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MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE : APR 13 1990

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approvable state of NDA 19-546, Isradipine, Sandoz Research Institute

TO : Director, Office of Drug Evaluation I, HFD-100

The Division recommends approval of NDA 19-546. The attached materials are the support for that recommendation. The attached Summary Basis of Approval can be taken to represent my review. The following comments are meant to provide an overview.

There is no question, isradipine lowers blood pressure in hypertensive man. Studies 332, 301, 302, 303 and 304, each adequate and well controlled, each multicenter, and in aggregate involving 575 randomized patients, found statistically significant differences between isradipine and each respective control agent and favored isradipine. Measurements of blood pressure were taken at the interdosing interval in each of these trials.

A twice daily regimen is adequately supported by time course information found in studies 9 and 332, by the magnitude of blood pressure effect at the interdosing interval in studies 332, 301, 302, 303 and 304 and indirectly by the magnitude of blood pressure effect at the interdosing interval found in a once-a-day trial (study 308).

It is reasonable to conclude that dizziness, flushing and edema are the principal side effects of isradipine and that these side effects are dose related. Maybe fatigue belongs in this list but I don't know what to make of that. The upper end of dosing is side-effect limited and is somewhere around 15 to 20 mg, daily (7.5 mg to 10 mg bid). So, I think the upper end of dosing has been explored.

The lowest dose studied, in major trials, was 2.5 mg bid. This dose is more effective than placebo and represents a reasonable starting dose as reflected in the draft package insert.

Most detail is reasonably touched upon (i.e., elderly, drug interactions) and on the surface, this is an untroubled straightforward calcium antagonist antihypertensive agent that behaves like one might expect and has a reasonable duration of action.

Sandoz is not currently seeking an anti-anginal claim and have little data, at the moment, for or against.

In spite of what appears to be straightforward, there are some wrinkles.

Hepatotoxicity

I do not think isradipine has hepatotoxic effects. The saga of their early experience (a bioavailability study) is adequately chronicled in the SBA (starting on page 144 of the attached draft). At the end of that story, I am sorry to say, one is left hung; it does not clearly clear isradipine of blame. Nonetheless, as development was in progress, my judgment was that the rechallenge data was clear enough to allow full development to go on. The overall results of the clinical development program does clear isradipine of any hepatotoxicity and the early result was a "red herring."

The entire "liver function" data base is nicely reviewed as an appendix to the attached draft SBA. A number of different alogrithms were devised for searching through the 1,858 subjects exposed to isradipine during development in order to find 14 cases that needed to be examined in detail. Eleven of these 14 cases received isradipine, two received placebo and one received hydrochlorothiazide. None of the 14 cases are, to my eye, suggestive of drug induced liver abnormalities. There is, consequently, no reason to worry about isradipine and the liver. The sponsor had very bad luck with one of their first studies. There is nothing more to make of that.

Carcinogenic Potential

This area is the most difficult area to reasonably interpret. On the surface, the sponsors observed what could be interpreted as dose-related carcinogenic effects in both rats and mice and dose-related chromosomal abberations in V79 Chinese Hamster cells. It is obviously hard to argue that, in this regard, isradipine is not troubled. Yet, that is precisely the case, these findings are not bothersome. The "argument," if there is one, revolves around what to describe in labeling.

A look at the data related to these findings seem a relevant exercise, prior to making interpretations.

Mouse Carcinogenicity Study. Charles River CD-1 mice were randomly assigned to one of 5 groups according to the following diagram. Drug was administered in the diet for 104 weeks.

80.0 mg/kg/day
15.0 mg/kg/day
2.5 mg/kg/day
Control
Control

The 80 mg/kg/day group is at a dose equivalent to 4 grams a day for a 50 Kg man with the maximal dose recommended for use in man being 40 mg/day (20 mg, bid) or 20 mg (10 mg, bid). So the mouse study was at doses of 100 to 200 the maximal recommended human dose. Two orders of magnitude is not an unreasonable "safety margin."

At none of the doses was there an obvious drug related effect observed on mortality, body weight, or any of the functional variables measured. So although these observations attest to the relative safety of isradipine dosing in mice (compared to man), the study did not include doses that were at an obvious maximal tolerated dose in mice. There was a trend for the male animals to have had a decreased survival as a function of dose ($p = 0.038$) so the maximally tolerated dose was not missed by much.

The results for all tumor bearing animals are reproduced from Dr. Harris' review below. In my judgment, there was no particularly relevant, or meaningful, finding produced by this analysis. The table does show the potential (which turns out to become a real) problem since animals could be classified as dying or alive (i.e., subgroups) but needing to be sacrificed.

Type of Death	Sex	Pooled Controls	Low	Mid	High
Naturally Dying	M	49%	47%	47%	40%
	F	47%	64%	57%	63%
Terminal Sacrificed	M	66%	88%[a]	85%[b]	72%
	F	78%	79%	77%	77%
Natural & Terminal Combined	M	57%	66%	66%	51%
	F	72%	71%	66%	69%

a $p = 0.018$, comparison to pooled Controls
b $p = 0.030$, comparison to pooled Controls

A display of any tumor that one might, after inspection of the data, consider to be related to dose (also from Dr. Harris' review) is shown below. Once

again, by inspection, I see nothing I would consider striking. From the vantage point of dose related effects, a 320 fold alteration of dose produced no obvious dose-related effect. If there is a dose-related oncological effect of isradipine, one would have to argue that the smallest dose studied was "over-the-top" of the dose-response curve. There is, in my judgment, no biologically-relevant dose-response information in this data.

The statistics reviewed by Mordecai Friedberg found a statistically significant ($p = 0.004$) positive dose-response relationship for hepatocellular carcinoma in male mice (using the method of Peto, et al.) which had a less significant p ($p = 0.011$) if hepatocellular carcinoma and nodular proliferations of the liver were lumped. The statistical review is careful to point out that the term "positive dose-response relationship" refers not to a monotonically increasing effect as a function of dose but rather to "the linear component of the effect of treatment."

