TABLE 22

ISRADIPINE SAFETY UPDATE - 8/89

FREQUENCY OF ABNORMAL SGPT

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	2	2.8
	11	22	20	0	0.0
Phase III - Hypertension***					
Isradipine	101	230	241	2	2.0
Captopril	33	64	85	0	0.0
Enalapril	18	30	52	0	0.0
Diltiazem	54	131	110	1	1.9

*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.

TABLE 23

ISRADIPINE SAFETY UPDATE - 8/89

FREQUENCY OF ABNORMAL LIVER FUNCTION 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	251	5	6.9
	11	22	20	0	0.0
Phase III - Hypertension***					
Isradipine	101	231	241	3	3.0
Captopril	33	64	85	0	0.0
Enalapril	18	36	52	1	5.6
Diltiazem	54	131	110	3	5.6

*Based upon maximum values for pre-study drug and post-study drug and the following "abnormal" values:

SGOT - 100 U/L
SGPT - 100 U/L
LDH - 300 U/L
Total Bilirubin - 2.0 mg/dl
Alkaline Phosphatase - 200 U/L

**Includes all congestive heart failure studies.
***Includes data for Study No. 352 which was not available for the last safety update.

TABLE 24 A
ISRADIPINE SAFETY UPDATE - 8-89
INCIDENCE RATES OF ALL ADVERSE REACTIONS
ISRADIPINE TREATED PATIENTS ONLY
N 81

BS-MISCELLANEOUS

ARPNAME	NEW
LACRIMATION	1.23
TEETH/MOUTH PAIN	1.23

BS-SKIN

ARPNAME	NEW
BRUISE	1.23
ERYTHEMA (SKIN RASH)	1.23
PRURITUS	1.23

BS-MUSCULO-SKELETAL

ARPNAME	NEW
BACK, ACHE/PAIN	3.70
LEGS, MISC. ACHE	1.23
NECK PAIN/SORE/STIFF	1.23

BS-RESPIRATORY

ARPNAME	NEW
COUGHING	4.94
NASAL CONGESTION	2.47
SINUSITUS/SINUS	2.47

BS-CARDIOVASCULAR

ARPNAME	NEW
CHEST PAIN	4.94
EDEMA	3.70
EPISTAXIS (NOSE	1.23
PALPITATION	2.47

BS-GASTRO INTESTINAL

ARPNAME	NEW
ABDOMINAL DISCOM	1.23
DIARRHEA	3.70
*FLATULENCE	1.23

* New adverse reaction since last Safety Update

Table 24 A

TABLE 24 A
ISRADIPINE SAFETY UPDATE - 8-88
INCIDENCE RATES OF ALL ADVERSE REACTIONS
ISRADIPINE TREATED PATIENTS ONLY
N=91

BS=UROGENITAL

ARPNAME	NEW
DYSURIA (DIFFICU	1.23
IMPOTENCE	3.70
POLLAKIURIA	3.70

BS=CENTRAL NERVOUS SYSTEM

ARPNAME	NEW
ANXIETY	2.47
APPETITE LOSS/ANOREXIA	1.23
*DEPRESSION/ENNUI	1.23
DIZZINESS	4.94
DROWSY	1.23
ENERGY DECREASE	1.23
*EPILEPTIFORM EVENT	1.23
FATIGUE	7.41
HEADACHE	13.58
INSOMNIA	2.47
LIBIDO DECREASE/	3.70
TINNITUS	1.23

BS=AUTONOMIC NERVOUS SYSTEM

ARPNAME	NEW
FLUSHING	1.23
TINGLING	1.23

BS=38

ARPNAME	NEW
ANY ADVERSE REAC	55.58

* New adverse reaction since last Safety Update

Table 24 A

TABLE 24 B
ISRADIPINE SAFETY UPDATE - 8-89
INCIDENCE RATES OF ALL ADVERSE REACTIONS EXCLUDING THOSE
NOT DUE TO DRUG - ISRADIPINE TREATED PATIENTS ONLY
N=81

BS=MISCELLANEOUS

ARPNAME	NEW
LACRIMATION	1.23

BS=SKIN

ARPNAME	NEW
* BRUISE	1.23
PRURITUS	1.23

BS=MUSCULO SKELETAL

ARPNAME	NEW
BACK, ACHE/PAIN	1.23
LEGS, MISC. ACHE	1.23

BS=RESPIRATORY

ARPNAME	NEW
COUGHING	1.23

BS=CARDIOVASCULAR

ARPNAME	NEW
CHEST PAIN	1.23
EDEMA	2.47
PALPITATION	2.47

BS=UROGENITAL

ARPNAME	NEW
IMPOTENCE	3.7
POLLAKIURIA	3.7

* New adverse reaction since last Safety Update

TABLE 24 B
ISRADIPINE SAFETY UPDATE - 8-89
INCIDENCE RATES OF ALL ADVERSE REACTIONS EXCLUDING THOSE
NOT DUE TO DRUG - ISRADIPINE TREATED PATIENTS ONLY
N=11

BS=CENTRAL NERVOUS SYSTEM

ARPNAME	NEW
ANXIETY	1.23
APPETITE LOSS/AN	1.23
* DEPRESSION/ENNUI	1.23
DIZZINESS	3.70
DROWSY	1.23
ENERGY DECREASE	1.23
FATIGUE	8.17
HEADACHE	8.64
INSOMNIA	1.23
LIBIDO DECREASE/	3.70
TINNITUS	1.23

BS=AUTONOMIC NERVOUS SYSTEM

ARPNAME	NEW
FLUSHING	1.23
TINGLING	1.23

BS=89

ARPNAME	NEW
ANY ADVERSE REAC	35.8

* New adverse reaction since last Safety Update

TABLE 25 A
ISRADIPINE SAFETY UPDATE - 8-89
INCIDENCE RATES OF ALL ADVERSE REACTIONS
ACTIVE CONTROL TREATED PATIENTS ONLY
N=18

BS=MISCELLANEOUS

ARPNAME	NEW
ARMS, MISC. ABNO	1.14
*CHILLS	1.14
LACRIMATION	1.14
*WEIGHT GAIN	1.14

BS=SKIN

ARPNAME	NEW
*INFLAM TISSUE (C	1.14
*URTICARIA (HIVES	1.14

BS=MUSCULO-SKELETAL

ARPNAME	NEW
BACK, ACHE/PAIN	2.27
FEET/HAND, PAIN	2.27
JOINT PAIN	2.27
LEGS, MISC. ACHE	1.14
MUSCLE PAIN/ACHE	1.14
NECK PAIN/SORE/S	1.14
SHOULDER PAIN	2.27

BS=RESPIRATORY

ARPNAME	NEW
CHEST CONGESTION	1.14
COUGHING	6.82
NASAL CONGESTION	3.41
RHINORRHEA	2.27
SINUSITUS/SINUS	1.14

BS=CARDIOVASCULAR

ARPNAME	NEW
CALVES, CRAMPS	1.14
CHEST PAIN	2.27
CRAMPS, LEG	1.14
DYSPNEA	1.14
*ECG/EKG ABNORMAL	1.14
EDEMA	3.41
*FIBRILLATION	1.14

* ... reaction since last Safety Update

Table 25

TABLE 25 A
ISRADIPINE SAFETY UPDATE - 8-89
INCIDENCE RATES OF ALL ADVERSE REACTIONS
ACTIVE CONTROL TREATED PATIENTS ONLY
N=88

BS=CARDIOVASCULAR

ARPNAME	NEW
PALPITATION	4.55

BS=GASTRO-INTESTINAL

ARPNAME	NEW
* APPETITE INCREAS	2.27
CONSTIPATION	2.27
DIARRHEA	4.55
NAUSEA	1.14
* RECTAL GAS	1.14
* STOOLS, BLOOD IN	1.14
VOMITING	3.41

BS=UROGENITAL

ARPNAME	NEW
DYSURIA (DIFFICU	1.14
IMPOTENCE	2.27
POLLAKIURIA	3.41
* PROSTATITIS (INF	1.14

BS=CENTRAL NERVOUS SYSTEM

ARPNAME	NEW
*ANXIETY	1.14
DIZZINESS	2.27
DROWSY	3.41
ENERGY DECREASE	1.14
EYES, PRESSURE B	1.14
FATIGUE	3.41
HEADACHE	9.09
INSOMNIA	1.14
LETHARGY	1.14
LIBIDO DECREASE/	1.14
* NUMBNESS R HAND	1.14
* TREMOR	1.14
VERTIGO	1.14

* New adverse reaction since last Safety Update

TABLE 25 A
ISRADIPINE SAFETY UPDATE - 8-89
INCIDENCE RATES OF ALL ADVERSE REACTIONS
ACTIVE CONTROL TREATED PATIENTS ONLY
N=78

BS=AUTONOMIC NERVOUS SYSTEM

ARPNAME	NEW
DRY MOUTH	2.27
* DRY THROAT	1.14
FLUSHING	3.41
HYPERHIDROSIS	1.14
VISUAL DISTURBAN	2.27

BS=12

ARPNAME	NEW
ANY ADVERSE REAC	59.09

* New adverse reaction since last Safety Update

TABLE 25 B
ISRADIPINE SAFETY UPDATE - 5-89
INCIDENCE RATES OF ALL ADVERSE REACTIONS EXCLUDING THOSE
NOT DUE TO DRUG - ACTIVE CONTROL TREATED PATIENTS ONLY
N=68

