cc. ORIG NDA 19546
HFD-110
HFD-110 CSO

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

AUG 30 1988

NDA 19-546

I. Introduction

II. Clinical Pharmacology

III. Efficacy Studies

1. Pivotal Studies

1) Multicenter placebo controlled studies of safety and efficacy in mild to moderate hypertension. Studies #301 (page 42), 302 (page 48)

2) HCTZ controlled study of safety and efficacy in hypertension. Study #303 (page 56)

2. Positive Control Studies

1) Propranolol controlled Study of safety and efficacy in hypertension. Study #304 (page 61)

2) Prazosin Controlled Study of safety and efficacy in hypertension. Study #305 (page 68)

3) HCTZ Controlled Study of safety and efficacy in hypertension. Study #307 (page 74)

4) HCTZ Propranolol Controlled Study of PN-200 and HCTZ combined. Study #307 (page 74)

3. Other Studies in Hypertension

1) Long term Open Label Study of safety and efficacy in mild hypertension (page 82)

2) European Studies of safety and efficacy in hypertension (page 86)

3) Conclusions.

4. Pilot and Special Studies

PREFACE

Isradipine (trade name Dynacirc, code PN-200)is a calcium channel blocking agent of the dihydropyridine class of which several are commercially available. Isradipine is presented for approval in the treatment of mild to moderate hypertension.

The studies are introduced by a review of the important role of calcium in all cells and therefore the potential of wide clinical application of calcium channel blocking agents. This class of drug acts on the voltage sensitive calcium channel and is of particular importance in smooth muscle where its effect on hypertension is exerted. The pharmacological actions are given exhaustive treatment in the preclinical section.

The data presented in support of the application, gathered from over 1000 patients, are contained in 163 volumes. Pharmacokinetics, pharmacodynamics, and dose ranging studies support the Phase Three studies. There are six major clinical studies in hypertension, two of which are placebo controlled and critical. The drug is shown to be superior to placebo, equal at least to beta blockers, compatible with a diuretic HCTZ, and superior to an alpha blocker.

The data from all the studies indicate isradipine is safe. The statement could be made without reservation were it not for the calamatous occurrence of abnormal liver function in one pharmacokinetic study. The high incidence of abnormal liver function tests found subsequently was thoroughly explored and there has been no further suggestion of liver toxicity, an occasional abnormality since that episode being readily accounted for. Side effects can be almost attributed to the pharmacologic effects of the drug.

Additional data are furnished by European studies consistent with domestic data. A long term safety study is still in progress.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA 19-546

Applicant: Sandoz

General Information:

a. Name of drug:

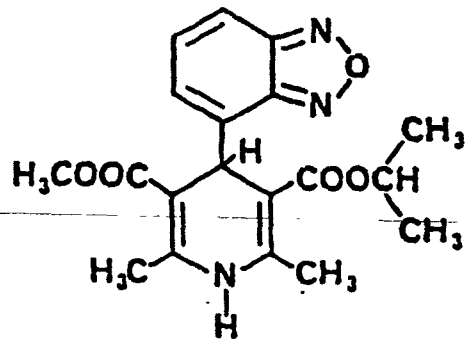
(1) Generic: Isradipine

(2) Trade: Dynacirc

(3) Code: PN 200-110, PN 200, PN

(3) Chemical structure

PN-200-110 is a dihydropyridine derivative. Its structural formula is:



Molecular Formula: $C_{19}H_{21}N_3O_5$

Molecular Weight: 371.39

Molecular formula: $C_{19}H_{21}N_3O_5$ NDA 19-546
Molecular weight: 371.4

This compound, a yellow crystalline powder, is relatively light stable in dry form. When dissolved, its stability is strongly influenced by the solvent. Solutions should therefore be protected against light.

b. Pharmacologic Category: Calcium channel blocker.

c. Proposed indication: Mild hypertension.

d. Route of administration and dosage form: Oral capsules 5, 10, 20 mg b.i.d.

e. Related drugs: Nifedipine

Manufacturing controls: Please see Chemistry Review.

Pharmacology

a. Pharmacodynamics

(1) Isradipine belongs to the dihydropyridine class of calcium channel blocking agents. The primary pharmacologic action of clinical utility is the ralaxation of smooth muscle with resultant decrease of peripheral vascular resistance and lowering of arterial blood pressure.