		Treatment Group			
Finding	Sex	Control	Low	Mid	High
(a) Carcinoma Hepatocellular	M	12%+	19%	10%	25%*
	F	2%	4%	0%	4%
(b) Nodular Proliferation of the Liver	M	10%	11%	10%	16%
	F	5%	4%	1%	1%
(c) (a) and (b) combined	M	22%	24%	19%	31% (*)
	F	7%	9%	1%	4%
(d) Hyperplasia in Adrenal Cortex	M	4%	6%	7%	1%
	F	3%	0%	3%	0%
(e) Adenoma & Carcinoma in the Adrenal Cortex	M	22%	17%	31%	18%
	F	1%	1%	3%	0%
(f) (d) and(e) combined	M	25%	23%	34%	19%
	F	4%	1%	6%	0%
(g) Inflammation of the Stomach Mucosa	M	10%	17%	26%*	20%*
	F	13%	26%*	21%	20%
(h) Hyperplasia in the Stomach Mucosa	M	9%	13%	29%*	19%*
	F	14%	20%	19%	23% (*)
(i) Hyperplasia & Neoplasia of the Stomach Mucosa	M	10%	13%	29%*	20%*
	F	14%	20%	21%	23% (*)

* Significant increase compared to control; Fisher's exact test $p \leq 0.05$.

(*) Probably significant increase over control since:
(i) $0.05 < \text{Fisher's p-value} \leq 0.10$
and (ii) Mantel-Haenszel p-value ≤ 0.05

+ Test for positive linear trend was significant; however, the result is difficult to interpret since the incidence rates do not follow a linear pattern.

In November 1989, Sandoz submitted another analysis which contained:

a) A re-analysis (re-reading of slides and re-analysis) of the mouse liver,
b) A review of historical control liver tumor data,
c) A rat liver toxicity review,
d) A discussion of SAR analysis, and
e) A discussion of the biology of liver neoplasia in the mouse.

The liver tissue sections from male mice were re-read by an independent veterinary pathologist under blinded circumstances. The reason for re-reading the sections seems legitimate. The field had evolved new criteria for morphological diagnosis. The "new" data are represented by the following table reproduced from the sponsor's submission.

STATISTICAL SUMMARY OF HEPATIC NEOPLASTIC LESIONS IN MALE MICE FROM PN 200-110 MICE CARCINOGENICITY STUDY (#T-1343) a

		TREATMENT GROUP b					
TUMOR TYPE	SEX	CONTROL I & II	CONTROL I	CONTROL II	LOW III	MID IV	HIGH V
ADENOMA HEPATOCELLULAR	M	14.3%	12.9%	15.7%	10%	14.3%	18.5%
CARCINOMA HEPATOCELLULAR	M	3.8%	1.4%	5.7%	8.6%	2.9%	10% c
COMBINED ADENOMA HEPATOCELLULAR AND CARCINOMA HEPATOCELLULAR	M	18%	15%	22%	19%	17%	29% d

a) SEE APPENDIX I FOR FULL STATISTICAL REPORT.
b) NUMBER OF ANIMALS PER GROUP = CONTROL I-70, CONTROL II-69, LOW DOSE-70, MID DOSE-70, HIGH DOSE-70.
c) SIGNIFICANT INCREASE PAIR-WISE COMPARED TO CONTROL I ONLY BUT NOT TO CONTROL II.
d) TEST FOR POSITIVE LINEAR TREND WAS SIGNIFICANT; COMBINED CONTROLS.

The re-read did not substantively change the raw data; all numbers changed a little bit. If anything, a more intuitive dose-related effect is present in this "new" raw data; in particular with respect to hepatocellular carcinoma.

Of moderate importance to thinking about the significance (biologically) of the findings of the Sandoz mouse study is the data they present as representing historical controls, studies conducted by others, in the CD-1 mouse strain. This data is shown in the following Figures 1 and 2. It seems clear that, particularly for hepatocellular carcinoma, the incidence of tumor in the Sandoz study is well within the incidence observed in historical controls.

Dr. Harris, our pharmacology reviewer, and Dr. Resnick think the relevant historical controls should be Sandoz's own studies in their own laboratories (150 mice from 3 different studies, which found 0% incidence). The data in Figure 1 include 0% incidence. So I think the point is made. The incidence of hepatocellular adenoma and/or carcinoma, in this strain, is highly variable (ranging from 0% to 23%) and Sandoz's own controls in the study at issue had a high incidence, compared to historical control data.

Figure 1
Percent Incidence of Hepatocellular Adenoma in Untreated CD-1 Male Mice from Color Studies and from Study with Compound PN 200-110