BS=MISCELLANEOUS

ARPNAME	NEW
* CHILLS	1.14

BS=SKIN

ARPNAME	NEW
* INFLAM TISSUE (C	1.14
* URTICARIA (HIVES	1.14

BS=MUSCULO SKELETAL

ARPNAME	NEW
JOINT PAIN	1.14
NECK PAIN/SORE'S	1.14
SHOULDER PAIN	2.27

BS=RESPIRATORY

ARPNAME	NEW
* CHEST CONGESTION	1.14
COUGHING	4.55
NASAL CONGESTION	2.27

BS=CARDIOVASCULAR

ARPNAME	NEW
* CALVES, CRAMPS	1.14
* ECG/EKG ABNORMAL	1.14
EDEMA	3.41
PALPITATION	4.55

BS=GASTRO-INTESTINAL

ARPNAME	NEW
* APPETITE INCREAS	2.27
CONSTIPATION	2.27
DIARRHEA	2.27
NAUSEA	1.14
* RECTAL GAS	1.14
* STOOLS, BLOOD IN	1.14

* New adverse reaction since last Safety Update

TABLE 25 B
ISRADIPINE SAFETY UPDATE - 8-89
INCIDENCE RATES OF ALL ADVERSE REACTIONS EXCLUDING THOSE
NOT DUE TO DRUG - ACTIVE CONTROL TREATED PATIENTS ONLY
N=58

BS-GASTRO-INTESTINAL

ARPNAME	NEW
VOMITING	2.27

BS-UROGENITAL

ARPNAME	NEW
DYSURIA (DIFFICU	1.14
IMPOTENCE	2.27
POLLAKIURIA	2.27

BS-CENTRAL NERVOUS SYSTEM

ARPNAME	NEW
DIZZINESS	2.27
DROWSY	3.41
ENERGY DECREASE	1.14
EYES, PRESSURE B	1.14
FATIGUE	2.27
HEADACHE	6.82
INSOMNIA	1.14
LETHARGY	1.14
LIBIDO DECREASE/	1.14
* NUMBNESS R HAND	1.14
* TREMOR	1.14

BS-AUTONOMIC NERVOUS SYSTEM

ARPNAME	NEW
* DRY MOUTH	2.27
DRY THROAT	1.14
FLUSHING	3.41
* HYPERHIDROSIS	1.14
VISUAL DISTURBAN	1.14

BS-ALL

ARPNAME	NEW
ANY ADVERSE REAC	42.05

* New adverse reaction since last Safety Update

Table 25 B

The following Table describes incidence of most frequently reported events (> 2%) for isradipine and controls where events were considered posibly or probably drug related.

Most Frequently Reported ADRs, Possibly/Probably Related

ADR	Isradipine (N=81)	Active Control (N=88)
Headache	8.6	6.8
Fatigue	6.2	2.3
Decreased Libido	3.7	1.1
Impotence	3.7	2.3
Pollakiuria	3.7	2.3
Dizziness	3.7	2.3
Edema	2.5	3.4
Palpitations	2.5	4.6
Cough	1.2	4.6
Drowsy	1.2	3.4
Flushing	1.2	3.4
Shoulder Pain	0	2.3
Nasal Congestion	0	2.3
Dry Mouth	0	2.3
Total No Reporting at least one new ADR	36	42

Except for fatigue, sponsor states that the incidences for each group are similar. It appears that headache and decreased libido are more common with isradipine. The higher incidence of cough in the control groups is probably due to the ACE inhibitors.

A total of 20 patients were reported to have at least one newly occurring severe reactions after isradipine. At least 11% of all isradipine patients reported at least one severe ADR which is similar to the 8% in SU-1. Only three patients were discontinued due to ADRs, all in heart failure studies. The reasons for withdrawal are presented in Table [illegible] with all other patients withdrawn. In the hypertension studies, only 3 were reported with severe ADRs. These included depression, anxiety, backpain, dental pain, fatigue, ankle tenderness and impotence.

For the remaining patients, there were a variety of "severe" ADRs. Fatigue was reported severe in 3 patients, the other events by one patient each. These included bradycardia, edema of lower extremities, vertigo, headache, nervousness/tremulousness, diverticulosis, asthma, URI, CHF, atrial fibrillation, GI bleeding, dyspnea, nausea and diarrhea.

Tables 27A and B describe the incidence rate by week of the most common ADRs in SU-2. The A Table consists of all ADRs and B of those with a possible drug relationship. Comparing SU-2 and SU-1, the results are similar but with a higher incidence of fatigue at Week 4, in Su-2 (5% vs 1.2%). In contrast to SU-1, there are no fixed dose protocols in SU-2 that would allow for a dose response ADR relationship to be investigated.

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The following Table describes incidence of most frequently reported events (> 2%) for isradipine and controls where events were considered posibly or probably drug related.

Most Frequently Reported ADRs, Possibly/Probably Related

ADR	Isradipine (N=81)	Active Control (N=88)
Headache	8.6	6.8
Fatigue	6.2	2.3
Decreased Libido	3.7	1.1
Impotence	3.7	2.3
Pollakiuria	3.7	2.3
Dizziness	3.7	2.3
Edema	2.5	3.4
Palpitations	2.5	4.6
Cough	1.2	4.6
Drowsy	1.2	3.4
Flushing	1.2	3.4
Shoulder Pain	0	2.3
Nasal Congestion	0	2.3
Dry Mouth	0	2.3
Total No Reporting at least one new ADR	36	42

Except for fatigue, sponsor states that the incidences for each group are similar. It appears that headache and decreased libido are more common with isradipine. The higher incidence of cough in the control groups is probably due to the ACE inhibitors.

A total of 20 patients were reported to have at least one newly occurring severe reactions after isradipine. At least 11% of all isradipine patients reported at least one severe ADR which is similar to the 8% in SU-1. Only three patients were discontinued due to ADRs, [redacted] The reasons for withdrawal are presented in Table [illegible] with all other patients withdrawn. In the hypertension studies, only [illegible] were reported with severe ADRs. These included depression, anxiety, backpain, dental pain, fatigue, ankle tenderness and impotence.

For the remaining patients, there were a variety of "severe" ADRs. Fatigue was reported severe in 3 patients, the other events by one patient each. These included bradycardia, edema of lower extremities, vertigo, headache, nervousness/tremulousness, diverticulosis, asthma, URI, CHF, atrial fibrillation, GI bleeding, dyspnea, nausea and diarrhea.

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TABLE 27 A

ISRADIPINE SAFETY UPDATE - 8/89

INCIDENCE RATES FOR ISRADIPINE TREATED PATIENTS
BY WEEK OF ALL ADVERSE REACTIONS
CONTROLLED STUDIES (351, 352, 354) IN HYPERTENSION

INCIDENCE (%)

Week n	1 1	2 81	3 0	4 80	5 0	6 79	7 0	8 79	9 1	10 77	11 0	12 52
Adverse Reaction												
Edema	0	0	--	1.3	--	2.5	--	2.5	0	2.6	--	0
Dizziness	0	2.5	--	2.5	--	1.3	--	0	100	0	--	0
Headache	0	6.2	--	3.8	--	5.1	--	8.9	0	6.5	--	7.7
Flushing	0	0	--	0	--	0	--	0	0	1.3		1.9
Fatigue	0	3.7	--	5.0	--	2.5	--	2.5	0	2.6	--	0
Palpitations	0	0	--	1.3	--	1.3	--	1.3	0	2.6	--	0
Chest Pain	0	0	--	0	--	0	--	0	0	1.3	--	0
Tachycardia	0	0	--	0	--	0	--	0	0	0	--	0
Shortness of Breath	0	0	--	0	--	0	--	0	0	0	--	0
Abdominal Pain	0	0	--	0	--	1.3	--	1.3	0	1.3	--	1.9

Table 27 A

TABLE 27 B

ISRADIPINE SAFETY UPDATE - 8/89

INCIDENCE RATE FOR ISRADIPINE TREATED PATIENTS BY WEEK
OF ADVERSE REACTIONS IN WHICH A DRUG RELATIONSHIP COULD
NOT BE EXCLUDED BY THE INVESTIGATOR
CONTROLLED STUDIES (331, 352, 354) IN HYPERTENSION

INCIDENCE (%)

Week n	1 1	2 81	3 0	4 80	5 0	6 79	7 0	8 79	9 1	10 77	11 0	12 52
Adverse Reaction												
Edema	0	0	--	1.3	--	1.3	--	1.3	0	2.6	--	0
Dizziness	0	2.5	--	1.3	--	0	--	0	100	0	--	0
Headache	0	2.5	--	1.3	--	2.5	--	5.1	0	3.9	--	3.8
Flushing	0	0	--	0	--	0	--	0	0	1.3	--	1.9
Fatigue	0	3.7	--	5.0	--	2.5	--	1.3	0	2.6	--	0
Palpitations	0	0	--	1.3	--	1.3	--	1.3	0	2.6	--	0
Chest Pain	0	0	--	0	--	0	--	0	0	0	--	0
Tachycardia	0	0	--	0	--	0	--	0	0	0	--	0
Shortness of Breath	0	0	--	0	--	0	--	0	0	0	--	0
Abdominal Pain	0	0	--	0	--	0	--	0	0	0	--	0

C3-00023

Drop Outs

For SU-2, there were 281 patients randomized with 50 (18%) being discontinued prior to completion. The main reasons for withdrawal are listed below.

