

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20850

ADMINISTRATIVE DOCUMENTS

K. Bongibrammi

NOV 10 1998

RHPM Review of Labeling

NDA: 20-850 Micardis (telmisartan) 40 and 80 mg Tablets

Date of submission: November 3, 1998

Date of receipt: November 4, 1998

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Background: On September 25, 1998, Dr. Temple signed an approvable letter for NDA 20-850, Micardis (telmisartan) 40 and 80 mg Tablets, requesting labeling identical in content to the enclosed draft package insert, draft cartons and blisters included in the July 15, 1998 submission, and draft professional sample cartons for 80 mg included in the September 10, 1998 submission.

The approvable letter also asked the firm to submit their assurance that a lower dosage strength tablet will be developed promptly, including a description of information that will be submitted to support the lower dosage strength tablet, along with a proposed timeline.

In addition, we asked them to change the dissolution specification to "Q₁ % in minutes."

On October 19, 1998, Drs. Temple, Lipicky, Fenichel, Nuri, Srinivasichar, Berninger, Fadiran, Resnick, Ms. Norden and I met with Boehringer Ingelheim to discuss the package insert. By the end of the meeting, we agreed to revisions of the labeling

In a submission dated October 6, 1998, the firm agreed to the revised dissolution specification.

In a submission dated October 15, 1998, the firm submitted final printed cartons. In a submission dated October 23, 1998, the firm submitted package inserts and blisters and a commitment to develop a 20 mg tablet, including a description of information that will be submitted and a proposed timeline. After review of the package inserts in the October 23, 1998 submission, we asked for additional changes.

The document control room removed the copies of the package inserts from the final printed blisters that will be distributed upon NDA approval.

Boehringer Ingelheim has now submitted final printed package inserts.

Review: I have reviewed the submitted final printed labeling, and contains all of the revisions we requested in our FAX of 11/3/98. Under

we gave the firm the choice of using instead of in the second sentence. The firm has chosen and placed it at the end of the sentence. I found no additional changes to the labeling.

Recommendation: I will prepare an approval letter for this NDA for Dr. Temple's signature.

151
Kathleen F. Bongiovanni

11-4-98

cc: NDA 20-850
HFD-110
HFD-110/KBongiovanni
HFD-110/SBenton
HF-2MedWatch

kb/11/4/98.

NOV 3 1998

RHPM Review of Labeling

NDA: 20-850 Micardis (telmisartan) 40 and 80 mg Tablets

Date of submission: October 23, 1998

Date of receipt: October 26, 1998

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Background: On September 25, 1998, Dr. Temple signed an approvable letter for NDA 20-850, Micardis (telmisartan) 40 and 80 mg Tablets, requesting labeling identical in content to the enclosed draft package insert, draft cartons and blisters included in the July 15, 1998 submission, and draft professional sample cartons for 80 mg included in the September 10, 1998 submission.

The approvable letter also asked the firm to submit their assurance that a lower dosage strength tablet will be developed promptly, including a description of information that will be submitted to support the lower dosage strength tablet, along with a proposed timeline.

In addition, we asked them to change the dissolution specification to "Q₁ % in 15 minutes."

On October 19, 1998, Drs. Temple, Lipicky, Fenichel, Nuri, Srinivasichar, Berninger, Fadiran, Resnick, Ms. Norden and I met with Boehringer Ingelheim to discuss the package insert. By the end of the meeting, we agreed to revisions of the labeling

In a submission dated October 6, 1998, the firm agreed to the revised dissolution specification. In a submission dated October 15, 1998, the firm submitted final printed cartons. In a submission dated October 23, 1998, the firm submitted final printed package inserts and a commitment to develop a 20 mg tablet, including a description of information that will be submitted and a proposed timeline.

Review: I have reviewed the submitted final printed labeling, and these are the differences from what was agreed to at the October 19, 1998 meeting.

According to Boehringer Ingelheim, the following changes were made in error:

Boxed Warning: the heading _____ was inadvertently omitted.

CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism and Elimination:
Two sentences at the end of this subsection were inadvertently omitted: _____

CLINICAL PHARMACOLOGY, Pharmacokinetics, Distribution: the word _____ was inadvertently added to the end of the last sentence in this subsection.

CLINICAL PHARMACOLOGY, Pharmacodynamics: the header was inadvertently changed to

ADVERSE REACTIONS: The third sentence had been changed from,

to "....,

BI states that rather than is an error and will be corrected.

The following are differences Boehringer Ingelheim has not planned to change:

CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency:

The reference should be
instead of ""

CLINICAL PHARMACOLOGY, Clinical Trials:

We asked the firm to provide data to support the range of blood-pressure lowering per dose. In a phone conversation on October 28, 1998, Ms. Heidi Reidies said that these data are from volume 1.128, pages 57 (diastolic) and 58 (systolic). The sentence now reads,

We asked the firm to revise the information on the effect of telmisartan when given to patients already treated with hydrochlorothiazide. They have added the following as the third paragraph:

WARNINGS, Hypotension in Volume- and Salt-Depleted Patients:

At the end of this subsection,

was revised to

PRECAUTIONS, General, Impaired Hepatic Function:

At the end of this subsection,

was revised to

PRECAUTIONS, Drug Interactions, Other Drugs:

BI has added the following:

DOSAGE AND ADMINISTRATION: A new first sentence has been added:

The reference after the third sentence is

This should be revised to

DOSAGE AND ADMINISTRATION, Special Populations: The second sentence should start a new paragraph. We asked the firm to refer to both the section and subsection in two spots in this paragraph (see PRECAUTIONS, General, Impaired Hepatic Function and Impaired Renal Function) and (see WARNINGS, Hypotension in Volume-Depleted Patients), and only the section is referred to (see PRECAUTIONS) and (see WARNINGS).