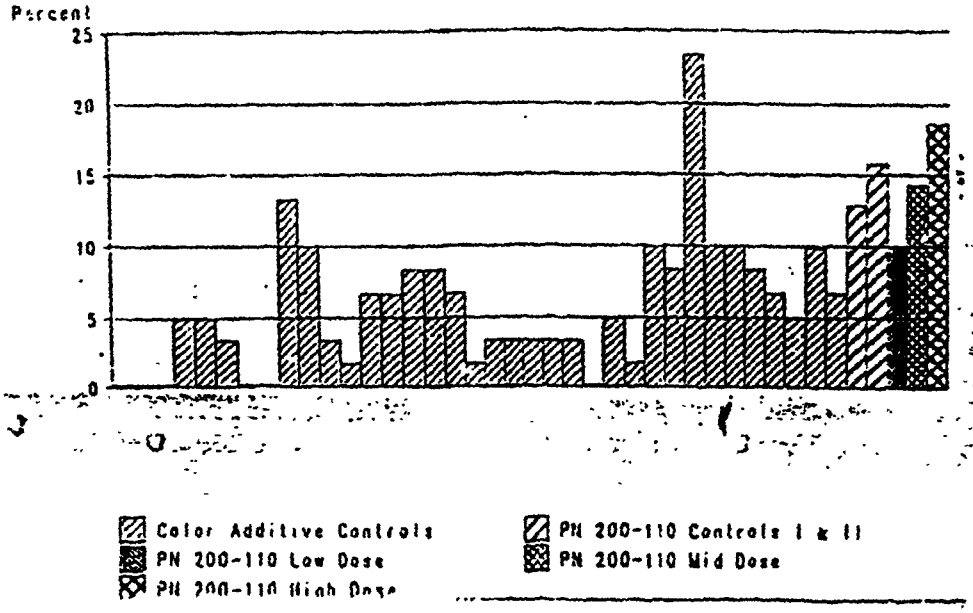
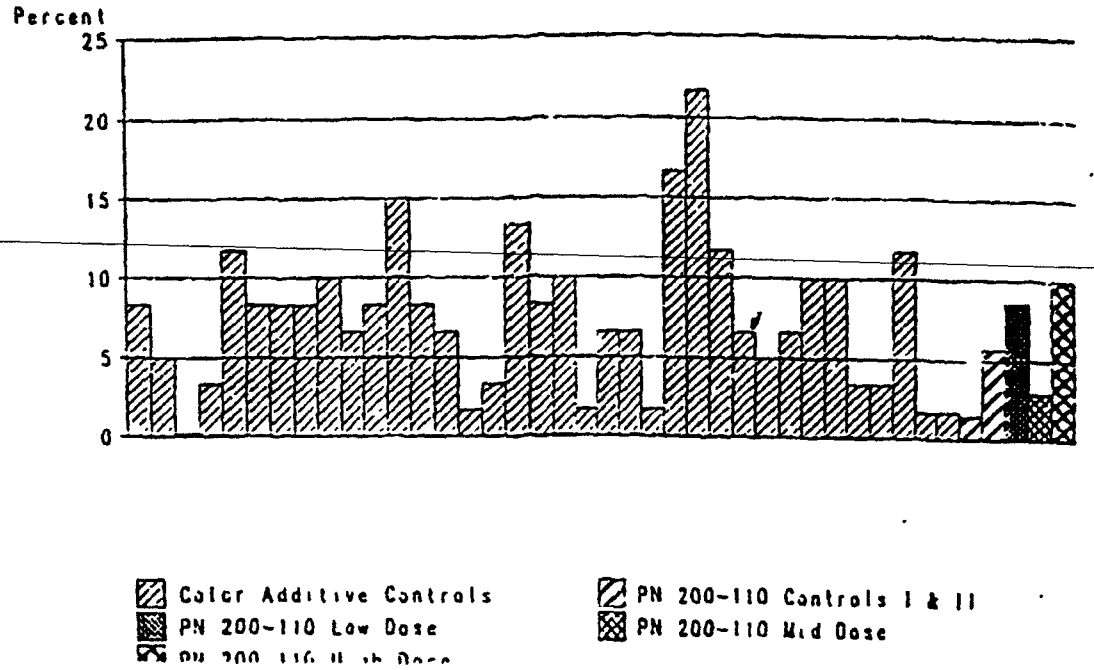


Figure 2
Percent Incidence of Hepatocellular Carcinoma in
Untreated CD-1 Male Mice from Color Studies
and from Study with Compound PN 200-110



So much for the data. From here on out, I admit lack of technical knowledge related to the kind of statistical tests that would be regarded relevant and/or definitive. It is clear that if one does some test on some data, one can get "statistical significance" at p = 0.004. In fact, the Sandoz analysis of the "new" data for sacrificed animals found a p = 0.039, different from our analysis of the original data but still a "small" p. This is consistent with the "new" data not being substantively different from the original data.

In my opinion, the findings of this study are at very best only marginally positive. One must, I think, recognize that the p value expressed for the linear trend cannot be interpreted in the conventional sense. The analysis that was performed is the equivalent of a subgroup analysis. All of the available data were inspected by multiple persons and a particular set of results was selected because it looked like it was different from the rest; then that particular subset was subjected to a "statistical test." I would guess, but have not performed the computation, that if the high-dose- group-male-hepatocellular-carcinoma number was 18% (not an unlikely number) the p value would have been much less impressive (i.e., would not have been as small). So, the analysis (i.e., p value) is highly dependent upon a single number in addition to being a subgroup analysis.

So, I do not see this particular finding as having any bearing on approvability. Isradipine should not on the basis of this data be considered a liver carcinogen;

not even in the mouse at doses over two orders of magnitude greater than that intended for use in man and apparently without dose-related (in a biological sense) effects.

I think that isradipine is approvable despite the mice. If one concluded that isradipine was a carcinogen, it would not be approvable. Isradipine has no particular uniqueness that would outweigh a carcinogenic liability. Since the data do not support a conclusion that isradipine is a carcinogen, it is approvable. But, an issue remains regarding labeling and/or post-marketing studies. It is not clear to me whether or not the findings in the mouse carcinogenicity study should appear in labeling. If I am comfortable that the finding bears no weight with respect to approval, why am I undecided about labeling?

The answer is no more complicated than truth in labeling. Approval is a judgment call. That the observations were made should not be hidden from public view simply because judgment does not preclude approvability on the basis of this finding. The statement needs to simply be factual and I see no particular need to make a value judgment related to the fact.

I would argue that another study (post-marketing) is warranted. Should it turn out to not replicate the original study, the liver tumor finding can be removed from labeling.

Rat carcinogenicity study. There are, in contrast to the mouse study, clear testicular Leydig cell tumor effects of isradipine in rats. In fact, this phenomenon is replicated within the data of the NDA (i.e., 2 studies found the same thing). There was no hint in these two studies of any propensity for liver neoplasia (thus clearly restricting a possible liver neoplasia effect from rodents to only male mice).

The Leydig cell neoplasia data from the first study are shown below. In contrast to the mouse findings the Leydig cell tumors are of absolutely no doubt.

The only tumor type significantly increased with treatment in this study was benign Leydig cell tumors. The tumor and related pathology for all groups is tabulated below:

Finding	Control 1 (n=75)	Control 2 (n=75)	Low (n=74)	Mid (n=75)	High (n=73)
Tumor bearing Animals	9	6	5	11	19
No. with Hyperplasia	2	1	1	1	6
Total* (either or)	10	7	6	12	23

*Animals with both tumors and hyperplasia are counted once in total.

Cox's Exact Test (one-tailed) was applied separately to the data recorded for animals dying naturally or terminally sacrificed. The respective p values are listed below:

Natural Death/Leydig Cell Tumors	p=.001
Sacrifice/Leydig Cell Tumors	p<.001
Natural Death/Tumors and Hyperplasia	p=.001
Sacrifice/Tumors and Hyperplasia	p<.001

The second study showed 1, 3, and 11 animals in the control, mid and high dose isradipine groups, respectively (about 22 male animals/group), that showed Leydig cell tumors. Both studies also showed decreased pituitary adenomas in the isradipine treated animals.