Reasons for Patient Discontinuation

Reason	SU-2 No	SU-2 % of Total	SU-1 % of Total
ADR	12	4.3	5.1
Non Drug related Illness	3	1.1	1.4
Uncooperative	7	2.5	2.0
Protocol Violation	3	1.1	1.4
Ineffectiveness	3	1.1	3.5
Other	23	8.2	3.8

Sponsor states that the high number of patients under "other" is due to a Sandoz decision to terminate Study 255 (12 patients CHF) due to slow patient enrollment. The specific reason for each patient's withdrawal is given in Table 28.

In this group of patients, 19 had been randomized to isradipine; 7 were withdrawn due to ADRs, only two in hypertensive trials. The reasons were headache and dizziness. There were two in [redacted] and 3 in CHF, receiving 15-22.5 mg/day.

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In the 3 hypertension studies included in SU-2, 14/169 (8.3%) were discontinued from the trials. A total of 4 (2.4%) were withdrawn from Phase III studies after randomization due to ADRs; of these 2/81 were receiving isradipine.

Long Term Studies

Table 29 summarizes those studies in long term safety. The data were obtained from the open-label, long term extension protocols and Study 351, a one year, randomized, placebo controlled study.

In addition to 47 new patients evaluated, another 31 had data included in evaluation described in SU-1 but continued receiving isradipine in open label, long term studies subsequent to analysis of SU-1. In this analysis only data not previously analyzed are included. Those patients who continued into long term protocols from short term studies, had their short term data and long term data combined for continuity.

Table 28
Isradipine Safety Update - 8-89
Listing of All Patients Discontinued
From the Short Term Phase Since t Last Update

Study No.	Patient No.	Treat-ment +	Total Daily Dose (mg)+	Weeks in Study	Reason
208	101	PL		2 days	adverse reaction - irregular heart rate, dizziness, lethargy, weakness
	155	IS	15	7	adverse reaction - angina
221	102	PP	120	6	illness not due to drug - died of AIDS in hospital
222	3	PP	180	10	no tapering week - prior phlebitis causing edema
	152	PP	180	10	no tapering due to good antianginal response
223	103	IS	22.5	10	protocol violation - took Izcrdil
	151	PL		5	Could not tolerate chest pain on placebo
	152	IS	7.5-15	5	adverse reaction - chest pain during tapering off wee
255	1029	PL		1	adverse reaction/protocol violation - patient required frequent nitroglycerin for angina
	1030	PL		5	adverse reaction - dizziness and nausea
	1031	IS	15	3	adverse reaction - hospitalization for progressive CHF
	1035	IS	7.5	1	hospitalization for CHF with acute pulmonary edema

+IS = Isradipine
PL = Placebo
PP = Propranolol
EN = Enalapril
CP = Captopril
DZ = Diltiazem
NF = Nifedipine

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

Table 28 (cont'd)
Isradipine Safety Update - 8-89
Listing of All Patients Discontinued
From the Short Term Phase Since the Last Update

Study No.	Patient No.	Treat-ment +	Total Daily Dose (mg)+	Weeks in Study	Reason
255	1036	IS	7.5	1	hospitalized due to car accident - patient died of these injuries
	1076	PL		10	progression of CHF
	1079	IS	15	6	adverse reaction - dyspnea, edema, shortness of breath, nocturia, rapid irregular heart beat, orthopnea, weight gain
	3001	PL		5	study discontinued
	3002	IS	15	4	study discontinued
	3026	PL		6	study discontinued
	3027	IS	15	6	study discontinued
	3028	PL		5	study discontinued
	3030	PL		5	study discontinued
	3031	IS	7.5	2	study discontinued
	3032	PL		2	study discontinued
	3051	PL		6	study discontinued
	3076	PL		5	study discontinued
	3077	IS	7.5	2	illness not drug related - admitted to hospital - GI bleeding
	3078	PL		2	illness not drug related - claudication with revascularization of left leg
	3079	IS	15	3	study discontinued
	3080	IS	7.5	2	study discontinued
	4026	IS	22.5	10	adverse reaction - shortness of breath
	7030	PL		4	mild increase in SGPT

+IS = Isradipine
PL = Placebo
PP = Propranolol
EN = Enalapril
CP = Captopril
DZ = Diltiazem
NF = Nifedipine

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

Table 28 (cont'd)
Isradipine Safety Update - 8-89
Listing of All Patients Discontinued
From the Short Term Phase Since the Last Update

Study No.	Patient No.	Treat-ment +	Total Daily Dose (mg)+	Weeks in Study	Reason
255	7078	IS	7.5	2	patient and family request
	7079	PL		4	uncooperative
326	5	NF	60	per 1	uncooperative
	6	PL		per 2	uncooperative
	7	NF	60	per 1	uncooperative
331	130	EN	20	9	study drug ineffective
	510	EN	10	10	noncompliance
	515	EN	5	2	uncooperative - alcohol abuse
352	*127	IS	10	8	uncooperative - failed to return
	115	CP	150	10	uncooperative - failed to return
	*170	CP	150	4	study drug ineffective
354	1011	IS	2.5	4	adverse reaction - headaches
	1060	DZ	120	8	patient moved
	3002	DZ	240	8	adverse reaction - lethargy, blurred vision, flushing
	3009	IS	2.5	2	patient moved
	3056	DZ	120	2	failed to return
	5025	DZ	240	4	study drug ineffective
	6008	DZ	120	2	adverse reaction - cough, flushing, nasal congestion sleeplessness
	6011	IS	2.5	9	adverse reaction - dizzines

+IS = Isradipine
PL = Placebo
PP = Propranolol
EN = Enalapril
CP = Captopril
DZ = Diltiazem
NF = Nifedipine

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

* Patient was entered into center 4, but received center 1 medication

TABLE 20

LONG TERM SAFETY TRIALS

No. of Subjects Entered	No. of Subjects Completed 6 mos.	No. of Subjects Completed 1 yr.	No. of Subjects Completed 2 yrs.	Discontinued	No. of Deaths	Objectives	Dosage	Duration of Study Drug Administration/ Design	Remarks
	--	(106)*	--	(64)*	(1++)*	Assess long term safety and efficacy of isradipine compared to placebo when administered alone or in combination with other antihypertensives in the treatment of hypertension	Isradipine: 2.5 mg bid - 10 mg bid; or placebo	12 mos. double-blind randomized, parallel group design, placebo controlled	Study completed.
47††	28††	16††	2††	20††	4††	Assess long term safety	Isradipine: 5 mg - 22.5 mg per day administered in divided doses	Up to 2 years or more; open-label, non-controlled	Including both the SU-1 and SU-2 data bases, the mean duration of treatment was ~40 weeks (range <1-250 weeks) at a mean dose of ~12 mg/day. At least one adverse reaction was reported by ~68% of the patients, but these were generally encountered early in the study. In about half of these patients, adverse reactions were not reported on a recurring basis. The additional long term data analyzed in SU-2 confirms long term safety of isradipine.
558†)*	(455†)*	(336†)*	(96†)*	(222†)*	(6†)* 3+				

In the long term data submitted in Safety Update -1 are: 5, 10, 206, 252 Center 5, 301-C, 301-D, 301-F, 302-B, 302-C, 302-D, 303-D, 303-C, 304-A, 304-C, 7-B, and 307-C, 350 Centers 2, 3, 5, 6, and 7, 351 Centers 1-7, and 352 Centers 2 and 3.

tive heart failure treated in an emergency use protocol and not included in the data base for this report died suddenly while receiving isradipine. idered by the investigator as contributing to the event. An additional patient (Study No. 303-C, Patient No. 316) died 2 months after being erm study due to malignant lymphoma. This patient had been on 10 mg/day of isradipine for a total of 16 weeks. The investigator did not believe ributed to this death. Another patient (Study No. 350 LT, Patient No. 307) died 3 weeks after isradipine had been discontinued: this patient had been l with ataxia and diplopia; cause of death was attributed to cerebral spinal fluid infection and resulting complications. placebo treated group, died in automobile accident.

that includes those patients from no. 351.

numbers include: 17, 204, 208, 222, 223, 253, 254, and 255 Centers 1, 5 and 7. The four deaths indicated above all involved patients being treated le their long term data were not included in the long term data be analyzed for SU-1, these four cases were reported in the SU-1 update.

Table 20

Demographics

Table 30 summarizes background demographics. The Table also identifies those patients entering long term studies according to their treatment in short term trials.

A total of 47 new patients with a mean age of 63 years (43-83) were included; 81% were male and 85% caucasian. The corresponding percentages for SU-1 were: 57 years, 64% caucasian. The prescribed dose of isradipine was 5-22.5 mg/day with hypertension studies using 2.5 mg-10 mg bid, with a few patients receiving drug once a day. In angina and CHF, the dose was 7.5 mg tid. The mean daily dose was similar to SU-1 and was not recalculated.

Figure 1 displays the number of patients receiving drug by month (SU-1 and SU-2 combined). It is seen that 485 patients received isradipine for at least 6 months, 367 for 12 months and 98 for 24 months and 84 for over 24 months. Figure 2 represents data for the 47 new patients in SU-2.