HOW SUPPLIED:

been replaced by

has

Dr. Berninger would like the phrase
after

moved to just

Regulatory Action:

I met with Drs. Temple and Behrman on November 2, 1998. We reviewed the labeling, and Dr. Temple decided on further revisions (see attached). I FAXed a copy to the firm on November 3, 1998. They will review the changes, and if they are acceptable, they will submit revised final printed labeling.

cc: NDA 20-850
HFD-110
HFD-110/KBongiovanni
HFD-110/SBenton
HF-2MedWatch
kb/10/28/98; 11/3/98..

~~15~~
Kathleen F. Bongiovanni

11-3-98

MAR 2 1998

REQUEST FOR TRADEMARK REVIEW

883

TO: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D. HFD-530
9201 Corporate Blvd. Rm N 461

FROM: Division of: Cardio-Renal Drug Products
Attention: Robert Wolters

HFD-110
Phone: 594-5376

DATE: October 21, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Proprietary Name: Micardis

NDA/ANDA [REDACTED] 8

Trademark status: Yes

Company Name:
Boehringer Ingelheim

Other proprietary names by the same firm for companion products:

Established name including dosage form and strength:
Telmisartan 40 & 80 mg

Indications for use including dosing schedule (may be a summary if proposed statement is lengthy):
Treatment of hypertension

Comments from the submitter: (concerns, observations, etc.)
This name was previously submitted to the L&N committee last March.

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Consult #883 (HFD-110)

MICARDIS

telmisartan

The Committee noted one sound-alike/look-alike conflict with the following marketed product: MICALCIN. The committee feels there is a low potential for mix-up with these names. There were no misleading aspects found with the proposed name.

The Committee has no reason to find the proposed proprietary name unacceptable.

IS/ 2/18/98, Chair
CDER Labeling and Nomenclature Committee

CC: NDA 20-850

HFD-110

HFD-110 / Short (Berninger / Bongiovanni)

KB

771

REQUEST FOR TRADEMARK REVIEW

MAY 29 1997

TO: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D. HFD-530
9201 Corporate Blvd. Rm N 461

FROM: Division of: Cardio-Renal Drug Products
Attention: Robert Wolters

HFD-110
Phone: 594-5376

DATE: March 17, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Proprietary Name: Micardis

NDA/ANDA IND

Trademark status: Yes No Pending

Company Name: Boehringer Ingelheim

Other proprietary names by the same firm for companion products:

Established name including dosage form and strength:

Telmisartan Tablets 40 and 80 mg

Indications for use including dosing schedule (may be a summary if proposed statement is lengthy):

Treatment of hypertension

Comments from the submitter: (concerns, observations, etc.)

A NDA will be submitted in September 1997.

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Consult #771 (HFD-110)

MICARDIS

telmisartan tablets, 40 and 80 mg

There were no look-alike/sound-alike conflicts or misleading aspects found in the proposed proprietary name.

The Committee has no reason to find the proposed proprietary name unacceptable.

ISI 5/22/97, Chair
CDER Labeling and Nomenclature Committee

Longman

AUG 25 1998

MEMORANDUM

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

DATE: AUG 25 1998

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

/S/

SUBJECT: Approval (approvable) of NDA 20-850, Micardis (telmisartan), Boehringer Ingelheim Pharmaceuticals

TO: Director, Office of Drug Evaluation I, HFD-101

Introduction

Telmisartan is an angiotensin II receptor blocker. NDA 20-850 unambiguously identifies telmisartan as an antihypertensive agent and shows telmisartan not to be differentiable from placebo with respect to adverse effects. The NDA data contain no surprises. The Division thinks telmisartan should be approved for use as an antihypertensive.

The attached reviews document the content of NDA 20-850; many studies, much to review. Dr. Karkowsky summarizes the reviews nicely. Dr. U's Medical Review contains much documentation and insightful analyses. Dr. Fadran documents the biopharmaceutical portions of the NDA, Dr. Nuri documents the clinical and carcinogenicity statistical analyses. Drs. DeFelice, Jagadeesh and Resnick document the animal toxicology and the satisfaction of the Executive Carcinogenicity Assessment Committee. Dr. Beminger documents manufacturing and controls as well as the satisfaction of the labelling committee. The Establishment Evaluation Report is complete and the Boehringer Ingelheim facility in CT was found satisfactory. Five clinical trial sites have been inspected and found to have no objectional conditions. I have little to add.

The Basis of Approval

Telmisartan certainly decreases all casual cuff blood pressures measured (systolic, diastolic) at trough (in the order of 7 to 14 mm Hg systolic and 6 to 8 mm Hg diastolic; placebo subtracted) when telmisartan is administered once-a-day (at a dose of 80 mg, a qualification to be expanded below). All other measures of blood pressure (e.g., ambulatory blood pressure monitoring data) also find an antihypertensive effect.

In the placebo controlled trial results (1455 randomized to telmisartan, 380 to placebo) the only statistically (nominal) significant differences between telmisartan and placebo for 27 categories of Adverse Events were more headache and more palpitation in the placebo group, and more pharyngitis in the telmisartan group. A number of different analyses of the Adverse Effect data were conducted; for example, there was no effect of dose on the incidence of adverse effects. In general it is reasonable to conclude that telmisartan and placebo were not differentiable. Long-term trials (not placebo controlled) did not show any qualitative difference in the telmisartan adverse effect profile.

Of the 3,445 patients involved in hypertension trials, there were 3 deaths. One patient (221 in 502.202), receiving 120 mg telmisartan for about 3 weeks, developed chest pain that led to 2 emergency room (ER) visits but the patient refused the ER recommendations for hospitalization and after about one or 2 weeks (2 ER visits) arrived at the hospital dead-on-arrival. The second patient (2018, 502.214) had a fatal cardiac arrest after 13 days of telmisartan therapy. The third patient (4167/5961, in the open-label continuation of trial 502.210 had a stroke and died. Although there were no such events in the placebo population (note one of the 3 above deaths was after the placebo-controlled duration of the trial), I see no signal here and consider the data entirely consistent with not distinguishing telmisartan from placebo.