(2) Other actions: Negative inotrophy is a property of calcium channel blocking agents in general. This effect of cardiac function in animals and humans is overcome by the attendant increase in cardiac output with reduction of systemic vascular resistance. Effects on other endocrine systems are uncertain, but a hyperglycemia is aggravated by interference with the calcium channel. The pervasive influence of calcium on cellular physiology leads to the expectation that the calcium channel blocker might be of benefit in angina pectoris, bronchial asthma, heart failure, and cardiac arrhythmias. Similarities with nifedipine expected from the molecular structure are summarized from the extensive experience with laboratory animals.

In phase one and two, the drug was tested in Europe in seven studies for pharmacokinetics, tolerance and bioavailability and eight studies for the efficacy on hypertension. There was no clear cut effect on blood pressure in normal subjects. Brief flattening of T-waves of the ECG was seen in one patient receiving 0.5 mg and two who received 2 mg IV. In larger doses, orthostatic tachycardia was seen. First order kinetics with 2 hr half life was shown in a small and incomplete study. Other studies demonstrated peak response levels. A large first pass effect was shown to yield a bioavailability of 18%. Minimum drug accumulation was shown in the steady state. AUC has been measured with varying doses and studies with isotopic labelled drug indicated that there is no isotopic effect on metabolism or on

bioavailability. The metabolites identified appear to be without pharmacologic activity. Headache was the most commonly reported side effect. Some patients complained of dizziness and there were a few instances of tachycardia but specific relation to fall in blood pressure was rare.

Half lives of 2 hours and 12 hours have been reported. The the half life has been found half that of nifedipine. Elimination in man is predominantly in the urine after 80% biotransformation by the liver; 95% of circulating drug is bound to albumin. Detailed discussion of the pharmacokinetics with implication of dose proportionality are found in the pharmacology review

Biotransformation studies show that metabolites 11 & 5 accumulate in blood. Hemodynamic studies in comparison with PN 200-110 indicate that both compounds have negligible activity; both metabolites were identified in the toxicity animal species (rat and dog). Other major metabolites (14 + 16) found in man are also devoid of pharmacological activity.

b. Toxicology

(1) Subacute and chronic-acute studies have shown no suggestion of serious toxic effects and a reasonable margin of safety. The major source of concern from the animal studies is the Leydig cell tumors. These are found frequently in other situations and are believed in this case to result in hypothalamic-pituitary over stimulation. Evidence gathered to date indicates that this effect is not likely to cause serious problems. Complications bordering on the catastrophic occurred in the dose ranging studies with volunteers gathered from the ranks of professional drug testers. It is difficult to imagine a population that could be deliberately chosen to exhibit more abnormal liver function test than that group of alcoholics, addicts, and other sorts of social misfits selected for Study 310. The finding of elevated trans-aminase levels in this population prompted vigorous re-study of the subjects recounted in Study 398. This study along with experience with long term studies make it seem most unlikely that the drug is hepatotoxic. An occasional elevated alkaline phosphatase level is of doubtful significance.

No evidence has been shown for teratology or carcinogenicity in the various species studied. Details of these studies are found in the pharmacology review. The burden imposed on the liver for metabolism of this drug requires consideration of drug-drug interaction with other drugs metabolized by the same hepatic mechanisms.

Of minor consideration are the mild diuretic effect and edema formation, both of which can be conceived of as the result of vasodilation. Electrolyte imbalance does not appear to accompany shifts in fluid distribution.

Clinical Background

a. Therapeutic and adverse effects shown early in the experiences with the drug are similar to those described in the investigation of nifedipine. Headache, flushing, edema, light headedness are the most frequent side effects noted. Repeated reference is made to the desirable absence of fluid retention or postural hypotension.

b. Experience with other calcium channel blocking agents --most notably nifedipine-- are given as evidence that the drug Dynacirc may have other clinical applications including asthma migraine and peripheral vascular disease. Subtle differences in the stereochemistry of the receptor macromolecule accounts for variability of the response of different organs to the drug and to quantitative differences in the actions of drugs with very similar molecules.