Clinical Laboratory Tests

Refer to attached sponsor's summary

TABLE 30
ISRADIPINE LONG TERM PATIENTS
SUMMARY OF BACKGROUND - SAFETY UPDATE 3-89
[redacted]

ORIGINAL PATIENT GROUPS DURING DB STUDY PHASE

CATEGORY / STATISTIC	PN	OTHER RX	PLACEBO	ANGI.XOVER	TOTAL
AGE (YEARS)					
N	22	6	9	10	47
MEDIAN	63.5	62.5	65.0	65.0	64.0
MEAN	61.9	63.0	64.4	64.7	63.1
STD	9.23	3.03	5.73	6.27	7.41
MIN	43.0	59.0	57.0	58.0	43.0
MAX	83.0	67.0	72.0	77.0	83.0
HEIGHT (INCHES)					
N	22	6	9	10	47
MEDIAN	68.0	71.0	70.0	66.5	69.0
MEAN	67.6	71.0	68.9	67.2	68.2
STD	4.68	0.63	4.11	3.85	4.17
MIN	59.0	70.0	63.0	60.0	59.0
MAX	75.0	72.0	75.0	74.0	75.0
WEIGHT (LBS)					
N	22	6	9	10	47
MEDIAN	180.5	217.0	218.0	170.0	180.0
MEAN	187.3	215.3	195.3	172.8	189.3
STD	43.36	27.37	55.59	24.86	41.89
MIN	121.0	180.0	98.0	140.0	98.0
MAX	271.0	256.0	267.0	233.0	271.0
SEX					
MALE	15 (68%)	6 (100%)	7 (78%)	10 (100%)	38 (81%)
FEMALE	7 (32%)	0 (0%)	2 (22%)	0 (0%)	9 (19%)
TOTAL	22	6	9	10	47

PN = ISRADIPINE

Table 30

03-0010

TABLE 30
ISRADIPINE LONG TERM PATIENTS
SUMMARY OF BACKGROUND - SAFETY UPDATE 8-89
[redacted]

ORIGINAL PATIENT GROUPS DURING DB STUDY PHASE

CATEGORY / STATISTIC	PN	OTHER RX	PLACEBO	ANGI.XOVER	TOTAL
RACE					
CAUCASIAN	18 (82%)	5 (83%)	7 (78%)	10 (100%)	40 (85%)
NEGRO	3 (14%)	1 (17%)	2 (22%)	0 (0%)	6 (13%)
AMERICAN INDIAN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ORIENTAL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
OTHER	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
TOTAL	22	6	9	10	47
SKIN					
NORMAL	18 (82%)	3 (50%)	7 (78%)	10 (100%)	38 (81%)
ABNORMAL	4 (18%)	3 (50%)	2 (22%)	0 (0%)	9 (19%)
TOTAL	22	6	9	10	47
EYES,EAR,THROAT					
NORMAL	14 (64%)	4 (67%)	7 (78%)	6 (60%)	31 (66%)
ABNORMAL	8 (36%)	2 (33%)	2 (22%)	4 (40%)	16 (34%)
TOTAL	22	6	9	10	47
RESPIRATORY					
NORMAL	16 (73%)	5 (83%)	7 (78%)	9 (90%)	37 (79%)
ABNORMAL	6 (27%)	1 (17%)	2 (22%)	1 (10%)	10 (21%)
TOTAL	22	6	9	10	47

TABLE 30
ISRADIPINE LONG TERM PATIENTS
SUMMARY OF BACKGROUND - SAFETY UPDATE 8-88
[redacted]

ORIGINAL PATIENT GROUPS DURING DB STUDY PHASE

CATEGORY / STATISTIC	PN	OTHER RX	PLACEBO	ANGI.XOVER	TOTAL
CARDIOVASCULAR					
NORMAL	5 (23%)	6 (100%)	0 (0%)	1 (10%)	12 (26%)
ABNORMAL	17 (77%)	0 (0%)	9 (100%)	9 (90%)	35 (74%)
TOTAL	22	6	9	10	47
MUSCULOSKELETAL					
NORMAL	15 (68%)	3 (50%)	9 (100%)	7 (70%)	34 (72%)
ABNORMAL	7 (32%)	3 (50%)	0 (0%)	3 (30%)	13 (28%)
TOTAL	22	6	9	10	47
GASTROINTESTINAL					
NORMAL	13 (59%)	3 (50%)	7 (78%)	5 (50%)	28 (60%)
ABNORMAL	9 (41%)	3 (50%)	2 (22%)	5 (50%)	19 (40%)
TOTAL	22	6	9	10	47
GENITO-URINARY					
NORMAL	17 (77%)	5 (83%)	6 (67%)	9 (90%)	37 (79%)
ABNORMAL	5 (23%)	1 (17%)	3 (33%)	1 (10%)	10 (21%)
TOTAL	22	6	9	10	47
ENDOCRINE					
NORMAL	15 (68%)	6 (100%)	4 (44%)	10 (100%)	35 (74%)
ABNORMAL	7 (32%)	0 (0%)	5 (56%)	0 (0%)	12 (26%)
TOTAL	22	6	9	10	47

03-001CS

TABLE 30
ISRADIPINE LONG TERM PATIENTS
SUMMARY OF BACKGROUND - SAFETY UPDATE 8-89
[redacted]

ORIGINAL PATIENT GROUPS DURING DB STUDY PHASE

CATEGORY / STATISTIC	PN	OTHER RX	PLACEBO	ANGI.XOVER	TOTAL
NEUROLOGICAL					
NORMAL	17 (77%)	8 (100%)	8 (89%)	10 (100%)	41 (87%)
ABNORMAL	5 (23%)	0 (0%)	1 (11%)	0 (0%)	6 (13%)
TOTAL	22	8	9	10	47
PSYCHIATRIC					
NORMAL	21 (95%)	8 (100%)	7 (78%)	10 (100%)	44 (94%)
ABNORMAL	1 (5%)	0 (0%)	2 (22%)	0 (0%)	3 (6%)
TOTAL	22	8	9	10	47

4. Clinical Laboratory Tests

In the previous analysis of the data in SU-1, a central lab, MetPath, performed the assays of the specimens collected from 218/558, or 39%, of the total number of patients entered into the long-term trial. Descriptive statistics, therefore, described for the MetPath data both the mean changes from baseline averaged over each 13 week interval of isradipine treatment, and the mean changes averaged over the entire treatment period. Similar descriptive statistics were not performed on the new database included in SU-2, since only 22 patients compared to 218 patients in SU-1, had their lab samples assayed by a central lab. However, as in SU-1 and discussed below, the frequency of newly-occurring abnormalities was determined for eight of the blood chemistry variables which included all new patients (N=47) and the new data (N=31) evaluated during the long-term trial.

a. Newly Occurring Abnormalities

In the present assessment of newly-occurring abnormalities, only the blood chemistry variables of glucose, creatinine, BUN, uric acid, alkaline phosphatase, LDH, SGOT, and SGPT were reviewed. These variables were considered most important in the assessment of long-term safety since the previous long-term analysis indicated that more than 5% of the patients developed new abnormalities in these variables. Furthermore, the previous analysis of the long-term data in SU-1 did not reveal any relevant changes in the hematological, urinalysis, and other blood chemistry variables. Moreover, the amount of new long-term data included in SU-2, was less than 10% compared to the vast experience analyzed previously and discussed in SU-1. If, however, a patient was discontinued because of a clinically relevant abnormality in those variables not included in the present formal analysis, than the patient and reason would be identified later in this report. However, no patient was discontinued because of laboratory abnormalities.

Regarding the 8 chemistry variables listed above, and under consideration in SU-2, the long-term laboratory data for all new patients (N=47), and the new data from the 31 patients previously mentioned, were evaluated separately and newly-occurring abnormalities were identified and displayed after the following adjustments were made to the laboratory normal ranges:

- Chemistry Variables - All 8 variables were adjusted +15%.

A patient was considered to have a newly-occurring laboratory abnormality in these variables if all the pre-isradipine or baseline evaluations for a particular variable were within the adjusted normal range and the patient had at least one evaluation while receiving isradipine 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. These are the same procedures which were used in the analysis of the long-term data in SU-1.

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 following randomization (i.e., a further increase of at least 15% from their pre-dose value), then this patient was also considered to have a newly-occurring laboratory abnormality.

These same rules also applied in assessing the frequency of abnormal laboratory determinations.

1. Blood Chemistries

Table 31 summarizes the frequencies of newly-occurring abnormalities for each of the 8 blood chemistry variables evaluated in this report. The results were obtained from the group of 47 new patients involving approximately 200 separate determinations for each variable and are presented as the number of patients with newly-occurring abnormalities and the number of determinations which were abnormal.

The total incidences over 1-36 months of treatment for the 47 new patients are summarized in the table below. The results from SU-1 are also presented for comparison. The total number with "base" may not be exactly 47 since some patients may not have had a baseline value for comparison.