The Leydig cell tumor phenomenon can reasonably be attributed to hormonal effects in the rat; namely an effect on LH receptors. The mechanism remains incompletely described and somewhat speculative. Hormonal effects of isradipine that were seen in the rat (changes in LH, FSH, prolactin) were looked for in man, during clinical trials, and found to be absent.

Thus, the Leydig cell phenomenon can most reasonably be attributed to a permissive, or modulated," dose-dependent effect in rats (not mice or dogs) and therefore is not a relevant factor to approval or non-approval considerations but does belong in the labeling.

In Vitro Tests. In general, these tests did not have positive findings. Our pharmacologists did not think the Chinese Hamster cells were a reflection of mutagenicity. I agree with that position.

Summary of Carcinogenicity. The NDA is being forwarded to you for your consideration with our resolution of "carcinogenicity labeling." The summary above is a capsular view of the data; I hope you agree that the findings do not preclude approvability.

Attached to the labeling is Dr. Harris' review of the labeling and his suggestions for what the labeling should say. Dr. Resnick and I have reviewed (and Dr. Resnick has edited) this review and concur with Dr. Harris' suggestions. We recommend adoption of Dr. Harris' suggestions.

The sponsor has sent in their suggestions. These are also attached. I recommend their suggestions be rejected.

BIOPHARMACEUTICS

The Division of Biopharmaceutics has done a thorough review of the submission and think that the influence of metabolites on protein binding of isradipine, at steady state, and at the highest dose be studied post-marketing. Although their observation is correct, we do not know the answer to that question. I cannot agree that it is important enough to answer to require a post-marketing study. The safety and effectivenss of isradipine is defined by the data included within the NDA. It is conceivable that if the doses for angina need to be raised, that we would require such a study.

SUMMARY

The Division recommends approval of isradipine for use in hypertension. The attached marked-up draft, with carcinogenicity suggestions, represents my view of labeling. A clean draft is available for your pen.

The last safety update review is appended. There is no need for further safety updates.

Raymond J. Lipicky, M.D.

cc: Orig. NDA
HFD-110
HFD-110/CSO
HFD-110/RLipicky
ef:sb/cb:3/23/90:3/26/90:
ef:3/28/90:4/12/90:4/13/90:#3073F
Draft:Rumble/4/2/90

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: NOV 15 1990

FROM: Director, Office of Drug Evaluation I, HFD-100

~~SUBJECT: Isradipine (Dynacirc, Sandoz), NDA 19-546~~

TO: Raymond Lipicky, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110

This NDA is, as you say, fairly straightforward. There is no doubt isradipine lowers BP and no doubt that it is a once a day drug. It appears to have properties similar to other dihydropyridine calcium channel blockers: small increases in HR (with palpitations); edema; not much heart block; no significant effect on QRS or QT. I have just a few comments and questions:

1. SBA

Much of the SBA is quite good. There is some excess description of studies that are not germane (I have removed it) but also failure to discuss even briefly, studies that seem relevant (330, 331, 350, 352), probably because they are incomplete or were completed after initial filing. These should be at least identified in a table. The safety discussion does not give a description of the data base: kinds of studies, numbers of patients, dose/duration, population demographics, domestic, foreign. etc.; i.e., the kind of presentation called for in the Clinical/Statistical guideline. It should be provided prior to final approval. I can see from the MORs that total exposure is extensive and adequate so this is a matter of SRA repair and documentation, not approvability.

The "liver appendix" is a nice summary and analysis but as it shows no plausible drug-related liver injuries (no drop-outs due to LFT abnormalities except patient 303-327, not a persuasive case as minor elevations were present at screening visit) I think it can be omitted from the SBA. This is not a strong feeling; if you prefer, keep it in.

I thought some of the references to the PK screen helped, and as you did not remove all later references, some of the earlier ones (e.g., p 18) are necessary.

As you can see from notes on p 35 of the SBA. I did not think the elderly clearly had meaningfully higher Cmax or AUC; see, e.g., Table 6 (p 30) and figure 5 (p 37). It is important to resolve this for labeling purposes, but at this point I see no good basis to recommend a different dosing schedule in older patients.

The half-life is given (Table 6, p 30, text, p 46) as about 8 1/2 hours but in figures 1 and 2 (p 29, 33) the half-life looks more like 1 1/2 hours, at least while plasma levels are above 2 ng/mL. It is not clear the terminal half-life is most relevant here. We need to resolve this for labeling.

The putative greater effect in patients with higher BP (p 103) does not seem very well-supported.

2. Duration of action; retention of effect at interdosing interval

Studies 332 (b.i.d.) and 308 (o.d. dosing) both measured BP at trough (12 or 24 hours after dosing, and show retention of 50% of peak effect at 12 hours, but studies 301 (see p 81), 302, 303, and 304 did not measure BP at the interdosing interval. These studies do confirm the BP lowering effect but do not themselves support b.i.d. dosing. The active control studies, 303, 304 and others cannot be used in promotion to compare isradipine to other agents, especially to claim greater effectiveness; without comparison of effects throughout the dosing interval, isradipine, with its large peak effect, could look better than slow, steady diuretics and beta-blockers but 12- and 24-hour control might not be as good. The letter should include the following statement after the 7th paragraph: "We should point out at this time that we believe the comparative studies submitted to the application, none of which measured blood pressure at trough, do not constitute a basis for comparative claims, as they are comparing the peak effect of a drug with fairly large peak-trough difference (isradipine) to drugs with relatively constant effects over 24 hours (beta-blockers, diuretics)."

3. Carcinogenicity testing

It appears you and the CAC agree with regard to the animal studies. The labeling will need to reflect that conclusion.

4. Limited further safety update

The last safety update was more than a year ago and further trials and marketing may have relevant information. The approvable letter should request a limited further update covering:

a. All deaths in clinical trials, including CRFs.

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

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

5. Marked up labeling is attached. There are some questions that the Division needs to consider. We will need a clean mark-up of the labeling, perhaps after a discussion. Note there are a few issues to resolve, including

a) What to say about half-life
b) What to say about effects on PK of age, liver function and impact on Dosing and Administration.