Table 1. Principal clinical pharmacological characteristics of dihydropyridine calcium antagonists

Characteristic	Nifedipine	Nisoldipine	Nicardipine	Nimodipine	Felodipine	Nitrendipine
Elimination half-life (h)*	2	2-3	2	?	14	12
Duration of effect (h)	4	8-10	8	?	20	12
Vascular selectivity	Coronary and periph. arterial	Coronary and periph. arterial	Coronary and periph. arterial	Cerebral	Coronary and periph. arterial	Peripheral arterial
Effect on systemic resistance	↓↓	↓↓↓	↓↓		↓↓	↓↓
Effect on heart rate	Reflex ↑	Reflex ↑	Reflex ↑		Reflex ↑	Reflex *
Effect on myocardial contractility	↓	? none	? none	none	Minimal ↓	? none
Usual dose (mg)	10-20 tid	10-20 tid	30 tid	30 tid	10 od to bid	20 od to bid
Commonest indications	Angina, hypertension	Angina, hypertension	Angina, hypertension	Migraine, subarachnoid haemorrhage	hypertension; ? heart failure	Hypertension

* ... due to administration or may be dose dependent. The values listed may also be inaccurate due to inadequate analytical procedures. The duration of pharmacological effects may exceed half-life due to the presence of active metabolites.

Distinctive clinical characteristics of these drugs are tabulated below. Whether Isradipine will be set apart from these agents awaits broader clinical experience.

PHASE I HEMODYNAMIC STUDIES IN NORMAL MALE VOLUNTEERS

Study no.	Investigator	No. of Subjects Entered	No. of Subjects analyzed: Valid	No. of Subjects analyzed: Invalid	No. of Subjects discontinued	No. of Deaths	Objectives	Dosage	Duration of Study Drug Administration/ Design	Results	Remarks
1	A. Nelson, M.D.	30	30	0	0	0	Assess the safety following single oral doses	2.5, 5, 10, 15, and 20 mg administered as single doses or placebo	1 dose, 32-hour follow-up, double-blind, randomized, parallel group design	Dose-related decreases in diastolic b.p. were observed 1-2 hours post 10 mg, 15 mg, and 20 mg doses. No dose response relationship for resting pulse rate in doses ≤ 10 mg, and no changes in systolic b.p. were observed. Mild adverse reactions were reported following 20 mg.	All doses are safe, but single doses of ≤5 mg are better tolerated.
2	A. Nelson, M.D.	41	41	0	1	0	Assess the safety following multiple oral dosing	Stage I: 10 mg bid for 3 days or placebo Stage II: 5 mg bid for 1 day + 10 mg bid for 2 days or placebo Stage III: 2.5 mg tid for 1 day + 5 mg tid for 1 day + 7.5 mg tid for 1 day or placebo Stage IV: 2.5 mg tid for 2 days + 5 mg tid for 2 days + 7.5 mg for 3 days tid or placebo All stages:	Multiple dosing 32 hour follow-up after last dose; double-blind, randomized, parallel group design	No changes occurred in systolic b.p., but diastolic b.p. decreased (maximum 8 mm Hg) in doses ≥15 mg/day. Resting pulse rate increased after doses ≥15 mg/day (maximum 99 bpm).	20 mg bid is safe, but better tolerated if the starting dose is no more than 2.5 mg tid, and the dose is increased slowly over a few days.
3	A. Nelson, M.D., J. Medeiros, M.D. and M. Wells, M.D.	11	11	0	0	0	Partial range finding of the 2HA-118 in subjects who previously manifested elevated serum transferase following IV 2HA-118 administration	10 mg	Single dose, open-label 14 days follow-up as inpatients	2/9 subjects re-challenged showed no changes in SGOT/SGPT. 2/9 subjects showed increases in SGOT/SGPT but levels were much less than previously observed. 2 subjects not re-challenged due to persistent elevations of SGOT/SGPT.	Requested by FDA; results did not indicate that 2HA-118 was hepatotoxic.

Table 2

Table 3

[illegible] STUDIES IN PATIENTS WITH [illegible] HYPERTENSION, ANGINA, [illegible]
[illegible], CONGESTIVE HEART FAILURE, [illegible]