NEWLY-OCCURRING ABNORMALITIES

VARIABLE	NO. OF PATIENTS/ TOTAL N - % SU-1	SU -2	NO. OF DETERMINATIONS/ TOTAL N - % SU-1	SU -2
Glucose (high)	113/539 21.0%	7/46 15.2%	277/3607 7.7%	14/202 6.9%
Creatinine	35/533 6.6%	5/46 10.9%	63/3517 1.8%	6/190 3.2%
BUN	45/507 8.9%	4/46 8.7%	84/3315 2.5%	7/203 3.4%
Uric Acid	31/531 5.8%	0/46 0	51/3353 1.5%	0/192 0
Alkaline Phosphatase	86/535 16.1%	6/46 13%	366/6485 5.6%	13/218 6.0%
LDH	43/523 8.2%	9/46 19.6%	61/6183 1.0%	10/222 4.5%
SGOT	76/541 14.0%	3/46 6.5%	158/6541 2.4%	4/223 1.8%
SGPT	79/523 15.1%	2/43 4.7%	212/6284 3.4%	2/200 1.0%

1. Blood Chemistries (Cont'd)

Overall, these results are remarkably similar to the long-term results already presented and discussed in SU-1. The only variables which differ are the numbers of patients with an elevated creatinine or LDH on at least one occassion which increased from 6.6% in SU-1 to 11.4% in SU-2 for creatinine, and 8.2% in SU-1 to 20% in SU-2 for LDH. There was also a slight increase in the number of abnormal determinations for these variables. These results are probably related to the new patient population included in this update the majority of whom are patients with heart failure. Three of the patients with elevated creatinine, and six patients with elevated LDH were patients with heart failure.

The remaining patients with elevated creatinine were angina patients, while the remaining cases of LDH evaluations were patients with hypertension. In no case did creatinine exceed 2.0 mg/dl. In one of the hypertensive patients, LDH increased from a baseline value of 136 U/L to 809 U/L after 30 weeks of treatment (upper limit for LDH had been raised to 611 U/L). However, at 38 weeks, LDH was 134 U/L, and at 52 weeks, SGOT was 54 U/L and SGPT was 32 U/L. The elevated LDH above the revised upper limit seems to be due to other factors and not an indication of liver toxicity.

For the liver function variables of SGOT and SGPT, a lower incidence of elevations was noted in the SU-2 database for the 47 new patients indicating that there were no more frequent elevations for these variables with the extended experience. Furthermore, there was no overall apparent increase in incidences of patients or number of determinations with newly-occurring abnormalities over each subsequent 13-week interval of treatment for any of the variables evaluated. Furthermore, none of these patients were discontinued from the long-term study because of laboratory abnormalities.

1. Blood Chemistries (Cont'd)

A total of 31 patients previously included in the long-term safety data in SU-1 had additional safety data collected for SU-2. These data have also been analyzed. The number of patients with newly-occurring abnormalities are shown below:

VARIABLE	NO. OF PATIENTS WITH NEWLY OCCURRING ABNORMALITIES
Glucose (high)	0
Creatinine	0
BUN	3
Uric Acid	0
Alkaline Phosphatase	2
LDH	1
SGOT	2
SGPT	1

In three patients with elevated BUN, the highest value observed was 29 U/L after 9-12 months of long-term treatment with no evidence of progressive changes.

One case of elevated SGOT involved a value of 43 U/L after 53 weeks of long-term treatment, which returned to normal at week 57. The second case of elevated SGOT and one case of elevated SGPT occurred in the same patient described below on pg. 39.

One of the cases involving elevated alkaline phosphatase developed in a patient after 49 weeks into the long-term protocol. Values were at Week 49, 143 U/L; Week 58, 177 U/L, and Week 67, 155 U/L. No other follow-up reports were available at this time.

1. Blood Chemistries (Cont'd)

In this new long-term database consisting of 78 patients, values in excess of 100 IU/L were observed for SGOT and SGPT in only 1 patient as opposed to 20 and 23 patients, respectively, in SU-1. A SGOT value of 123 U/L was noted in one hypertensive patient at Week 55 three weeks after isradipine had been withdrawn and the patient had completed a one-year trial At this timepoint SGPT was 79 U/L, LDH was 223 U/L, and alkaline phosphatase was 223 U/L. Both SGOT and SGPT were in the range of 20-40 U/L, LDH was 152-170 U/L, and alkaline phosphatase was 144 U/L up to and including Week 52. Only alkaline phosphatase was slightly elevated. No follow-up readings are available, but all these values were essentially normal up to Week 52. Since there was no indication of progressive changes during the course of treatment, it is likely that other factors may have contributed to this elevation.

a. Newly Occurring Abnormalities

In conclusion, analysis of the clinical laboratory data did not reveal any new or significant problems relative to long-term isradipine administration. In fact, since the results from the increased experience in the two Safety Updates are remarkably similar, it can be concluded that isradipine is safe and does not result in any clinically relevant problems.

TABLE 31
ISRADIPINE LONG TERM DATA
SAFETY UPDATE - 8-89
ABNORMALITIES FOR CHEMISTRY
BY VARIABLE, BY ISRADIPINE INTERVAL

TREATMENT ISRADIPINE

		MONTHS					
		1-3		4-6		7-9	
		PATIENT TOTAL	DETERMIN TOTAL	PATIENT TOTAL	DETERMIN TOTAL	PATIENT TOTAL	DETERMIN TOTAL
LAB VARIABLE	TYPE						
GLUC	N TO H	2	3	2	3	0	0
	ABNORM WORSE	4	4	1	1	1	2
	TOT NORM BASE	26	57	17	25	11	14
	TOT WITH BASE	44	69	28	40	19	28
CREAT	N TO H	2	3	0	0	1	1
	ABNORM WORSE	0	0	0	0		
	TOT NORM BASE	38	70	27	38	18	24
	TOT WITH BASE	43	80	28	38	18	24
BUN	N TO H	2	4	1	1	0	0
	ABNORM WORSE	2	2	0	0	0	0
	TOT NORM BASE	35	76	24	34	17	23
	TOT WITH BASE	44	82	28	40	18	24
URICAC	N TO H	0	0	0	0	0	0
	ABNORM WORSE	0	0	0	0	0	0
	TOT NORM BASE	[illegible]	69	26	37	18	23
	TOT WITH BASE	43	81	[illegible]	40	18	24
ALKPHOS	N TO H	0	0	0	0	1	1
	ABNORM WORSE	0	0	1	2	1	1
	TOT NORM BASE	41	86	28	41	17	25

(CONTINUED)

N = NORMAL H = HIGH

TABLE 30
ISRADIPINE LONG TERM PATIENTS
SUMMARY OF BACKGROUND - SAFETY UPDATE 8-88
[redacted]

CATEGORY I STATISTIC	ORIGINAL PATIENT GROUPS DURING DB STUDY PHASE: PN	OTHER RX	PLACEBO	ANGI.XOVER	TOTAL
CARDIOVASCULAR					
NORMAL	5 (23%)	6 (100%)	0 (0%)	1 (10%)	12 (26%)
ABNORMAL	17 (77%)	0 (0%)	9 (100%)	9 (90%)	35 (74%)
TOTAL	22	6	9	10	47
MUSCULOSKELETAL					
NORMAL	15 (68%)	3 (50%)	9 (100%)	7 (70%)	34 (72%)
ABNORMAL	7 (32%)	3 (50%)	0 (0%)	3 (30%)	13 (28%)
TOTAL	22	6	9	10	47
GASTROINTESTINAL					
NORMAL	13 (59%)	3 (50%)	7 (78%)	5 (50%)	28 (60%)
ABNORMAL	9 (41%)	3 (50%)	2 (22%)	5 (50%)	19 (40%)
TOTAL	22	6	9	10	47
GENITO-URINARY					
NORMAL	17 (77%)	5 (83%)	6 (67%)	8 (80%)	37 (79%)
ABNORMAL	5 (23%)	1 (17%)	3 (33%)	1 (10%)	10 (21%)
TOTAL	22	6	9	10	47
ENDOCRINE					
NORMAL	15 (68%)	6 (100%)	4 (44%)	10 (100%)	35 (74%)
ABNORMAL	7 (32%)	0 (0%)	5 (56%)	0 (0%)	12 (26%)
TOTAL	22	6	9	10	47

Table 30

TABLE 30
ISRADIPINE LONG TERM PATIENTS
SUMMARY OF BACKGROUND - SAFETY UPDATE 8-89
[redacted]

ORIGINAL PATIENT GROUPS DURING DB STUDY PHASE

CATEGORY / STATISTIC	PN	OTHER RX	PLACEBO	ANGI.XOVER	TOTAL
NEUROLOGICAL					
NORMAL	17 (77%)	6 (100%)	8 (89%)	10 (100%)	41 (87%)
ABNORMAL	5 (23%)	0 (0%)	1 (11%)	0 (0%)	6 (13%)
TOTAL	22	6	9	10	47
PSYCHIATRIC					
NORMAL	21 (95%)	6 (100%)	7 (78%)	10 (100%)	44 (94%)
ABNORMAL	1 (5%)	0 (0%)	2 (22%)	0 (0%)	3 (6%)
TOTAL	22	6	9	10	47

C3-00107

4. Clinical Laboratory Tests

In the previous analysis of the data in SU-1, a central lab, MetPath, performed the assays of the specimens collected from 218/558, or 39%, of the total number of patients entered into the long-term trial. Descriptive statistics, therefore, described for the MetPath data both the mean changes from baseline averaged over each 13 week interval of isradipine treatment, and the mean changes averaged over the entire treatment period. Similar descriptive statistics were not performed on the new database included in SU-2, since only 22 patients compared to 218 patients in SU-1, had their lab samples assayed by a central lab. However, as in SU-1 and discussed below, the frequency of newly-occurring abnormalities was determined for eight of the blood chemistry variables which included all new patients (N=47) and the new data (N=31) evaluated during the long-term trial.

a. Newly Occurring Abnormalities

In the present assessment of newly-occurring abnormalities, only the blood chemistry variables of glucose, creatinine, BUN, uric acid, alkaline phosphatase, LDH, SGOT, and SGPT were reviewed. These variables were considered most important in the assessment of long-term safety since the previous long-term analysis indicated that more than 5% of the patients developed new abnormalities in these variables. Furthermore, the previous analysis of the long-term data in SU-1 did not reveal any relevant changes in the hematological, urinalysis, and other blood chemistry variables. Moreover, the amount of new long-term data included in SU-2, was less than 10% compared to the vast experience analyzed previously and discussed in SU-1. If, however, a patient was discontinued because of a clinically relevant abnormality in these variables not included in the present formal analysis, than the patient and reason would be identified later in this report. However, no patient was discontinued because of laboratory abnormalities.