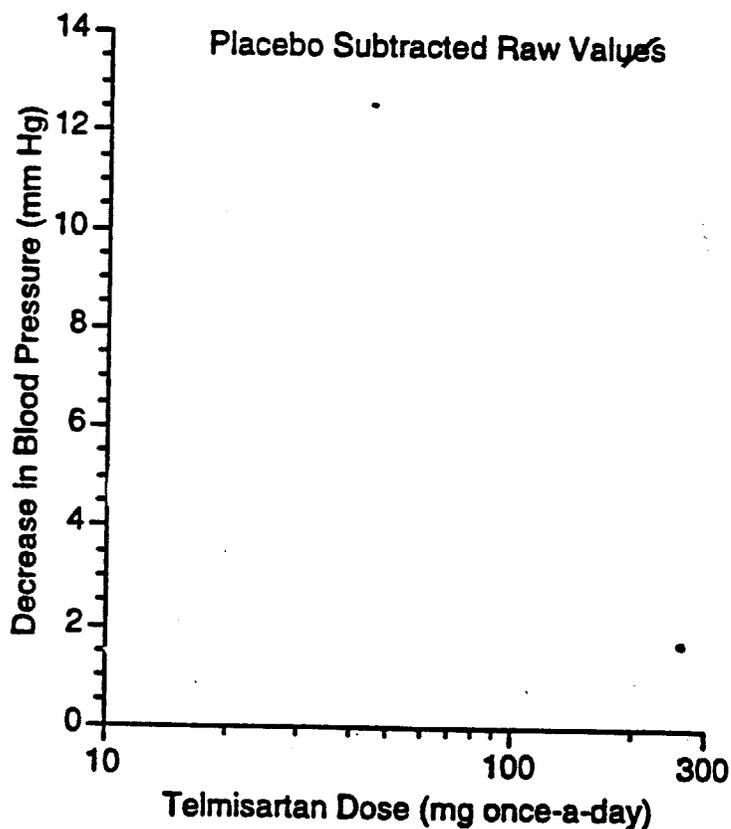
In a single 3-month enalapril-controlled trial involving patients with congestive heart failure (301 patients randomized to telmisartan and 77 randomized to enalapril) there were 5 deaths (1.7%) in the telmisartan population and 3 (3.9%) in the enalapril population. Of course it is known that in patients with congestive heart failure, enalapril has favorable effect on mortality. So, this is another smatter of data that does not raise any suspicion about the safety of telmisartan. It could be viewed as reassuring.

Discontinuation for adverse events was twice as frequent in the placebo group (308 randomized patients) than in telmisartan groups (1455 randomized patients). It is difficult to decide what adverse effects (except for postural hypotension, which I think is attributable to telmisartan and occurs rarely) should be listed as the most common side effects of telmisartan.

Some Token Detail

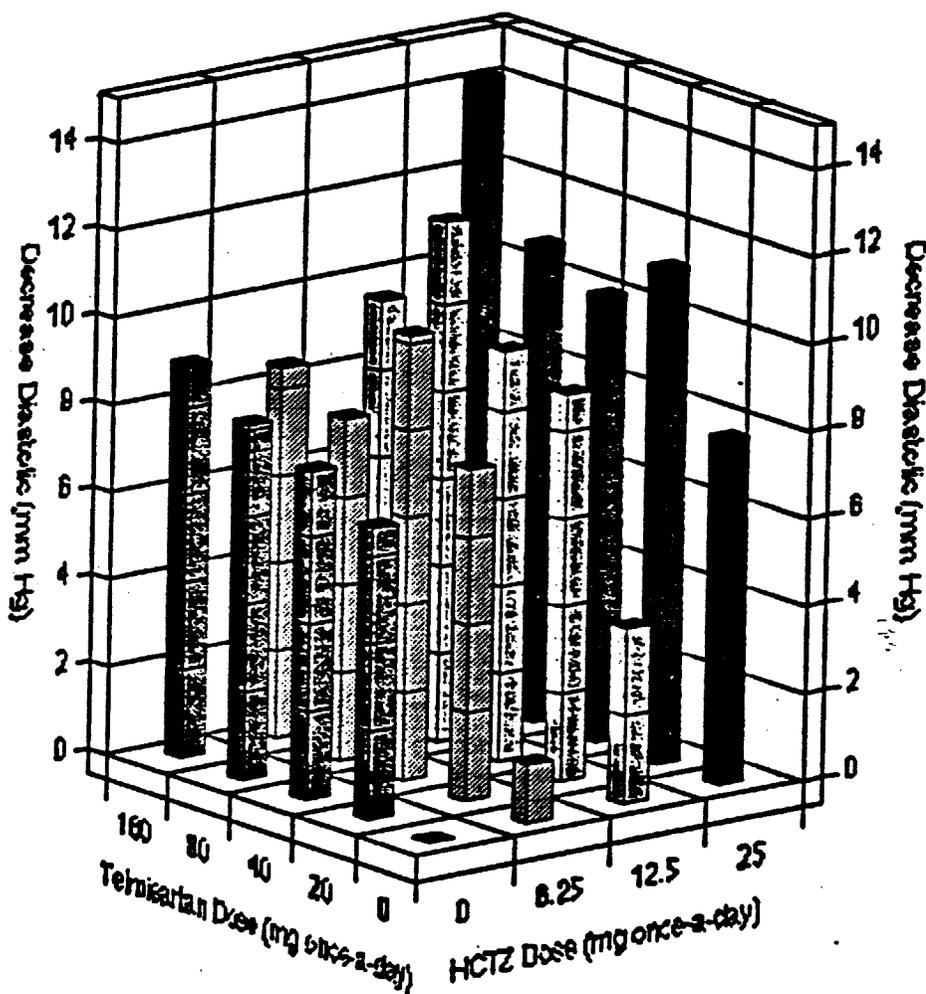
The results of trial 502.203 (274 randomized patients) and trial 502.204 (807 randomized patients) contribute as much information as necessary. The other 18 trials submitted to the NDA confirm the results of these 2 but contribute little more insight.