Study No.	Investigator	No. of Subjects Entered	No. of Subjects Analyzed*		No. of Subjects Discontinued	No. of Deaths	Objectives	Dosage	Duration of Study Drug Administration/ Design	Results	Remarks
			Valid	Invalid							
7	[illegible], M.D.	21	20	1	1	0	Assess the safety and efficacy in the treatment of hypertension compared to placebo	2.5 mg bid - 10 mg bid or placebo, followed by a 2-wk off dosing period	6 weeks; double-blind, parallel group, randomized, design; followed by a 2-wk double-blind off dosing period	After 5-6 weeks, the mean b.p. reduction following bid dosing from baseline for the PN 200-110 group was [illegible]/14.1 mm Hg (systolic/diastolic). For the placebo group, the mean reduction was [illegible] mm Hg. The between group difference for diastolic b.p. was statistically significant (p<0.01). The mean increase in pulse rate for the PN 200-110 group was 3.7 bpm.	PN 200-110 administered bid was safe and effective in the management of hypertension. Blood pressure control was not maintained during off dosing of PN 200-110 in a very small group of patients.
9	F. Gilbert [illegible], M.D.	16	16	0	0	0	Assess the acute oral dose response pharmacodynamics of four doses of PN 200-110 administered as single doses to hypertensives	2.5 mg, 5 mg, 10 mg and 20 mg, single doses of each	Total duration = 9 days; double-blind, randomized, Latin Square design	Dose-related reductions in supine and standing b.p. were observed achieving a maximum mean reduction 17-37 mm Hg systolic and 16-25 mm Hg in the supine position. Maximum mean increases (11-23 bpm) in resting pulse rate were not dose related for doses between 2.5 mg and 10 mg.	Safe and well tolerated. Dose related reductions in b.p. were achieved, duration of action suggests a bid dosage regimen in the management of hypertension.
11	J. Mitchell, M.D., Ph.D. and [illegible], M.D., Ph.D.	24	22	2	0	0	Assess the safety and efficacy in the treatment of hypertension compared to placebo	2.5 mg bid - 10 mg bid or placebo, followed by a 2-wk off dosing period	7 weeks; double-blind, randomized, parallel group design; followed by a 2-wk double-blind off dosing period	After 7 wks, the mean b.p. reduction following bid dosing from baseline for the PN 200-110 group was 14/10 mm Hg (supine systolic/diastolic). For the placebo group, the mean change was [illegible] mm Hg. The between group differences were statistically significant (p<0.01). The mean increase in resting pulse was 7 bpm.	PN 200-110 administered bid was safe and effective in the management of hypertension. Blood pressure control was not maintained during off dosing of PN 200-110 in a very small group of patients.
6	R. Ross, M.D. and B. [illegible],	30	20	6	10	0	Assess the safety and efficacy of PN 200-110 in the treatment of stable, effort-induced angina patients using exercise tolerance compared to placebo	2.5 mg tid - 5 mg tid or placebo	4 days of active treatment; double-blind, randomized, crossover design	Compared to placebo, PN 200-110 resulted in a statistically significant decrease in ST segment change while prolonging exercise duration slightly.	PN 200-110 was safe and well tolerated. The ST segment change and slight increase in total exercise time supported efficacy but clinical significance was not achieved.

*Analyses for safety include all subjects

02-00123

Table 3 Cont

Study No.	Investigator	No. of Subjects Entered	No. of Subjects Analyzed: Valid	No. of Subjects Analyzed: Invalid	No. of Subjects Dropped Out	No. of Weeks	Objectives	Dosage	Duration of Study Drug Administration/ Design	Results	Remarks
10	E. Grossman, M.D.	13	11	2	1	0	Assess the safety and acute hemodynamic effects in patients with congestive heart failure	5 mg and 10 mg single oral dose	Total duration - 3 days; single-blind placebo baseline controlled trial	Statistically and clinically significant dose-related changes indicating hemodynamic improvement, e.g. ↑ cardiac output, ↓ vascular resistance and ↓ mean pulmonary capillary wedge pressure were observed at rest during exercise. Peak effect was observed 1-2 hrs post dose and was evident 3 hrs post	Safe and well tolerated; dose-related improvement in cardiac performance at rest and during exercise.
12	M. Weiss, M.D.	8	6	2	1	0	Assess the safety and acute hemodynamic effects in patients with left-sided congestive heart failure	2.5 mg - 10 mg administered as single oral dose on two separate test days	Total duration - 3 days; single-blind placebo baseline controlled trial	Due to the small number of patients evaluated, statistical significance was not achieved in any of the variables. Trends were noted for dose related improvement in cardiac function, e.g. ↑ cardiac output, ↓ vascular resistance, ↓ mean right atrial pressure at rest and during exercise.	Safe and well tolerated.
14	M. Gordon, M.D.	17	17	0	0	0	Assess the safety and efficacy in patients with exercise induced hypotension compared to placebo	2.5 mg and 10 mg as single oral doses or placebo	3 single doses 1 dose/day for 3 days, double-blind, randomized, crossover trial	No changes in resting cardiac function were noted, there was a consistent trend for the 20A-138 to attenuate exercise induced hypotension measured hemodynamically.	Safe and well tolerated. The 20A-138 appears to be safe in patients with hypotension.
17	J. Hagerman, M.D.	23	20	3*	3*	1 (losing contact prior to the 20A-138 treatment)	Assess the safety and efficacy in the treatment of chronic, benign pneumatic compression boots	2.5 mg BID - 5 mg TID	4 week; single-blind placebo baseline controlled trial	Based on 30-day caliper data, there were no significant differences in the consistency or frequency of total ulcers between the 20A-138 and placebo. The average increase in heart rate was only 4 bpm.	Safe and well tolerated. The 20A-138 was not effective in controlling chronic benign ulcers, but quality inspection, the 20A-138 was not carcinogenic.