There are also some new parts for the sponsor to add or develop, including

a) Electrophysiology paragraph and perhaps a summary of hemodynamic effects,

b) A hypotension precaution, using nicardipine labeling as a model.

c) A CHF precaution, also using nicardipine wording.

d) A better Interactions Precaution, including the Fentanyl statement (see nicardipine), and a paragraph about the extent of concomitant use and the drugs involved

e) A revised ADR section, expanding the table to include all ADRs at or above 1% and using information from all sources, at least for the less common reactions. This will include looking through foreign post-marketing reports, foreign controlled studies, etc.

Robert Temple

Robert Temple, M.D.

cc:
HFD-100/Chron File
HFD-100/NDA File
HFD-100/Carter
HFD-101/Botstein
HFD-110
HFD-110/CSO
RT:jp:11/13/90
Revised:RT:jp:11/15/90(2)

Medical Review of Dynacirc (isradipine) Capsules
NDA 19-546
Reviewer- Basil Friedman, M.D.

Summary review found on pages 1-6

Note: Additional medical review done by Robert Kimball, M.D.

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FINAL NDA

SEP 15 1988

DYNACIRC - SUMMARY

N D A 19,546

The data forwarded to me by Sandoz Research consisted of 46 volumes. These were divided into three main sections: Phase I/II studies, Phase III hypertension studies and "Other" clinical studies.

Phase I/II

This section consisted of 12 protocols, as follows: There were two dose toleration studies in volunteers, a liver rechallenge study, safety/efficacy in hypertension, dose response pharmacodynamics in hypertension, ascending dose in hypertension, angina study, two studies in congestive heart failure, bronchospasm, study in PVCs and a study on reproductive hormone levels in volunteers.

1. The dose response studies showed that PN 200-110 (PN) caused increases in atrial and ventricular rates and that, if not titrated carefully, causes side effects, mainly headache and tachycardia. Dose should not be administered as a single dose but as divided doses two or three times a day.

2. Due to the high incidence of abnormal liver function tests in studies with normal volunteers, a liver rechallenge test was performed. Subjects who had developed abnormal tests in the previous study were now rechallenged. The incidence of elevated liver enzymes in this second study was not unduly high. Experts consulted by the sponsor concluded that the abnormal tests were not drug related. It appears that some of the subjects were alcoholics, some drug abusers etc. It is unclear why this population would be recruited for a phase I study. From a retrospective view point, it is possible that the original volunteers may have contracted hepatitis. They had been housed in a motel and school dormitory and the discovery of elevated enzymes was consistent with the incubation period for hepatitis.

3. The hypertension study (protocol 7) demonstrated efficacy of PN compared to placebo at a dose of 2.5 - 10.0 mg bid. It appeared that results were only significant after 3 weeks.

4. Acute dose response study in hypertensives showed efficacy in hospitalized patients.

5. Placebo controlled, ascending dose study in hypertensives was a well designed study showing efficacy of the drug.

6. Placebo controlled study in angina patients did not show efficacy over placebo. The method of randomizing pts confounded the study.

Protocol 301

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ulticenter Evaluation of the Safety and Efficacy of Four
of PN 200-110 Administered as Fixed Ascending Doses in the
nent of Hypertension Compared to Placebo

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Birmingham, AL

Manuel Velasquez, M.D.
Milwaukee County Medical
Complex
Hypertension Section
Milwaukee, WI

Alexander Shepherd, M.D.
Department of Pharmacology
University of Texas Health
Science Center
San Antonio, TX

Dates of Study: March 20, 1984 to March 7, 1986.

Objective

To determine the efficacy and safety of four doses of PN 200-110 (PN), administered twice a day in a fixed ascending manner, compared to placebo in patients with mild to moderate essential hypertension.

Design

This was a double-blind, parallel group, randomized, multi-center, placebo controlled study.

Population

Two hundred and three (203) male and female patients with essential hypertension were randomized into the double-blind study. To qualify for entry into the double-blind phase, the patients were to have, on the final day of a 3 week washout period, a supine diastolic blood pressure (SDBP) of > 100 mm Hg. In addition, for those washed out from active treatment, if the average SDBP was not > 100 mm Hg at the end of the first two weeks of washout, the SDBP was to demonstrate an overall increasing trend towards 100 mm Hg. A decreasing trend in SDBP was not to be observed. This was defined as: if the SDBP for each evaluation day of the washout was less than that of the previous evaluation and had decreased by > 10 mm Hg compared to first evaluation day, patient was excluded even if SDBP > 100 mm Hg at end of washout period. Patient was also excluded if SDBP exceeded 120 mm Hg [illegible] of the washout period.

Exclusion criteria included abnormal baseline laboratory tests, malignant or severe hypertension, angina pectoris, MI within previous 6 months, arrhythmias, CHF not controlled by digitalis alone, bradycardia, first degree heart block or PR interval > 0.23 sec, history of alcohol or drug abuse, cerebral vascular insufficiency, creatine > 2.0 mg%, certain specified medications, or conditions that could interfere in evaluation of stud. drug.

Study Plan

Medication was supplied as identically appearing capsules of PN 2.5 mg, 5 mg, 7.5 mg or 10 mg or placebo. Dosing schedule is summarized in Table 1 and evaluation schedule in Table 2. There was an initial 3 week single blind placebo wash out period during which all patients received placebo 1 capsule bid. before breakfast and supper. Qualified patients (as previously described) were randomized to one of 5 groups. They were stratified based on SDBP > 100 mm Hg, < 105 mm Hg and > 105 mm Hg.

Group 1 received placebo for 5 weeks. Group 2 received 2.5 mg PN bid for 5 weeks; Group 3 received 2.5 mg bid for one week and 5 mg bid for the rest of the trial. Group 4 received 2.5 mg bid for one week, 5 mg bid for second week and 7.5 mg bid for weeks 3, 4 and 5. Group 5 received 5 mg bid first week, 7.5 mg bid week 2, 10 mg bid weeks 3, 4 and 5. Dose was increased automatically unless investigator decided not to increase based on systolic blood pressure and investigator's discretion, or adverse reactions. (Systolic blood pressure criteria not defined). If this occurred, dose was reduced to that of previous week and maintained. If ADR continued, dose could be reduced in step wise fashion. Dose in group 2 could not be decreased as this was the lowest permissible dose. At end of 5 weeks, patient could enter an open label, long term protocol. These patients are identified in Table 3.