Regarding the 8 chemistry variables listed above, and under consideration in SU-2, the long-term laboratory data for all new patients (N=47), and the new data from the 31 patients previously mentioned, were evaluated separately and newly-occurring abnormalities were identified and displayed after the following adjustments were made to the laboratory normal ranges.

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- Chemistry Variables - All 8 variables were adjusted +15%.

A patient was considered to have a newly-occurring laboratory abnormality in these variables if all the pre-isradipine or baseline evaluations for a particular variable were within the adjusted normal range and the patient had at least one evaluation while receiving isradipine 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. These are the same procedures which were used in the analysis of the long-term data in SU-1.

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 following randomization (i.e., a further increase of at least 15% from their pre-dose value), then this patient was also considered to have a newly-occurring laboratory abnormality.

These same rules also applied in assessing the frequency of abnormal laboratory determinations.

1. Blood Chemistries

Table 31 summarizes the frequencies of newly-occurring abnormalities for each of the 8 blood chemistry variables evaluated in this report. The results were obtained from the group of 47 new patients involving approximately 200 separate determinations for each variable and are presented as the number of patients with newly-occurring abnormalities and the number of determinations which were abnormal.

The total incidences over 1-36 months of treatment for the 47 new patients are summarized in the table below. The results from SU-1 are also presented for comparison. The total number with "base" may not be exactly 47 since some patients may not have had a baseline value for comparison.

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NEWLY-OCCURRING ABNORMALITIES

VARIABLE	NO. OF PATIENTS/ TOTAL N - % SU-1	SU -2	NO. OF DETERMINATIONS/ TOTAL N - % SU-1	SU -2
Glucose (high)	113/539 21.0%	7/46 15.2%	277/3607 7.7%	14/202 6.9%
Creatinine	35/533 6.6%	5/46 10.9%	63/3517 1.8%	6/190 3.2%
BUN	45/507 8.9%	4/46 8.7%	84/3315 2.5%	7/203 3.4%
Uric Acid	31/531 5.8%	0/46 0	51/3353 1.5%	0/192 0
Alkaline Phosphatase	86/535 16.1%	6/46 13%	366/6485 5.6%	13/218 6.0%
LDH	43/520 8.2%	9/46 19.6%	[illegible] 1.0%	10/222 4.5%
SGOT	76/541 14.0%	3/46 6.5%	158/6541 2.4%	4/223 1.3%
SGPT	79/523 15.1%	2/43 4.7%	212/6234 3.4%	2/200 1.0%

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1. Blood Chemistries (Cont'd)

Overall, these results are remarkably similar to the long-term results already presented and discussed in SU-1. The only variables which differ are the numbers of patients with an elevated creatinine or LDH on at least one occassion which increased from 6.6% in SU-1 to 11.4% in SU-2 for creatinine, and 8.2% in SU-1 to 20% in SU-2 for LDH. There was also a slight increase in the number of abnormal determinations for these variables. These results are probably related to the new patient population included in this update the majority of whom are patients with heart failure. Three of the patients with elevated creatinine, and six patients with elevated LDH were patients with heart failure.

The remaining patients with elevated creatinine were angina patients, while the remaining cases of LDH evaluations were patients with hypertension. In no case did creatinine exceed 2.0 mg/dl. In one of the hypertensive patients, LDH increased from a baseline value of 136 U/L to 909 U/L after 30 weeks of treatment (upper limit for LDH had been raised to [illegible]). However at 18 weeks LDH was [illegible] U/L, and at 30 weeks, SGOT was [illegible] U/L and SGPT was [illegible] U/L. The elevated LDH above the revised upper limit seems to be due to other factors and not an indication of liver toxicity.

For the liver function variables of SGOT and SGPT, a lower incidence of elevations was noted in the SU-2 database for the 47 new patients indicating that there were no more frequent elevations for these variables with the extended experience. Furthermore, there was no overall apparent increase in incidences of patients or number of determinations with newly-occurring abnormalities over each subsequent 13-week interval of treatment for any of the variables evaluated. Furthermore, none of these patients were discontinued from the long-term study because of laboratory abnormalities.

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1. Blood Chemistries (Cont'd)

A total of 31 patients previously included in the long-term safety data in SU-1 had additional safety data collected for SU-2. These data have also been analyzed. The number of patients with newly-occurring abnormalities are shown below:

VARIABLE	NO. OF PATIENTS WITH NEWLY OCCURRING ABNORMALITIES
Glucose (high)	0
Creatinine	0
BUN	3
Uric Acid	0
Alkaline Phosphatase	2
LDH	1
SGOT	2
SGPT	1

In three patients with elevated BUN, the highest value observed was 29 U/L after 9-12 months of long-term treatment with no evidence of progressive changes.

One case of elevated SGOT involved a value of 42 U/L after 52 weeks of long-term treatment, which returned to normal at week 57. The second case of elevated SGOT and one case of elevated SGPT occurred in the same patient described below on pg. 39.

One of the cases involving elevated alkaline phosphatase developed in a patient after 49 weeks into the long-term protocol. Values were at Week 49, 143 U/L; Week 58, 177 U/L, and Week 67, 155 U/L. No other follow-up reports were available at this time.

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1. Blood Chemistries (Cont'd)

In this new long-term database consisting of 78 patients, values in excess of 100 IU/L were observed for SGOT and SGPT in only 1 patient as opposed to 20 and 23 patients, respectively, in SU-1. A SGOT value of 123 U/L was noted in one hypertensive patient at Week 55 three weeks after isradipine had been withdrawn and the patient had completed a one-year trial At this timepoint SGPT was 79 U/L, LDH was 223 U/L, and alkaline phosphatase was 223 U/L. Both SGOT and SGPT were in the range of 20-40 U/L, LDH was 52-170 U/L, and alkaline phosphatase was 144 U/L up to and including Week 52. Only alkaline phosphatase was slightly elevated. No follow-up readings are available, but all these values were essentially normal up to Week 52. Since there was no indication of progressive changes during the course of treatment, it is likely that other factors may have contributed to this elevation.

a. Newly Occurring Abnormalities

In conclusion, analysis of the clinical laboratory data did not reveal any new or significant problems relative to long-term isradipine administration. In fact, since the results from the increased experience in the two Safety Updates are remarkably similar, it can be concluded that isradipine is safe and does not result in any clinically relevant problems.

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TABLE 31
ISRADIPINE LONG TERM DATA
SAFETY UPDATE - 8-89
ABNORMALITIES FOR CHEMISTRY
BY VARIABLE, BY ISRADIPINE INTERVAL

TREATMENT ISRADIPINE

		MONTHS					
		1-3		4-6		7-9	
		PATIENT	DETERMIN	PATIENT	DETERMIN	PATIENT	DETERMIN
		TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL
LAB VARIABLE	TYPE						
GLUC	N TO H	2	3	2	3	0	0
	ABNORM WORSE	4	4	1	1	1	2
	TOT NORM BASE	26	57	17	25	11	14
	TOT WITH BASE	44	89	29	40	19	26
CREAT	N TO H	2	3	0	0	1	1
	ABNORM WORSE	0	0	0	0		
	TOT NORM BASE	38	70	27	36	18	24
	TOT WITH BASE	43	80	29	39	18	24
BUN	N TO H	2	4	1	1	0	0
	ABNORM WORSE	2	2	0	0	0	0
	TOT NORM BASE	35	76	24	34	17	23
	TOT WITH BASE	44	92	29	40	18	24
URICAC	N TO H	0	0	0	0	0	0
	ABNORM WORSE	0	0	0	0	0	0
	TOT NORM BASE	34	68	26	37	18	23
	TOT WITH BASE	41	81	29	40	19	24
ALKPHOS	N TO H	0	0	0	0	1	1
	ABNORM WORSE	0	0	1	2	1	1
	TOT NORM BASE	11	86	29	41	17	25

(CONTINUED)