Analyses for safety include all subjects.
*Patients patient was died.

PHASE III CLINICAL TRIALS IN PATIENTS WITH HYPERTENSION

Study no.	Investigator	No. of Subjects Entered	No. of Subjects Analyzed		No. of Subjects discontinued	No. of centers	Objectives	Dosage	Duration of Study Drug Administration/ Design	Results	Remarks
			Valid	Invalid							
301/A 301/B 301/C 301/D 301/E 301/F	A. Carr, M.D. M. Darlow, M.D. D. Hamilton, M.D. M. Schreuer, M.D. M. Velasquez, M.D. B. Zupaldi, M.D.	115*	115*	2*	12*	6	Assess the safety and efficacy of four doses administered as fixed combination tablets in the treatment of hypertension compared to placebo	2.5 mg bid - 10 mg bid or placebo	5 weeks; double-blind, randomized, parallel group design	All doses of FH 250-110 produced clinically and statistically significant b.p. reductions which achieved statistical significance from the parallel placebo group ($p<0.001$). The decreases were dose-related up to 15 mg/day. Increases in pulse rate (maximum 5 bpm) were not dose related in doses >10 mg/day. Incidences of palpitations and fatigue were dose-related.	Safe and well tolerated. When administered bid as monotherapy, FH 250-110 is effective in the management of hypertension.
302/A 302/B 302/C 302/D	M. Mitchell, M.D. F. Hunstad, M.D. and D. Garner, M.D. M. Wiest, M.D. V. Davidson, M.D.	76	64	10	7	1 (results for site)	Assess the safety and efficacy in the treatment of hypertension compared to placebo	2.5 mg bid - 10 mg bid or placebo	4 weeks; double-blind, randomized, parallel group design	FH 250-110 was clearly more effective than placebo in reducing b.p. Between group comparisons were statistically significant ($p<0.001$) for all b.p. variables at a mean dose = 12 mg titrated to normalize diastolic b.p.	Safe and well tolerated. When administered bid as monotherapy, FH 250-110 is effective in the management of hypertension.
303/A 303/B 303/C	C. Mitchell, M.D. M. Weiss, M.D. P. Lenart, M.D.	82	77	5	17	8	Assess the safety and efficacy in the treatment of hypertension compared to hydrochlorothiazide (HCTZ)	FH 250-110: 5.0 mg bid - 10 mg bid; or HCTZ: 25 mg bid - 50 mg bid	10 weeks; double-blind, randomized, parallel group design	Both study drugs effectively reduced sitting b.p. at mean daily doses of 12 mg FH 250-110 and 41 mg HCTZ titrated to normalize diastolic b.p. Pulse rate increased slightly for both agents.	Safe and well tolerated. When administered bid as monotherapy, FH 250-110 is as safe and effective as HCTZ.

*Analyses for safety include all subjects.

In the case of the multicenter studies listed in this table (Table 5), only the total number of subjects entered from all the centers will be listed. The number of subjects per center is listed in the Individual Clinical/Statistical Reports for the respective studies.

Table 4

PHASE III CLINICAL TRIALS IN PATIENTS WITH HYPERTENSION

Table 4 Cont.