Evaluations were done at weekly intervals as shown in Table 2. In addition to the standard measurements of vital signs etc, ambulatory blood pressures were recorded during placebo wash out period and end of active treatment in Center A (Dr Carr). In addition, effects of PN on urinary and plasma catecholamines, plasma renin activity and plasma norepinephrine were determined. Supine echocardiograms were also done. Center C (Dr Hamilton) evaluated effects of study drug on renin-angiotensin-aldosterone system. Methodology is specified in report.

Results

A total of 208 patients were randomized into double blind phase (How many were initially enrolled?). A total of 187 patients completed the study and were considered completely valid for efficacy analysis. There were 11 partially valid patients and 7 totally invalid for efficacy analysis. Distribution of patients per groups is shown in

Status	5 mg	10 mg	15 mg	20 mg	Placebo	Total
Valid	35	34	33	41	39	182
Partially Valid	4	4	6	0	2	16
Invalid	1	2	2	0	0	5
Total	40	40	41	41	41	203

Reasons for stating data to be invalid are presented in Table 4. Table 5 presents these data by center. Number of valid patients by week is shown below:

Group	Week 1	2	3	4	5
5 mg	39	38	38	37	35
10 mg	38	37	34	34	34
15 mg	39	39	39	38	38
20 mg	41	41	41	41	41
Placebo	41	41	40	39	39
	198	196	192	189	187

All patients had essential hypertension. The mean age was 51.5 years (range 22 - 77); 72% were male; 42% caucasian, 58% black (range per group 49 - 66%). Demographic data by group is listed in Table 6. Tables 7 and 8 summarize the daily dose by group for valid and partially valid patients. The mean dose for valid patients during weeks 3 - 5 was 5 mg for 5 mg group, 9.5 mg (10 mg group), 13.9 mg (15 mg) and 17.1 (20 mg). A number of patients did not receive their assigned dose due to various reasons. Three patients in 10 mg group did not have their titration series properly dispensed and they received 5 mg. Two in 15 mg group also had incorrectly titrated dose and 2 had ADRs (dizziness; chest pain & short of breath). In 20 mg group, 7 patients did not receive proper dose: 3 incorrectly titrated and 4 ADRs (palpitation & fatigue; headache; increased pulse & nervous; chest pain & short of breath.)

Interactions

Table 9 summarizes results of interactions as well as efficacy results by investigator by treatment. None of the interactions for blood pressure or pulse rate were statistically significant (treatment x investigator; treatment x time; and treatment x investigator x time).

Efficacy

Efficacy was analyzed both within groups (comparison to baseline and between groups). In addition, patient response was categorized as < 10 mm Hg (category 1), > 10 mm Hg but > 5 mm Hg (category 2), > 5 mm Hg but < 10 mm Hg decrease (category 3 and < 5 mm Hg decrease (category 4).

Titration Period Week 1.

Tables 10 and 11 summarize results of first week active treatment when patients were receiving lowest dose of PN or placebo. Table 10 presents data by pre-determined group while Table 11 by actual dose received (i.e. groups 2, 3 and 4 combined and group 5). SDBP results are summarized below:

Mean Change from Baseline Valid and Partially Valid Patients

Group	n =	Randomized Dose mg bid	Change mm Hg	Actual Dose mg bid	n=	Change mm Hg
1	41	Placebo	- 4.5	Placebo	41	- 4.5
2	39	2.5 mg	- 10.0	2.5 mg	116	- 9.6
3	38	2.5 mg	- 10.1	5.0 mg	41	- 14.4
4	39	2.5 mg	- 8.6			
5	41	5.0 mg	- 14.4			

All changes were statistically significant from baseline at $p < 0.001$. All active groups were statistically different from placebo. Table 11 presents results according to prescribed dose. Active groups are statistically different from placebo. There also appears to be a dose response effect between the two doses of PN. The PN groups had a statistically significant increase in heart rate compared to placebo (4 - 5 bpm). Approximately 44% of active patients had at least a 10 mm Hg decrease in SDBP after 1 week in 2.5 mg bid groups and 68% in 20 mg group receiving 5 mg bid while in placebo group only 21% had a 10 mm Hg reduction.

Week 2.

Tables 12 and 13 present results for week 2 as defined above. All 5 groups had statistically significant decreases in SDBP compared to baseline. All 4 active groups had changes that were statistically significant from placebo for all blood pressure variables. Supine diastolic changes by group were:

Placebo n = 41 - 5.3 mm Hg
5 mg n = 38 [illegible] mm Hg
10 mg n = [illegible] [illegible] mm Hg
15 mg n = [illegible] [illegible] mm Hg
20 mg n = 41 [illegible] mm Hg

Results by actual dose received were: Placebo - 5.1 mm Hg; 5 mg - 11.4 mm Hg; 10 mg - 13.7 mm Hg; 15 mg - 15. mm Hg. A dose response effect is present in these data. Each group was statistically better than placebo. Table 13 presents results of statistical inference tests comparing changes from baseline between each group at week 2. The differences between 5 mg and 15 mg for standing and supine diastolic blood pressure was statistically significant. There was also borderline statistics for these variables between 10 mg and 15 mg. Highest dose PN increased pulse rate by 4 - 5 bpm. At end of week 2, 66% patients in 5 mg group had a decrease in SDBP of > 10 mm Hg

Week 3 - 5

Tables 14 and 15 present results for valid and "all" patients. Mean change from baseline for SDBP are shown below.

		Valid Patients		" ALL "
Placebo	n= 39	- 7.0	n = 40	- 6.5
5 mg	n= 35	- 13.9	n = 38	- 13.6
10 mg	n= 34	- 17.1	n = 34	- 17.4
15 mg	n= 38	- 17.2	n = 39	- 17.4
20 mg	n= 41	- 17.3	n = 41	- 17.1

During this period, all PN groups had statistically significant mean reductions from baseline in all variables and these reductions were superior to placebo. The reductions for groups 3, 4 and 5 were similar and slightly greater than for 5 mg group. Table 16 presents the results from statistical inference tests between groups. Table 17 is a summary of mean changes over the period based on actual dose taken.