N - NORMAL H - HIGH

Table 31

TABLE 31
ISRADIPINE LONG TERM DATA
SAFETY UPDATE - 8-89
ABNORMALITIES FOR CHEMISTRY
BY VARIABLE, BY ISRADIPINE INTERVAL

TREATMENT ISRADIPINE

		MONTHS					
		1-3		4-6		7-9	
		PATIENT TOTAL	DETERMIN TOTAL	PATIENT TOTAL	DETERMIN TOTAL	PATIENT TOTAL	DETERMIN TOTAL
LAB VARIABLE	TYPE						
ALKPHOS	TOT WITH BASE	43	91	31	45	19	29
LDH	N TO H	4	5	0	0	0	0
	ABNORM WORSE	1	1	0	0	0	0
	TOT NORM BASE	38	87	27	38	15	22
	TOT WITH BASE	44	98	29	42	19	29
SGOT	N TO H	1	1	1	1	0	0
	ABNORM WORSE	0	0	0	0	1	1
	TOT NORM BASE	42	90	29	38	18	28
	TOT WITH BASE	44	87	31	44	19	29
SGPT	N TO H	0	0	1	1	0	0
	ABNORM WORSE	0	0	0	0	1	1
	TOT NORM BASE	38	77	25	35	15	24
	TOT WITH BASE	41	84	29	40	16	28

Table 31

TABLE 31
ISRADIPINE LONG TERM DATA
SAFETY UPDATE - 8-89
ABNORMALITIES FOR CHEMISTRY
BY VARIABLE, BY ISRADIPINE INTERVAL

TREATMENT ISRADIPINE

		MONTHS					
		10-12		13-15		16-18	
		PATIENT TOTAL	DETERMIN TOTAL	PATIENT TOTAL	DETERMIN TOTAL	PATIENT TOTAL	DETERMIN TOTAL
LAB VARIABLE	TYPE						
GLUC	N TO H	0	0	0	0	0	0
	ABNORM WORSE	1	1	0	0	0	0
	TOT NORM BASE	6	8	8	10	5	5
	TOT WITH BASE	13	16	11	14	6	6
CREAT	N TO H	0	0	0	0	0	0
	ABNORM WORSE						
	TOT NORM BASE	13	16	11	14	6	6
	TOT WITH BASE	13	16	11	14	6	6
BUN	N TO H	0	0	0	0	0	0
	ABNORM WORSE	0	0	0	0		
	TOT NORM BASE	10	12	8	12	6	6
	TOT WITH BASE	13	16	11	14	6	6
URICAC	N TO H	0	0	0	0	0	0
	ABNORM WORSE	0	0	0	0		
	TOT NORM BASE	11	13	10	13	6	6
	TOT WITH BASE	13	16	11	14	6	6
ALKPHOS	N TO H	3	4	2	3	0	0
	ABNORM WORSE	1	1				
	TOT NORM BASE	13	18	12	16	6	6

(CONTINUED)

Table 31

TABLE 31
ISRADIPINE LONG TERM DATA
SAFETY UPDATE - 8-89
ABNORMALITIES FOR CHEMISTRY
BY VARIABLE, BY ISRADIPINE INTERVAL

TREATMENT ISRADIPINE

		MONTHS					
		10-12		13-15		16-18	
		PATIENT TOTAL	DETERMIN TOTAL	PATIENT TOTAL	DETERMIN TOTAL	PATIENT TOTAL	DETERMIN TOTAL
LAB VARIABLE	TYPE						
ALKPHOS	TOT WITH BASE	15	20	12	18	6	6
LDH	N TO H	1	1	0	0	1	1
	ABNORM WORSE	1	1	0	0	0	0
	TOT NORM BASE	11	15	9	13	5	5
	TOT WITH BASE	15	20	12	16	6	6
SGOT	N TO H	0	0	0	0	0	0
	ABNORM WORSE	1	1	1	1	0	0
	TOT NORM BASE	14	18	12	16	5	5
	TOT WITH BASE	15	20	12	16	6	6
SGPT	N TO H	0	0	0	0	0	0
	ABNORM WORSE	0	0	0	0	0	0
	TOT NORM BASE	13	18	11	15	4	4
	TOT WITH BASE	14	19	12	18	5	5

Table 31

TABLE 31
ISRADIPINE LONG TERM DATA
SAFETY UPDATE - 8-89
ABNORMALITIES FOR CHEMISTRY
BY VARIABLE, BY ISRADIPINE INTERVAL

TREATMENT ISRADIPINE

		MONTHS					
		19-21		22-24		25-27	
		PATIENT	DETERMIN	PATIENT	DETERMIN	PATIENT	DETERMIN
		TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL
LAB VARIABLE	TYPE						
GLUC	N TO H	0	0	0	0	0	0
	ABNORM WORSE	0	0				
	TOT NORM BASE	2	3	3	3	2	2
	TOT WITH BASE	3	5	3	3	2	2
CREAT	N TO H	1	1	0	0	1	1
	ABNORM WORSE						
	TOT NORM BASE	3	5	3	3	2	2
	TOT WITH BASE	3	5	3	3	2	2
BUN	N TO H	0	0	0	0	0	0
	ABNORM WORSE						
	TOT NORM BASE	3	5	3	3	2	2
	TOT WITH BASE	3	5	3	3	2	2
URICAC	N TO H	0	0	0	0	0	0
	ABNORM WORSE						
	TOT NORM BASE	3	5	3	3	2	2
	TOT WITH BASE	3	5	3	3	2	2
ALKPHOS	N TO H	1	1	0	0	0	0
	ABNORM WORSE						
	TOT NORM BASE	3	5	3	3	2	2

(CONTINUED)

Table 31

TABLE 31
ISRADIPINE LONG TERM DATA
SAFETY UPDATE - 8-89
ABNORMALITIES FOR CHEMISTRY
BY VARIABLE, BY ISRADIPINE INTERVAL

TREATMENT ISRADIPINE

		MONTHS					
		19-21		22-24		25-27	
		PATIENT	DETERMIN	PATIENT	DETERMIN	PATIENT	DETERMIN
		TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL
LAB VARIABLE	TYPE						
ALKPHOS	TOT WITH BASE	3	5	3	3	2	2
LDH	N TO H	0	0	0	0	0	0
	ABNORM WORSE	0	0	0	0	0	0
	TOT NORM BASE	2	3	2	2	1	1
	TOT WITH BASE	3	5	3	3	2	2
SGOT	N TO H	0	0	0	0	0	0
	ABNORM WORSE			0	0	0	0
	TOT NORM BASE	3	5	2	2	1	1
	TOT WITH BASE	3	5	3	3	2	2
SGPT	N TO H	0	0	0	0	0	0
	ABNORM WORSE	0	0				
	TOT NORM BASE	2	3	2	2	1	1
	TOT WITH BASE	3	5	2	2	1	1

Table 31

TABLE 31
ISRADIPINE LONG TERM DATA
SAFETY UPDATE - 8-89
ABNORMALITIES FOR CHEMISTRY
BY VARIABLE, BY ISRADIPINE INTERVAL

TREATMENT ISRADIPINE

		MONTHS			
		28-30		1-36	
		PATIENT TOTAL	DETERMIN TOTAL	PATIENT TOTAL	DETERMIN TOTAL
LAB VARIABLE	TYPE				
GLUC	N TO H	0	0	3	6
	ABNORM WORSE			4	8
	TOT NORM BASE	1	1	28	128
	TOT WITH BASE	1	1	46	202
CREAT	N TO H	0	0	5	6
	ABNORM WORSE			0	0
	TOT NORM BASE	1	1	41	177
	TOT WITH BASE	1	1	46	190
BUN	N TO H	0	0	2	5
	ABNORM WORSE			2	2
	TOT NORM BASE	1	1	37	174
	TOT WITH BASE	1	1	46	203
URICAC	N TO H	0	0	0	0
	ABNORM WORSE			0	0
	TOT NORM BASE	1	1	40	172
	TOT WITH BASE	1	1	46	192
ALKPHOS	N TO H	0	0	4	8
	ABNORM WORSE			2	4
	TOT NORM BASE	1	1	44	203

(CONTINUED)

TABLE 31
ISRADIPINE LONG TERM DATA
SAFETY UPDATE - 8-89
ABNORMALITIES FOR CHEMISTRY
BY VARIABLE, BY ISRADIPINE INTERVAL

TREATMENT ISRADIPINE

		MONTHS			
		28-30		1-36	
		PATIENT	DETERMIN	PATIENT	DETERMIN
		TOTAL	TOTAL	TOTAL	TOTAL
LAB VARIABLE	TYPE				
ALKPHOS	TOT WITH BASE	1	1	46	218
LDH	N TO H	1	1	7	8
	ABNORM WORSE			2	2
	TOT NORM BASE	1	1	39	187
	TOT WITH BASE	1	1	46	222
SGOT	N TO H	0	0	2	2
	ABNORM WORSE	0	0	1	2
	TOT NORM BASE	0	0	44	204
	TOT WITH BASE	1	1	46	223
SGPT	N TO H			1	1
	ABNORM WORSE			1	1
	TOT NORM BASE			38	179
	TOT WITH BASE			43	200

Table 31

Evaluation of ADRs

Tables 32 and 33 summarize all ADRs by body system and individual reactions. The incidences are presented for each 3 month period up to 27 months and then any ADR over the entire interval of treatment.

For those reactions considered possibly or probably drug related, 26/47 (55%) reported at least one ADR with 34% reporting during the first 13 weeks of treatment. Only 21% reported ADRs on a recurring basis.

The most freqently reported body systems affected were cardiovascular, CNS and GI. The most frequently reported ADRs (by at least 5% of patients) are listed below.