Study No.	Investigator	No. of Subjects Entered*	No. of Subjects Analyzed† Valid	No. of Subjects Analyzed† Invalid	No. of Subjects Discontinued	No. of Deaths	Objectives	Dosage	Duration of Study Drug Administration/ Design	Results	Remarks
300/A 300/B 300/C	K. Engelman, M.D. F. Gilbert McMahon, M.D. J. Mitchell, M.D., Ph.D. and C. Nelson, M.D., Ph.D.	39	37	2	12	1 (rec'd propranolol)	Assess the safety and efficacy in the treatment of hypertension compared to propranolol	PN 200-110: 2.5 mg bid - 10 mg bid; or Propranolol: 40 mg bid - 240 mg bid	10 weeks; double-blind, randomized, parallel group design	Both study drugs effectively reduced b.p. but PN 200-110 produced greater mean decrements. The between group differences were statistically significant (p≤0.05) at mean daily doses of 12 mg PN 200-110 and 340 mg propranolol. PN 200-110 increased pulse rate 6 bpm (maximum) and propranolol decreased pulse rate (13 bpm maximum). Fewer PN 200-110 treated patients were discontinued for adverse reactions.	Safe and well tolerated. When administered bid as monotherapy, the results of this study suggest that PN 200-110 was more effective than propranolol in reducing b.p. This may be due to the patient population included in this study.
301/A 301/B 301/C	M. McAllister, M.D. A. Sowahara, M.A. and S. Swartz, M.D. V. Vardani, M.D.	39	39	0	9	0	Assess the safety and efficacy in the treatment of hypertension compared to prazosin	PN 200-110: 2.5 mg bid - 10 mg bid; or Prazosin: 2 mg bid - 8 mg bid	10 weeks; double-blind, randomized, parallel group design	Both study drugs effectively reduced b.p. but PN 200-110 produced greater mean decrements. The between group differences achieved statistical significance (systolic p≤0.001; diastolic p≤0.05) at mean daily doses of 9 mg PN 200-110 and 8.5 mg prazosin. Fewer patients reported adverse reactions with PN 200-110.	Safe and well tolerated. When administered bid as monotherapy, the results from this study suggest that PN 200-110 was more effective than prazosin in the management of hypertension.
302/A 302/B 302/C 302/D	A. Carr, M.D. J. Mitchell, M.D., Ph.D. and C. Nelson, M.D., Ph.D. M. Viner, M.D. M. Velasquez, M.D.	35	35	0	9	0	Assess the safety and efficacy of PN 200-110 combined with hydrochlorothiazide in the treatment of hypertension compared to propranolol combined with hydrochlorothiazide	PN 200-110: 2.5 mg bid - 10 mg bid; or Propranolol: 40 mg bid - 240 mg bid; both study drugs administered with constant dose of hydrochlorothiazide (≥50 mg/day)	10 weeks; double-blind, randomized, parallel group design	Both study drugs effectively reduced b.p. when administered concurrently with HCTZ. No significant between group differences were noted at mean daily doses of 13 mg PN 200-110 and 220-240 mg propranolol. PN 200-110 did not increase resting pulse rate but propranolol decreased pulse rate. Fewer PN 200-110 treated patients were discontinued because of adverse reactions.	Safe and well tolerated. When administered bid concurrently with ≥50 mg HCTZ/day, PN 200-110 is as safe and effective as the combination of HCTZ and propranolol.

†Analyses for safety include all subjects.

*In the case of the multicenter studies listed in this table (Table 4 Continued), only the total number of subjects entered from all the centers will be listed. The number of subjects per center is listed in the individual Clinical/Statistical Reports for the respective studies.

02-U0136

LONG TERM SAFETY TRIALS

Study No.	Investigator*	No. of Subjects Entered	No. of Subjects Analyzed		No. of Subjects Discontinued	No. of Centers	Objectives	Dosage	Duration of Study Drug Administration/ Design	Results	Remarks
			Valid	Invalid							
Long Term Studies	11 investigators who conducted double-blind, randomized, controlled, safety/ efficacy studies in hypertension or angina patients enrolled patients into a long term treatment phase on PH 203-110	136	136	0	36	1 (2)*	Assess long term safety	PH 203-110: 5 mg - 22.5 mg per day administered in divided doses	Up to a 1 year or more; open-label, non-controlled	The mean duration of treatment was 26.2 weeks at a mean dose of 12 mg/day. At least one adverse reaction was reported by 77% of the patients, but these were generally encountered early in the study. In half of these patients, adverse reactions were not reported on a recurring basis.	PH 203-110 was safe, well tolerated and effective over long term administration when administered in doses up to 22.5 mg/day for the treatment of hypertension or stable angina.

*Study centers included in the long term data are: 5, 206, 231-C, 301-B, 301-F, 307-B, 307-C, 303-B, 303-C, 304-A, 334-C, 304-B, and 307-B.

*Two patients with congestive heart and not included in the data base for this report also died while receiving PH 203-110. In neither case was PH 203-110 considered by the investigator contributing to the event.

Table 7

PHARMACOKINETICS

The findings of seven studies of absorption elimination and bioavailability reviewed briefly here are discussed more fully in the biopharmaceutics Review.