There were statistically significant mean differences between 5 mg and 15 mg for all blood pressure parameters, with 15 mg having greater mean decreases from baseline. Mean differences between 5 mg and 20 mg were statistically significant for standing blood pressures and SDBP (Table 18). There were slight mean increases of 2 - 5 bpm from baseline in supine and standing pulse.

Categorical responses for the average over this period were:

Treatment	n =	Number (%) Patients in Category			
		1	2	3	4
Placebo	39	5 (15)	8 (21)	9 (23)	16 (41)
5 mg	35	18 (51)	7 (20)	7 (20)	[illegible]
10 mg	34	23 (68)	5 (15)	4 (12)	1
15 mg	38	28 (74)	4 (11)	4 (11)	2 (5)
20 mg	41	32 (78)	5 (12)	3 (7)	1

Approximately 61% of all PN patients had at least a 10 mm Hg reduction in SDEP with 15 demonstrating normalization (< 90 mm Hg). The number of responders is greater in 15 mg and 20 mg groups. This analysis shows a dose response.

Endpoint Analysis - All Patients

Table 20 summarizes results of endpoint analysis for all patients. Data are presented graphically in figures 1 - 5. It may be seen that the full effect only occurs after 2 - 3 weeks treatment. There is a lack of dose response for pulse rate.

Safety

Table 22 lists newly occurring abnormalities. These occurred in 26/157 (18%) PN patients and 2/39 (8%) placebo. One PN patient was withdrawn due to tachycardia and edema; one due to ECG changes of tachycardia and atrial fibrillation.

Table 23 presents data for cardiovascullar abnormalities by group while Table 24 presents these data more specifically. Newly occurring events were reported in 51/161 (32%) PN group and 13/41 (32%) placebo. Incidence of palpitations was highest in 20 mg group (7 occasions in four patients), with 5 occassions in two 15 mg patients. Peripheral edema was more common in active group than placebo, but there was no dose response relationship. There was a total of 22 PN patients with edema, with highest incidence in 10 mg group. Atrial gallop was seen in 1 of 5 PN with most being with 20 mg.

Table 26 presents changes in chest x-ray and Table 28 ECG changes. Newly occurring x-ray events were reported in 6 PN and 2 placebo patients. Fifty three (33%) PN patients and 16 (39%) placebo had changes in their ECGs. There was no dose relationship. Table 29 is a summary of events by dose and time. There were statistically significant increases in ventricular rate (3 - 7 bpm) for all PN groups at all time points, except 20 mg at plateau. All other changes for PN were borderline significant from placebo. A statistically significant decrease from baseline was seen for P - R interval at least one time point for each strength. Except for week 1, these changes were not statistically significantly different from placebo. There were slight decreases for Q -T interval from baseline for each PN and were significant compared to placebo. These changes were not clinically significant and there was no evidence of a dose response.

Clinical Laboratory Tests

Tables 31 - 33 summarize laboratory data for all time points. The hematology variables that were statistically or borderline significant (WBC, bands, neutrophils, lymphocytes, monocytes, eosinophils and basophils) were not [illegible]

The only variables showing statistically significant differences from placebo for blood chemistry were BUN, alkaline phosphatase, SGOT, SGPT and potassium. There was no dose response for changes in SGOT or SGPT. The differences for alkaline phosphatase were noted mainly with 10 mg PN. The alkaline phosphatase changes were considered clinically relevant. Decrease in serum potassium was seen at week 3 for 10 mg, 15 mg and 20 mg groups and at weeks 5 and end point for 15 mg and 20 mg. There appears to be a dose relationship for changes in potassium. Table 37 lists the newly occurring values for blood chemistry

Glucose was elevated in a number of patients, but the significance is not clear. There was a higher incidence of elevated SGPTs and SGOTs in PN group (7/162 and 9/162) than in placebo 0/41 and 1/41). These results were considered clinically significant by the investigators but, as they were transient and not progressive in nature, sponsor regards them as not clinically significant.

Special Evaluations

Table 39 lists echocardiographic results from one center. Marginally significant decreases were noted in peak end systolic stress and end systolic volume and volume index and a significant increase in fractional shortening and ejection fraction for 20 mg compared to baseline. The 15 mg showed increase in ejection fraction and fractional shortening and decrease in posterior wall thickness.

There was a statistically significant increase in plasma renin activity from baseline for 5 mg and 20 mg PN as well as a dose related trend to increased plasma norepinephrine levels. In center C, there was increases in plasma renin activity prior to furosemide in 10 mg, 15 mg and 20 mg groups. These tended to be dose related. The increase with 15 mg was statistically significant compared to placebo. There were no significant changes in plasma aldosterone or in PRA. Increases in plasma norepinephrine were seen for all four PN groups compared to baseline, but were not dose related.

Table 44 lists results of 24 hour blood pressure monitoring and these are displayed in figures 7 - 14. No analysis was done due to the small number of patients tested.

Drop Outs

The number of patients withdrawn from the study by group is shown below:

Reason	5 mg	10 mg	15 mg	20 mg	Placebo
Lost to Follow up:		1			
ADR	2	4			
Treatment Failure	1		1		2
Uncooperative	1				
Other	1	1			
	5	6	1	0	2
	12.5%	15%	2.4%		4.3%

A total of 14 patients withdrew prematurely, 12 on PN and 2 placebo. Six were due to ADR; 2 in 5 mg group (headache, constipation; atrial fibrillation) and 4 in 10 mg group (edema and tachycardia; headache; headache; skin rash). One 5 mg patient required emergency surgery for dissection of aorta and a 10 mg patient had abnormal labs which investigator thought was due to hemolysis (why withdraw the patient then ?).

Adverse Reactions

Adverse reactions were reported by 48% 5mg, 43% 10 mg, 56% 15 mg, 56% 20 mg and 39% placebo patients. It appears as if there may be a dose response relationship for ADRs.

Percentage Patients Reporting ADRs by Week

Week	5 mg	10 mg	15 mg	20 mg	Plac
1	28	20	17	29	10
2	21	32	24	37	20
3	24	14	29	37	30
4	14	18	38	34	20
5	16	18	48	34	13
Weeks 1 -5	48	43	56	56	39

Table 45 lists, by patient, all ADRs reported in the study. Tables 46 and 47 present comparative ADRs by treatment. Less than 9% of the ADRs were regarded as severe. ADRs reported during placebo washout that did not change in intensity during double blind period were not recorded as ADRs.