Most Frequently Reported ADRs, At Least 5% Patients

	SU-2 (% Patients)		SU-1 (% Patients)	
	Total	Recurring	Total	Recurring
ADR N =	47	38	558	485
Edema	10.6	7.9	18.8	9.3
Headache	4.3	2.6	18.8	7.2
Dizziness	3.5	0	10.2	2.9
Palpitations	2.1	2.6	8.4	2.3
Fatigue	2.1	0	8.1	2.9
Abdominal Discomfort	2.1	2.6	5.4	0.8
Flushing	0	0	5.4	0.3
Chest Pain	8.5	0	4.8	0.6

Chest pain was only reported in patients with angina or CHF, not in those with hypertension.

The number of patients reporting ADRs decrease over time. Is this due to an actual decrease in ADRs or to the fact that, as studies progress, the patient is inclined to report less?

Drug related ADRs reported in SU-2 but not in SU-1 were: first degree heart block (CHF), hepatomegaly, canker sore and difficulty in urinating. None of these patients were withdrawn for any of these reasons.

Two patients had ECG changes as ADRs, both with CHF and both remained in the study. One patient had inferior myocardial infarction, LAD, intermittent left fasicular block, non specific ST wave changes and sinus tachycardia. These changes were reported from baseline to Week 12 of treatment with only sinus tachycardia being considered drug related. The second case was non specific ST-T changes intermittently up to Week 56.

There were 7 ADRs rated as severe for the 47 new patients. These were: general pain (angina patient), nausea/diarrhea (CHF), edema (CHF), angina (CHF), GI upset (HTN), backpain (HTN) and bladder infection (HTN).

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TABLE 32
ISRADIPINE LONG-TERM PATIENTS
ALL ADVERSE REACTIONS - SAFETY UPDATE 6-89
PATIENTS COUNT BY BODY SYSTEM WITH AT LEAST ONE AR BY IS-INTERVAL
NEW-NEWLY REPORTED (FIRST TIME DURING IS), RECU-RECURRENCES DURING IS
PER BODY SYSTEM
NOTE: TOTAL RECU-NO. PTS WITH AT LEAST ONE RECU.

	IS TREATMENT DURATION (MONTHS)																	
	MONTHS 1- 3		MONTHS 4- 6		MONTHS 7- 9		MONTHS 10-12		MONTHS 13-15		MONTHS 16-18		MONTHS 19-21		MONTHS 22-24			
	RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW			
	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW		
	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
BODY SYSTEM																		
MISCEL		2		5	3			1		1								
SKIN		2		2	1				1									
MUSCULOSKELETAL		3	3		2		2		1	1								
RESPIRATORY				3	1	1												
CARDIOVASCULAR		12	4	1	4	4	3	1	2		2		1	1	1			
GASTROINTESTINAL		5		2	1						1							
UROGENITAL		2		1	1			1										
CNS		4		1	1	3	1				1							
AUTONOMIC		1		1		1												

TABLE 32
ISRADIPINE LONG-TERM PATIENTS
ALL ADVERSE REACTIONS - SAFETY UPDATE 8-89
PATIENTS COUNT BY BODY SYSTEM WITH AT LEAST ONE AR BY IS-INTERVAL
NEW=NEWLY REPORTED (FIRST TIME DURING IS), RECU=RECURRENCES DURING IS
PER BODY SYSTEM
NOTE: TOTAL RECU=NO. PTS WITH AT LEAST ONE RECU.

	IS TREATMENT DURATION (MONTHS)			
	MONTHS 21-27		TOTAL	
	RECUNEW		RECUNEW	
	RECU	NEW	RECU	NEW
	N	N	N	N
BODY SYSTEM				
MISCEL			3	9
SKIN			2	4
MUSCULOSKELETAL			3	4
RESPIRATORY			1	4
CARDIOVASCULAR	1		6	19
GASTROINTESTINAL			1	7
UROGENITAL			1	4
CNS			2	10
AUTONOMIC				2

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TABLE 32
ISRADIPINE LONG TERM PATIENTS
ALL ADVERSE REACTIONS - SAFETY UPDATE - 8-89
NO OF PATIENTS REPORTING ANY AR BY ISRADIPINE INTERVAL
NEW-NEWLY REPORTED (FIRST TIME DURING IS), RECU-RECURRENCES DURING IS
NOTE: TOTAL RECU-NO. PTS WITH AT LEAST ONE RECU.

	IS TREATMENT DURATION (MONTHS)																	
	MONTHS 0- 3		MONTHS 4- 6		MONTHS 7- 9		MONTHS 10-12		MONTHS 13-15		MONTHS 16-18		MONTHS 19-21		MONTHS 22-24			
	RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW			
	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW		
	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
BODY SYSTEM																		
ALL BODYSYSTEM POOLED		22	7	6	11	2		1	5		3		2		1			

Table 32

TABLE 32
ISRADIPINE LONG TERM PATIENTS
ALL ADVERSE REACTIONS - SAFETY UPDATE - 8-88
NO OF PATIENTS REPORTING ANY AR BY ISRADIPINE INTERVAL
NEW=NEWLY REPORTED (FIRST TIME DURING IS), RECU=RECURRENCES DURING IS
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
	N	N	N	N
BODY SYSTEM				
ALL BODYSYSTEM POOLED	1		14	31

8:21 MONDAY, JULY 17, 1989 27

TABLE 33
ISRADIPINE LONG TERM PATIENTS
ALL ADVERSE REACTIONS - SAFETY UPDATE - 1 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 REC.

	IS TREATMENT DURATION (MONTHS)															
	MONTHS <1 - 3		MONTHS 4 - 6		MONTHS 7 - 9		MONTHS 10 -12		MONTHS 13 -15		MONTHS 16 -18		MONTHS 19 -21		MONTHS 22 -24	
	RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW	
	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW
	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OVERSE EACTION																
AIN/ACHE,MISC				1												
HILLS				1	1											
ONJUNCTIVITIS				1	1											
ARS DISORDER				1												
YELID ISORDERS				1	1			1								
EVER PYREXIA)		2														
HRDAT ISCOMFORT				1												
TCHING EYES		1														
ASH		1		2	1				1							
KIN (MISC BNORMALITY)				1	1											
ACK,ACHE/PAIN TC		2	2		2		2		1	1						
AND/FEET,PAIN ACHE ETC		1	1													
OINT PAIN				1												
LG PAIN				1												

CONTINUED)

New adve. reaction since the last safety update.

TABLE 33
ISRADIPINE LONG TERM PATIENTS
ALL ADVERSE REACTIONS - SAFETY UPDATE - 8-89
PATIENTS COUNT ONCE AN 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 <1 - 3		MONTHS 4 - 6		MONTHS 7 - 9		MONTHS 10 -12		MONTHS 13 -15		MONTHS 16 -18		MONTHS 19 -21		MONTHS 22 -24	
	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW
	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADVERSE REACTION																
COUGHING				3		1										
NASAL CONGESTION						1										
SINUSITUS/SINUS INFLAM						1										
ANGINA		1				1										
CHEST PAIN		1				2								1		
ECG/EKG ABNORMAL		1	1				1				1					
EDEMA		4	2	1	2	1	2		2		1		1		1	
HEART BLOCK		1														
HEART FAILURE		1														
HYPOTENSION(BL PRES LOW)		2														
LEG/FEET CRAMPS								1								
EPISTAXIS (NOSE BLEED)						1										
PALPITATIONS		1	1			1	1									
TACHYCARDIA		1														

(CONTINUED)

* New adverse reaction since the last safety update

Table 33

TABLE 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 1 - 3		MONTHS 4 - 6		MONTHS 7 - 9		MONTHS 10 -12		MONTHS 13 -15		MONTHS 16 -18		MONTHS 19 -21		MONTHS 22 -24			
	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW
ADVERSE REACTION	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ABDOMINAL DISCOMFORT				1		1												
DIARRHEA		1		1														
HEPATOMEGALY		1																
CANKER SORE		1																
NAUSEA		3																
STOOL LOOSE														1				
CYSTITIS (INFLAM BLADDER)										1								
PROSTATITIS(I-NFLAMMED PROSTATE		1																
URINARY STREAM FORCE OF				1		1												
URINARY INFECTED		1																
WEAKNESS		1																
DIZZINESS		2		1		2												
EQUILIBRIUM LOSS						1		1				1						

(CONTINUED)

Table 3.

TABLE 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 <1 - 3		MONTHS 4 - 6		MONTHS 7 - 9		MONTHS 10 -12		MONTHS 13 -15		MONTHS 16 -18		MONTHS 19 -21		MONTHS 22 -24	
	RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW		RECUNEW	
	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW	RECU	NEW
ADVERSE REACTION	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FATIGUE		2														
HEADACHE		1														
SYNCOPE		1														
TREMOR						1										
DRY MOUTH				1												
TINGLING						1										

Table 33

TABLE 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 -27		TOTAL	
	RECURREW		RECURREW	
	RECU	NEW	RECU	NEW
	N	N	N	N
ADVERSE REACTION				
PAIN/ACHE,MISC				1
CHILLS			1	1
CONJUNCTIVITIS			1	1
EARS DISORDER				2
EYELID DISORDERS			1	2
FEVER (PYREXIA)				2
THROAT DISORDERS				1
ITCHING EYES				1
RASH			2	3
SKIN (MISC ABNORMALITY)			1	1
BACK,ACHE/PAIN ETC			2	3
HAND/FEET,PAIN ACHE ETC			1	1
BODY PAIN				1
LEG PAIN				1

(CONTINUED)

Table 33