Study #3

1. Objective: Measurement of the absorption, blood levels, urinary, fecal and bile excretion of C14 tagged PN 200.

2. Materials and Methods of Subject Selection: Healthy males between 18 and 45 with no significant findings and no lab abnormalities. Subjects were within 15% of their ideal body weight. Subjects were excluded by clinical illness within the past two weeks; participation and investigational study within four weeks; administration of radioactivity within the past twelve months, Lab tests required for screening were uric acid, bilirubin, cholesterol, glucose, LDH, ALK Phosph, SGOT as well as urinalysis.

3. Summary of Results: Pharmacokinetic characteristics demonstrated by this study are shown in the table.

Parameter	5 mg		20 mg	
	Total Radioactivity	200-110	Total Radioactivity	200-110
Absorption (% Dose):	90-95	-	90-95	-
Blood Levels:				
Peak Time (h)	3	3	3	2
Peak Level (F)	1.247	-	1.191	-
(ng/mL or ng Eq/mL)	84	2.06	333	9.12
AUC, 0-120 h (ng Eq·h/mL)	1303	-	5605	-
0-4 h (ng·h/mL)	-	6.5	-	19.3
0-∞ (ng·h/mL)	-	10.6	-	-
Excretion (% Dose):				
Breath, 0-120 h	0	-	0	-
Urine, 0-72 h	59.4	0	66.2	0
0-120 h	59.7	-	66.8	-
Feces, 0-72 h	25.2	9.95	28.2	8.80
0-120 h	25.6	-	32.3	-
Total, 0-120 h	85.3	-	99.1	-

Two metabolites(type I and Type II) were shown to have half lives of 2.7 & 2.8 hours.with Type II having minimal tendency to accumulate

4. Safety: Monitored by physical and clinical laboratory tests, the single doses of 5 & 20 mg with tagged with 14_C was well tolerated.

Study #310

1. Objective: The object of this study was the evaluation of the bioavailability relationships of PN 200-110, oral solutions of 2.5, 5, and 10 mg in healthy male volunteers.

2. Materials and Methods: Eighteen male subjects meeting the criteria given in Study #3 entered the open-labelled, randomized, 3 X 3 Latin square study.

~~On the test day the blood samples for determination of the drug concentration~~ were collected from each subject. Thirty ml was collected before the dose and 10 ml at each time point after the dose: .33, .661, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 9.0 -and 12 hours after the medication.for measurement of Cmax, tmax, AUC, and absorption and elimination constants.

3. Results: PN 200-110 administered as an oral solution was absorbed rapidly, with peak levels of about 3000 pg/mL/mg at 1 h. The half-lives for the biphasic elimination were 0.3-0.4 and 1.9-2.9h. Increasing the dose from 2.5 to 5 and 10 mg resulted in statistically significant increases for the AUC and Cmax, but not tmax. Both AUC and Cmax exhibited a linear relationship with the dose in the 0-10 mg range studied.

4. Adverse Reaction: One subject left the study because of abdominal discomfort not considered related to medication. There were no untoward reactions to suggest unsafety of the drug in the course of the study. Subsequent examination of these subjects has raised the question of liver toxicity alluded to above.

5. Conclusion: The drug may be considered safe with the reservation that liver function is under review due to the findings of elevated trans-aminase. Results of rechallenge is found in Study 398.

Study #318:

1. Objective: To measure the intrasubject variability of bioavailability parameters

2. Design: Open label single dose of 10mg PN-200 in solution.

3. Materials and Methods: Sixteen volunteers entered the study. Thirteen of these completed the course of three doses of 10 mg. separated by a 7-day wash out.

4. Results: Three main pharmacokinetic parameters, AUC Cmax and tmax gave reproducible mean values for the three study periods, but there was considerable intrasubject variability so as not to meet the 70/70 rule. This variability is not considered crucial and is treated in the pharmaceutical review. Three dropouts included one with abnormal liver function, another with headaches. A third disappeared. Other side effects, notably headache, were mild.

5. Conclusions: Bioavailability is acceptable and there is no evidence that the drug is unsafe save for the question of liver toxicity under consideration in the rechallenge of the patents from study 310

Study #322 NDA 19-546

1. Objective: The objective of this study was to evaluate bioavailability of 2.5 and 10 mg capsules of PN 200 relative to a reference solution.