502.203. Study 502.203 was a randomized, placebo-controlled, parallel-group, dose-ranging trial (46 patients on placebo, 47 patients on 20 mg telmisartan, 47 patients on 40 mg telmisartan, 44 patients on 80 mg telmisartan, 45 patients on 120 mg telmisartan, 45 patients on 160 mg telmisartan). Of the 274 randomized patients, 273 were part of the prespecified intent-to-treat analysis. Telmisartan was administered orally once-a-day. The cuff blood pressure effect at trough after 28 days of double-blind therapy was the primary endpoint. The raw data (placebo subtracted) study result is shown in the following graph.



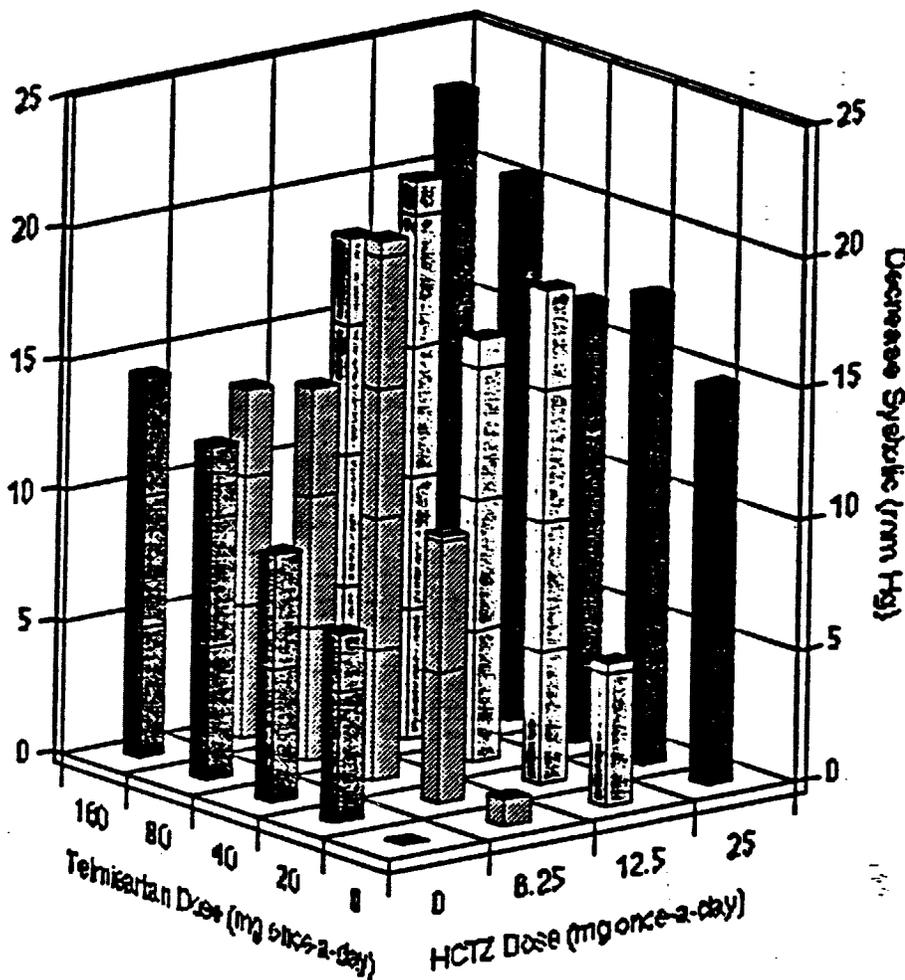
The discrepancy between systolic and diastolic dose-response is accentuated by this plot. Is there a continuously increasing effect of dose on systolic pressure (that is, at a dose of 1 gram there would be a yet greater effect), whereas for diastolic pressure there would be no such expectation? Obviously, that question cannot be answered from this trial. That is true when the other 18 trials are examined as well.

502.204. Study 502.204 was a randomized, placebo-controlled, parallel-group, dose-ranging, factorial trial that evaluated the effects of telmisartan alone, hydrochlorothiazide alone and the combination of telmisartan with hydrochlorothiazide. Dose ranges explored were 20 to 160 mg telmisartan (4 dose levels) and 6.25 to 25 mg hydrochlorothiazide (3 dose levels). A total of 828 patients were randomized and of these 818 form the intent-to-treat analysis that describes the findings of the trial. The raw data results and blood pressures measured at trough (placebo subtracted) are shown in the following graphs.



The graph shows immediately above diastolic blood pressure, where the placebo subtracted maximum change was 14 mm hg in the 160/25 group. The scale of the next graph is not the same as here, since the maximum systolic change (placebo subtracted) was 24 mm Hg. In both graphs, to my eye, the change in blood pressure increases monotonically for the groups where the concomitant medication was placebo (e.g., the dose response for telmisartan alone or HCTZ alone shows no tendency to "plateau", as was the case in study 502.203). There is some degree of wigwagging in the other dosage groups. None-the-less, it seems to me that it is reasonable to conclude from this study (502.204) that the data are most consistent with the effects of each drug, alone or in combination increasing as the dose of each is

increased. This single study does not prove such and such a conclusion is somewhat weakened by the results of 502.203. None of the other studies provide information on a wider dosing range, so I think it is not possible to be confident about the shape of the dose-response curve.



I would feel much better had the dose range exploration been from 3 mg to 1000 mg, such could have been done with some additional patients had doses been changed by a factor of 3 (3, 10, 30, 100, 300 and 1000). Then we would have better insight into what the dose-response really looks like. The 8 other trials (placebo and active controlled trials) randomized an additional 2813 patients, without adding appreciably to characterizing the effects of telmisartan. Having added 2 more dosing arms to 502.203 and 502.204 would have added only 300 more randomized patients to these two trials, in comparison that seems cheap enough to me.

I have focused upon these 2 trials because the results of these two trials provide all of the information I need in order to glean (even without a p value being cited), that telmisartan is an antihypertensive drug and may be used alone or in combination. Should the sponsor desire to have a fixed-dose combination product (telmisartan/HCTZ), there is enough information to approve such an NDA, were it to be submitted.