[redacted]

[redacted]

Discussion

Sponsor concludes that results demonstrate that bid PN resulted in clinically and statistically significant reductions in blood pressure for all four strengths. There were dose response reductions seen after one week and all reductions were statistically greater than placebo after week 2. Dose should be titrated every 2 - 3 weeks. About half the patients reported ADRs.

Reviewer's Comments.

1. This double blind, parallel group study demonstrated a dose response relationship in reduction in blood pressure. There does not appear to be a significant decrease in SDBP with a dose over 15 mg

2. There appears to be a higher incidence of adverse reactions with the higher doses.

3. Laboratory changes, especially SGOT, SGPT and alkaline phosphatase were clinically significant.

4. How many patients were initially enrolled and how many were discontinued prior to enrollment in double blind phase ?

5. Patients were to be randomized according to stratification of entry blood pressure. How did this affect the results ? These data are not supplied.

6. When was blood pressure measured in relation to administration of dose.

[redacted]

TAB

PN 200-110 St 301

(6 Centers - Investigators A thru F)

SUMMARY OF PATIENT STATUS BASED ON ENTRY CRITERIA, COMPLIANCE, VITAL SIGN DATA AND OTHER CRITERIA

Randomized Treatment Group

Status	PN 200-110				Placebo
	5 mg Group	10 mg Group	15 mg Group	20 mg Group	
Valid for Efficacy (187 Patients)	35 Patients	34 Patients	38 Patients	41 Patients	39 Patients
	103 312* 468*	101 316* 502	102 254 415* 621*	105 301* 416* 609*	104 304* 418 619*
	106 319* 504	108 324* 509	110 303* 417* 652	107 308* 422* 615*	113 310* 421* 653*
	115 326 506	111 329 513	112 309* 452*	114 311* 451* 616*	117 314* 453* 656*
	153 354* 514	155 355* 555	116 315* 457*	154 320* 456* 651*	152 318* 461*
	157 357* 554	156 359 601*	151 317* 467*	160 321* 465 657	155 329* 503
	165 405* 559	201 401* 610*	159 322* 505	163 327 469	161 328* 510
	203 408* 603*	209 406* 617*	162 330 508	205 332 501	204 331 515
	206 414* 606*	213 420* 622*	202 333 512	210 351* 507	208 352* 553
	212 419 618*	222 423* 655*	207 353* 552	214 358* 511	211 360 556
	223 424* 654*	255 455* 658*	215 356* 605*	216 402* 551	217 404 602
	253 454 659*	302* 459*	219 403 612	225 410* 557	221 407* 608*
	305* 463*	313* 462*	224 409* 620*	252 413* 604*	251 412* 614*
Partially Valid for Efficacy (11 Patients)	4 Patients	4 Patients	1 Patient	0 Patients	2 Patients
	220 460	218 411	464		109 458*
	323 613	307 611			
Invalid for Efficacy (5 Patients)	1 Patient	2 Patients	2 Patients	0 Patients	0 Patients
	306	164 558	361 607		
Total (203 Patients)	40 Patients	40 Patients	41 Patients	41 Patients	41 Patients

Note: Patient numbers assigned in each center:
Center A, Pt. #101-199; Center D, Pt. #401-499
Center B, Pt. #201-299; Center E, Pt. #501-599
Center C, Pt. #301-399; Center F, Pt. #601-699

*Patients entered open-label, long-term phase of treatment.

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TABLE 4

PN 200-110 STUDY NO. 301

REASONS FOR PARTIAL VALIDITY OR INVALIDITY FOR EFFICACY ANALYSIS

Patient No.	Treatment Group	Discontinuation Week	Valid Thru Week (or Invalid)	Last Prescribed Total Daily Dose (mg)	Reasons
220	PN 200-110 5 mg	3	3	5	Treatment Failure
306	5 mg	1	Invalid	5	Non-Compliant (also c/o - Wk. 1 - Adverse Reactions - Headache and Constipation) 75% of Required Med. Taken
323	5 mg	1	1	5	Adverse Reaction - Atrial Fibrillation
460	5 mg	5	4	5	Uncooperative
613	5 mg	5	4	5	Emergency Surgery (aortic dissection)
164	PN 200-110 10 mg	1	Invalid	N/A	Lost to follow-up - no data available for Week 1 Visit
218	10 mg	2	2	10	Adverse Reaction - Edema, Tachycardia
307	10 mg	2	2	10	Adverse Reaction - Headaches
411	10 mg	3	2	10	Adverse Reaction - Skin Rash
558	10 mg	1	Invalid	5	Adverse Reaction - Headache. Required doses not taken the day prior to and day of visit
611	10 mg	1	1	5	Abnormal Labs (elevated bilirubin, LDH, and SGOT but due to sample hemolysis as sample broke during centrifugation)
361	PN 200-110 15 mg	N/A	Invalid	15	Overall Compliance during Active Treatment = 73%
464	15 mg	3	3	15	Treatment Failure/Could Not Keep Appointments
607	15 mg	N/A	Invalid	15	Non-qualifying B.P. at End of Washout (mean diastolic 98 mm Hg)
109	Placebo	3	3	N/A	Treatment Failure
458	Placebo	2	2	N/A	Treatment Failure

TABLE 5

PH 200-110 STUDY NO. 301

NUMBER OF PATIENTS BY EFFICACY ANALYSES CLASSIFICATION

Investigator	PH 200-110 Randomized Treatment Group												Placebo			Total			Total
	5 mg Group			10 mg Group			15 mg Group			20 mg Group									
	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	
A	6	0	0	5	0	1	7	0	0	6	0	0	6	1	0	30	1	1	32
B	5	1	0	5	1	0	6	0	0	6	0	0	6	0	0	28	2	0	30
C	6	1	1	7	1	0	9	0	1	9	0	0	9	0	0	40	2	2	44
D	8	1	0	7	1	0	7	1	0	9	0	0	7	1	0	38	4	0	42
E	5	0	0	4	0	1	4	0	0	5	0	0	5	0	0	23	0	1	24
F	5	1	0	6	1	0	5	0	1	6	0	0	6	0	0	28	2	1	31
TOTAL	35	4	1	34	4	2	38	1	2	41	0	0	39	2	0	187	11	5	203

TABLE 5