2. Design: Randomized replicated 3 X 3 Latin square.

3. Materials and Methods: Twenty four healthy males were chosen by the established criteria These subjects in randomized sequence received either one 10 mg capsule, 4 2.5 mg caps or a 10mg reference solution of PN-200 and after five day intervals for washout, the other two preparations. . Blood was drawn 0 and 24 hrs post-dose for radioimmuno-assay of Cmax, tmax, AUC and for rate constants for absorption and elimination and lag time absorption.

4. Results: The drug was more rapidly absorbed when given in solution but AUC for the liquid and capsules was similar.

5. Safety: Symptoms of headache, dizziness, and flushing were mild and required no treatment. There were no dropouts.

6. Conclusion: Doses of 2.5 and 10 mg are safe and well tolerated.

Study #321

1. Objective: The object of this study was to assess the bioavailability of 5 and 10 mg doses of PN 200 in elderly healthy men.

2. Materials and Methods: Twenty-six men 65 years or older and meeting appropriate qualifications were admitted to the study. The subjects were divided into two equal groups from separate centers for construction of a 2 X 2 Latin square. Each subject received a single dose of 5 and of 10 dose with crossover after a 5-10 day washout. Safety was monitored by physical examination, ECG, chest film, and clinical chemistries. Blood samples were taken between 0 and 32 hours after each dose for measurement of peak plasma level time to max plasma level, AUC, and rate constants for absorption and elimination.

3. Results: The pharmacokinetic data collected in this study compared with that obtained from young healthy volunteers showed a statistically significant greater bioavailability in older subjects. This difference seems likely to result from diminished renal clearance and of slower metabolism of the drug by the liver.

4. Safety: All 26 subjects completed the study. One man developed a respiratory tract infection and was found to have altered liver function. Three instances of elevated liver enzymes were of doubtful significance. Hyperglycemia was increased in one diabetic. There were no other significant clinical pathological findings. One subject developed moderate systolic hypertension lasting 2 hrs Subjective symptoms were mild and self limited.

5. Conclusions: The bioavailability of PN 200-110 is greater in the elderly and the drug is as well tolerated in the older age group as in younger populations.

Study #313

1. Objective: To evaluate the influence of concomitant HCTZ administration on the bioavailability of PN-200 and vice versa.

2. Design: Open label randomized 3x3 replicated Latin Square.

3. Materials and Methods: Twenty-one men meeting the criteria each received a 10mg cap PN 200 and 50 mg HCTZ alone and in combination separate days.

3. Results: C max, t max , AUC, and elimination and absorption constants showed no effect on pharmacokinetics by either drug on the other.

4. Safety: Three subjects left the study after one day, one because of emesis, another because of dehydration. A third was supernumerary. One other subject was found to have have elevated liver enzymes and was included in study #398

5. Conclusions: PN-200-110 and HCTZ may be safely be given concomitantly.

Study #315

1. Objective: To evaluate effect of food on bioavailability of PN 200-110 capsules.

2. Design: Open label 2 period cross-over with 6-7 day washout.

3. Materials and Methods: Sixteen patients having fulfilled the criteria for acceptance to the study received a standard breakfast of orange juice, milk, bread, butter, eggs and bacon. Xanthine was proscribed on the test days. The group was divided into one fasting in which group the subject took the medication two hours after breakfast. Those in non-fasting state were medicated, 20 minutes after breakfast. In one sequence group was fasted on day one and fed on day two before receiving the medication. The other sequence of food was fed on days 1 and 2 respectively. Subjects remained at the facility until 12 hour post dose and ten blood samples were collected for measurement of the pharmacokinetic parameters used throughout these studies

4. Results: The drug was rapidly absorbed in fasting state. Peak levels was reached in 1.4 hours. There was 50 minute delay in absorption after eating. There was no difference in AUC in the fasting and post prandial states.

5. Safety: Nine of the sixteen patients experienced mild symptoms. Two subjects requiring aspirin for headaches One subject eliminated because methadone was found in the urine also had hepatitis profile positive for hepatitis A Convalescent Phase, Igg antibody and Hepatitis Core Antibody.

6. Conclusions: The drug is well tolerated in fed and fasting state. Food causes delay in absorption, but does not affect bioavailability.

Study #319

This is study was a replication of Study 310 confirming pharmacokinetic data of Study 310.

Results: Increasing the dose resulted in statistically significant increases of AUC and Cmax, but not tmax. AUC and Cmax were linearly correlated with the dose. This statement reflects the reproducibility of the results obtained in Study 310.

Safety: The safety data save for the complicating liver disease are comparable to those of Study #310 and support the contention that the drug is safe.