Although it is probably not a problem of appreciable magnitude, I think that the dose range for general marketing should not be left indefinitely with the lowest dose available being 40 mg telmisartan. The approvable 40 mg dosage form should become scored, so that 20 mg could be administered if desired. As seen in the above Figure, the mean effect of adding 20 mg of telmisartan to low doses of HCTZ (say

6.25 or 12.5 mg) on systolic blood pressure is appreciable (as much as 15 mm Hg). In some individuals the effect is obviously much greater. As described in the reviews, patients with renal disease, hepatic disease, and females achieve higher plasma concentrations of telmisartan for any dose. So, a 20 mg dose being the smallest dose available is still too high, in my opinion. I would push for a scored 20 mg dosage form also being available.

Both the scored 40 and the scored 20 mg dosage forms could be after approval (post-marketing). I will push fairly hard for that, but that is also one of those judgement calls that could go either way (neither way being for sure correct).

Of Some Interest

Plasma Concentration Response. On page 31 of Dr. U's medical review and page xv of Dr. Fadiran's summary of clinical pharmacology is a plot of plasma concentration vs inhibition of angiotensin-II pressor response in a trial that looked at only a single dose of telmisartan in 48 healthy, normal volunteers. It is pretty clear to me that an E_{max} model applies to the data, that an adequate dose range was explored for this purpose; plasma concentrations varied over several orders of magnitude (from less than 1 ng/ml to greater than 200 ng/ml) and the responses observed were from nil to close to 100%. The concentration that produced a 50% effect was around 5 ng/ml and the concentration that produced a 90% effect was around 65 ng/ml (e.g., to go from a 50% effect to a 90% effect required a 13 fold greater plasma concentration). I am not sure that I know how to apply this information, since the dose of angiotensin-II is an important determinant and the greatest plateau response only achieved about an 80% inhibition.

It is of some interest that the mean trough plasma concentration of telmisartan (see page 43 of Dr. Fadiran's review) were 47, 70.4 and 98.1 ng/ml for 40, 80 and 120 mg telmisartan administered once daily in one of the placebo-controlled antihypertensive trials (study 502.203, the results on blood pressure shown above). The standard deviations on each of the mean plasma concentrations were about equal to the mean point estimate, so the 95% confidence limits probably would include 0 and exceed 400 ng/ml in each of the dosing groups. In any event, they are well above the 5 ng/ml that constitute the data from the angiotensin-II challenge study. I am not sure that I know how to best interpret these data. It is comforting to know that such work is being conducted, maybe it will be interpretable by someone other than me.

I agree with the conclusion written by Dr. Fadiran (page xxii of the Clinical Pharmacology Review) that no dosage adjustment is necessary, despite the considerable variability (range being about 1 ng/ml to nearly 10,000 ng/ml) seen from the 1194 patients that had plasma concentrations drawn during the trials. Many diverse factors contribute to the variability of plasma concentrations, but the variability does not appear to have any known practical consequence.

Pharmacokinetic data. At best about 60% of orally administered telmisartan gets into the circulation. The absolute bioavailability is somewhat dose-dependent, suggesting some saturable mechanism. But what happens is not well defined. Food affects the bioavailability a little, but considering everything else I think it can be ignored. Patients can take telmisartan with meals or fasted and nobody will ever know the difference.

Females and patients with hepatic disease have much higher concentration of telmisartan than males. Patients with no kidneys have lower plasma concentrations even though telmisartan cannot be dialyzed. These are things that need to go in the package insert, and have been suggested in the mark-up.

Duration of effect. There are no once-a-day vs twice-a-day trials, so inferences with respect to duration of action come entirely from the once-a-day trials that were conducted. This topic is summarized nicely in Dr. U's review, pages 133 through 137. It seems to me that the doses of 80 mg and above will maintain a rather consistent 24 hour effect. At doses less than 80 mg, it would be fair to state that the effect diminishes as the interdosing interval is approached. Table 5.9.4.1, page 137 of Dr. U's review says to me that telmisartan doses below 80 mg are pretty much like that of 20 mg enalapril. Enalapril at 20 mg is sometimes (in some people) a once-a-day drug. None-the-less, I think that enalapril twice-a-day is a

more appropriate regimen. Of course, table 5.9.4.1 of Dr. U's review depicts only the first dose of telmisartan or enalapril in 2 trials. It is hard to infer that at steady state (say 4 weeks) of repetitive dosing the same comparison would hold.

Ambulatory blood pressure monitoring data were obtained in only one study (study 502.208). This was a placebo-controlled trial that has titrated active medication arms of amlodipine and telmisartan. Here, telmisartan (40 to 120 mg), looked better than 5 and 10 mg of amlodipine once-a-day by ABPM. By trough, using cuff, the placebo subtracted treatment effects were 14/7.0 (systolic/diastolic) for the amlodipine group and 15.2/7.4 for the telmisartan group, both significantly different from placebo, but not statistically significant one from the other. Sixty two percent (62%) of the telmisartan patients were receiving 80 mg or greater telmisartan doses (from 80 mg up there is not much question that telmisartan has a reasonable 24 hour effect), 60% of the amlodipine patients were receiving only 5 mg amlodipine (a fairly low dose of amlodipine). There is no question that both amlodipine and telmisartan are antihypertensive drugs, but the comparison is not terribly convincing, regarding duration of action of doses at steady-state.

Peak/trough measurements were made in trials 502.202, .203, .204. All estimates showed a 50% or greater peak/trough. The 20 and 40 mg doses of telmisartan being 50 and 66%; all other doses of telmisartan varying from 89 to 100%. The data are entirely consistent with the 20 and 40 mg doses of telmisartan having a shorter duration of action than those of 80 mg and greater.

I do not think telmisartan is a once-a-day drug, anymore than I think that enalapril is a once-a-day drug. If I had only myself to satisfy, I would label telmisartan as once or twice a day, despite there being no twice-a-day dosing regimen studied. This is a judgement call. It would not be entirely wrong to label telmisartan as a once-a-day drug.

Cough. Certainly telmisartan was not distinguishable from placebo for cough, (incidence of cough being 1.6% for placebo and 1.6% (identical numbers) for all telmisartan-treated patients in placebo-controlled trials. In the trials where enalapril was a positive control and lisinopril was a positive control, cough was nominally statistically significantly greater in the ACE inhibitor groups. So, I am inclined to think that like all angiotensin II blockers, telmisartan is not as likely to cause cough as are ACE inhibitors.

The sponsor has 2 trials ongoing that enroll patients with ACE inhibitor cough and randomize to telmisartan or an ACE inhibitor, where the primary endpoint is the incidence of cough. Until those trials are completed, we should not allow a claim of "no cough" to be made.

Final Thoughts or Comments

From my view, this is a relatively straightforward application and should be approved. The only additional data needed are the results of the "cough studies" that are ongoing, if the sponsor wishes to have a "no cough" claim. Otherwise there is no other information needed.

In particular, there should be no need for any more "safety updates," there is no possibility that it could affect our decision making.

A marked-up version of the package insert as well as an approvable letter are appended.

cc

Orig.

HFD-110

HFD-110/K Bongiovani/A Karkowsky/KU/C Resnick/G Jagadeesh/K Srinivasachar/C Berninger

HFD-710/K Mahjoob/W Nuri

HFD-860/A Parekh/E Fadiran

HFD-344/A ElHage

HFD-110/R Lipicky

sb/8/24/98;8/25/98

Please substitute the following graphs for those shown as Figure 2 and Figure 3 of my Memorandum Dated August 17, 1998.

Figure 2

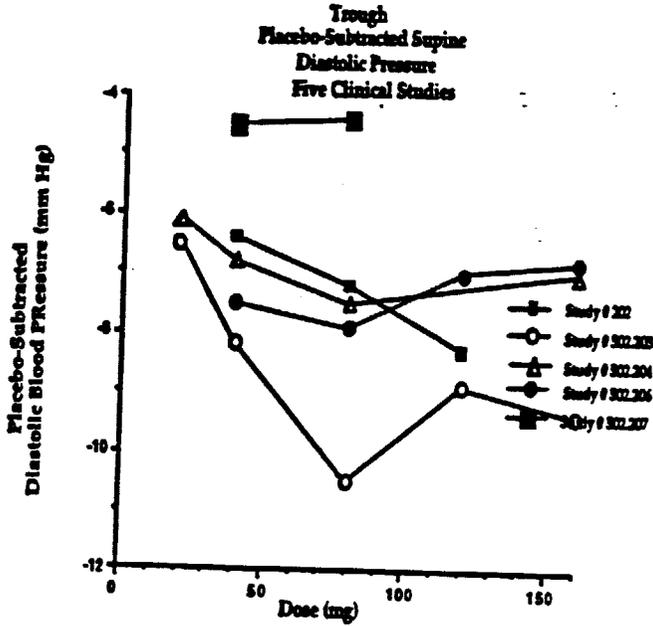
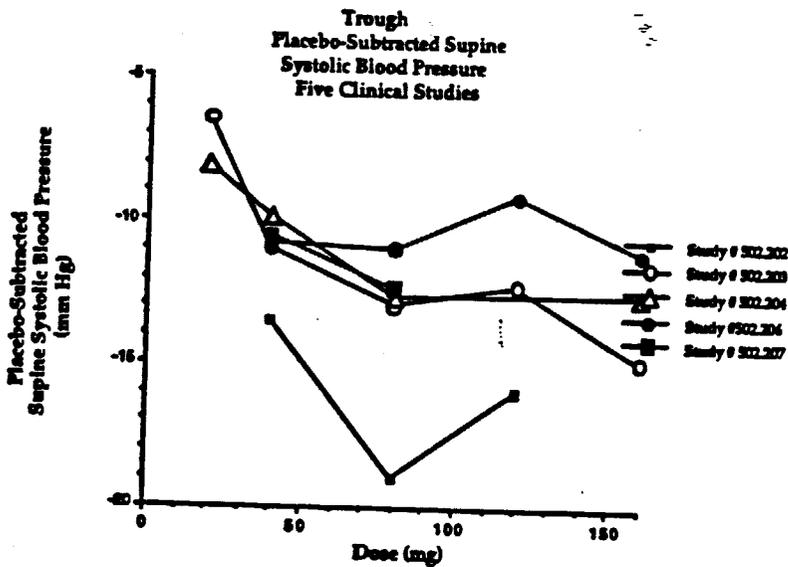


Figure 3



cc: NDA 20-850
HFD-110
HFD-110 / KBonjiovanni

151
9/10/98

K. Bongiovanni

AUG 17 1998

NDA 20-850 Telmisartan (Micardis®) Tablets for Hypertension August 17, 1998 page 1

MEMORANDUM



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

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader Division of Cardio-
Renal Drug Products HFD-110

ISI 8/13/98

TO: Dr. Robert Temple, Director, Office of Drug Evaluation I

THROUGH: Dr. Raymond Lipicky, Director, Division of Cardio-Renal Drug
Products, HFD-110

SUBJECT: Approvability of Telmisartan for the Treatment of Hypertension.

This memo will outline the rationale for approving telmisartan¹ for the treatment of hypertension. The data from six placebo-controlled studies strongly support the use of telmisartan, once daily in a dose range of between 20-160 mg. This dose range for telmisartan represents the flattened portion of the dose-response curve. Consequently, dose titrating above 40 mg daily affords little additional antihypertensive benefit. Dr. U's review notes no unusual safety concerns. My labeling comments are attached.

According to both Dr. Berninger and Dr. Srinivaschar, chemistry and manufacturing are acceptable. A few labeling issues, however, are still being resolved. Inspections were satisfactory. DSI audits found no glaring deficiencies. Two concerns raised by the CAC are presently being addressed by Dr. Resnick. One issue is whether the overall exposure (based on AUC) was adequate for the carcinogenicity studies. The CAC was also concerned about a marginally significant increase in thyroid C-cell adenomas. Both issues are apparently resolvable.

Telmisartan is structurally similar to several already approved angiotensin II blockers (see figure 1). Any deviation in behavior of this drug from already approved angiotensin blockers would be surprising.

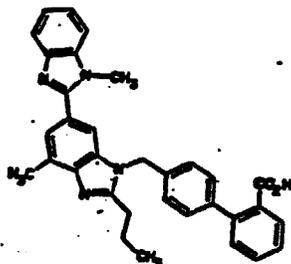
Telmisartan appears to be a blocker of angiotensin II, specifically the AT1 subtype receptors. No information suggests any preferential specificity of telmisartan binding to the AT1a and AT1b subtypes. Telmisartan displaced ¹²⁵I-angiotensin II from binding sites of rat lung membrane (a model system for AT1 subtype of angiotensin II receptors) with a K_i of 3.7 ± 1.7 nM. It was much less potent in ..

¹ (4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-1,1'-biphenyl]-2-carboxylic acid; CAS registry no. 144701-48-4)

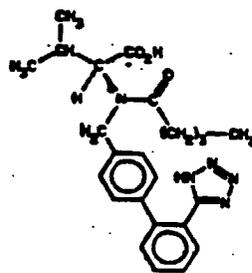
Figure 1.

Structure of Angiotensin II Blockers

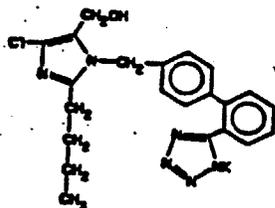
Telmisartan



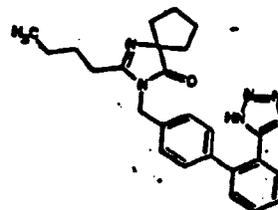
Valsartan



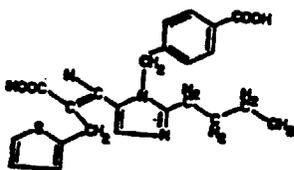
Losartan



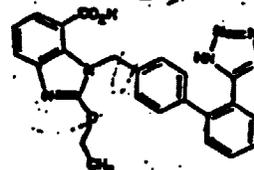
Irbesartan



Eprosartan



Candasaratan



displacing the iodinated angiotensin II from rat adrenal medulla (a model for AT₂ subtype angiotensin II receptors) ($K_i > 10 \mu\text{M}$). Telmisartan did not bind to α - or β -adrenergic, M₁-, M₂- or M₃- muscarinic, histamine, serotonin, endothelin ETA, adenosine, dopamine, neuropeptide Y, neurokinin or imipramine receptors.

Pharmacokinetics:

Mass balance studies were performed after a single 40-mg dose of ¹⁴C-labeled telmisartan either orally or intravenously, infused over 20 minutes. Overall plasma concentration of radioactivity was only slightly higher than parent telmisartan and paralleled its elimination throughout the observation period. Radioactivity was almost exclusively excreted in feces, with urine containing less than 1% of the administered dose. The pattern of excretion was the same whether telmisartan was administered orally or intravenously. In urine, a minority of the radioactivity (between 2-12% of the urinary radioactivity) was identified as the glucuronide conjugate of telmisartan. Only intact telmisartan was isolated from feces.

Telmisartan is extensively (>99.5%) bound to proteins at its usual plasma concentration range (ng/ml). Binding is predominantly to human serum albumin.

After intravenous administration of single doses of telmisartan ranging from 10-120 mg over 30 minutes, both C_{max} and AUC increased in a dose proportional manner. Peak concentration occurred at the end of infusion, with a subsequent rapid decline in the measured concentrations. By two hours after the end of the infusions, concentrations of telmisartan decreased to approximately 10% of those at peak. Plasma concentrations of telmisartan decline further, with a terminal half-life of between 19-23 hours. The volume of distribution was between 460-483 Liters (assuming a 70-Kg male this would be approximately 6.5-7.0 Liters/Kg). The rapid decline in the concentration of telmisartan after the end of the infusion, largely reflects redistribution into an extremely large tissue compartment.

The absolute bioavailability of telmisartan at 40 mg/day relative to an intravenous formulation was 42.4% (95% CI= 31.6-59.9 %). The absolute bioavailability of 160 mg telmisartan, relative to a 160 mg iv dose, was 57.5 % (96% CI=50.7-65.2).

Oral doses of telmisartan at doses of 10-160 mg (either as oral solutions, λ -cyclodextrin solutions, capsules, tablets and market image tablets) have been studied, either as single or as multiple dose regimens. Representative oral kinetics, in this case the data from an oral solution is tabulated below (Table 1; taken from Table 4 of Dr. Fadiran's review of study #502.201). The table is meant to illustrate some kinetic properties of telmisartan:

Table 1. Summary of Pharmacokinetic Parameters (Mean ± CV%) for Telmisartan Following Oral Administration (solution) on Day 1 and Steady State (Study 502.201)

Dose	C _{max}	C _{max, ss}	C _{min, day 1}	C _{min, ss}	AUC _{day 1}	AUC _{ss}	T _{max, ss}	Accumulation (AUC)
mg	ng/ml	ng/ml	ng/ml	ng/ml	ng·h/ml	ng·h/ml	hour	
10	8.94 ± 44	12.89 ± 36	3.54 ± 71	2.56 ± 49	81.77 ± 52	153 ± 47	2.0	2.0
20	29.7 ± 47	46.3 ± 59	12.37 ± 68	9.55 ± 71	276 ± 42	528 ± 56	2.0	1.8
40	70.4 ± 45	88.2 ± 44	9.38 ± 50	12.6 ± 30	486 ± 47	729 ± 47	1.5	1.5
60	159 ± 33	328 ± 41	38.17 ± 54	36.1 ± 32	1249 ± 38	2556 ± 43	0.51	2.0
80	366 ± 50	601 ± 84	25.6 ± 90	27.6 ± 108	1044 ± 38	2248 ± 81	0.50	2.0
100	767 ± 56	1041 ± 27	52.5 ± 58	36.6 ± 74	2284 ± 37	3403 ± 33	0.50	1.5
120	1131 ± 57	2017 ± 21	71.8 ± 58	51.6 ± 67	2946 ± 26	5743 ± 41	0.50	1.9
160	1520 ± 47	2871 ± 85	74.2 ± 73	43.1 ± 84	3177 ± 57	5357 ± 72	0.50	1.6

1. C_{max, day 1} and C_{max, ss} values deviate from dose proportionality.
2. AUC _{day 1} and AUC _{ss} also deviate from dose proportionality.
3. C_{min, day 1} and C_{min, ss} values deviate less from dose proportionality
4. For doses of ≥ 40 mg, C_{max}: C_{min} is usually greater than 7:1.
5. The accumulation ratio was approximately 1.5-2.0

Other studies with tablets or capsules² support the same conclusions.

There are clear gender difference in the pharmacokinetics of telmisartan as an oral formulation. The data from study 502.128 (from Dr. Fadiran's review) is shown as Table 2. C_{max} and AUC, either after the first day or after multiple doses, are substantially higher in females than males. Normal females were not enrolled into the intravenous studies. It is, therefore, not possible to definitively assign the gender differences to processes involved in absorption (including first pass effects) or to factors that alter the volume of distribution. The T_{1/2} that accounts for only a small fraction of the AUC in males is greater for females by approximately 50%.

Table 2. Study 502.128 Summary Statistics (Geometric Mean ± CV%) Based on Gender for the Oblong and Round Formulations

Parameter	Male (n=12)		Female (n=12)	
	Oblong Tablet	Round Tablet	Oblong Tablet	Round Tablet
C _{max}	355 ± 76	308 ± 76.6	981 ± 106	752 ± 76.7
C _{max ss}	289 ± 118	320 ± 70.4	899 ± 110	883 ± 100%
C _{pre}	10.8 ± 76.2	10.1 ± 71.9	25.3 ± 61	31.9 ± 101%
AUC 0-24	773 ± 52.4	720 ± 74.1	1780 ± 73.9	1560 ± 65%
AUC _{ss}	858 ± 74	930 ± 61	2040 ± 75	2380 ± 87.1
T _{1/2}	16.6 ± 34	16.1 ± 22	24.7 ± 37	24.3 ± 30

It is unclear how the kinetics of telmisartan are modified by gender. Population

² E.g., studies # 502.203, #502.202, #502.128, #502.124, #502.101, #502.201

pharmacokinetics suggest that there are gender differences in both absorption and distribution into the peripheral compartment (see below). It is unlikely that differences in conjugation (metabolism) are able to account for the substantial differences in kinetics. Since so little conjugated product is ultimately recovered from males, it is hard to argue that enhanced conjugation in males explains the large differences in plasma kinetics.

Population pharmacokinetics were performed from 5291 plasma samples collected from 1194 subjects enrolled into eight clinical studies and may shed some light on the gender difference in kinetics. Subjects were dosed in the range of 10-160 mg/day. Nearly 90% of the measurements coincided at peak 6 ± 5 hours or trough (24 ± 5 hours).

Concentrations of telmisartan covered a range of ng/ml to nearly ng/ml. Approximately 99% of the values in the range of ng/ml. Modeling the data to a two-compartment open-model with first order absorption, telmisartan clearance was related to gender, race, dose of telmisartan, alcohol consumption, cigarette smoking and HCTZ use. Absorption and the volume of the peripheral compartment was related to gender. Females showed a 62% lower peripheral compartment volume and a 30% lower clearance rate than males. Some racial differences in clearances were also noted. Telmisartan clearance for Hispanic: White:Black: Other were 0.72: 1: 1.42 :1.38, respectively.

Given the broad range of concentrations of telmisartan that was measured during the clinical studies, and the relative benign safety profile of telmisartan (see below), any gender-related kinetic differences are unlikely to be clinically meaningful.

Kinetics of telmisartan were only mildly altered by a high fat meal. After a 40-mg oral dose, C_{max} was decreased 20% AUC was not substantially altered. After a 160-mg dose, C_{max} was reduced by approximately 60% and the AUC was reduced by approximately 20%.

Telmisartan at concentrations of 0.1 to 10 μ M did not inhibit the metabolism of prototypical substrates for CYP1A2 (paracetamol as substrate); CYP3A4 (testosterone or nifedipine as substrate); there was modest inhibition of CYP2B6 (mephenytoin as substrate with its metabolism to nirvanol as the product); CYP2D6 (bufuralol as substrate) with somewhat greater inhibition against CYP2C19 (mephenytoin as substrate metabolism to 4-OH-mephenytoin as the product).

Efficacy:

Both Dr. U's and Dr. Nuri's review make it quite clear that telmisartan is an active antihypertensive. Six placebo-controlled studies (#502.202; #502.203; #502.204;

#504.206; #502.207; and #502.208), all in patients with mild to moderate hypertension support the once-daily dosing of telmisartan in the range of 20-160 mg. Treatment in these studies ranged from 4-12 weeks. Four of these studies (# 502.202; # 502.203 #502.204 and #502.206) were parallel groups; one of which (#502.204) was a parallel-group factorial-design study on top of hydrochlorothiazide (0, 6.25, 12.5 and 25 mg). Two of these studies also included enalapril as a positive control (#502.202 and #502.206). The other two studies (# 502.207 and #502.208) were dose-titration studies. Telmisartan doses could be increased among those who were non-responders (defined as not achieving a DBP \leq 90 mm Hg). Atenolol (#502.207) or amlodipine (#502.208) were included as a positive control group.

Dose response data was available for five of the six studies, the sixth study titrated all uncontrolled subjects. The effect on diastolic and systolic blood pressures at the end of treatment for studies # 502.202; # 502.203 #502.204 and #502.206 as well as the effect for study # 502.207 before any dose titration, are shown below (Figures 2 and 3, respectively).

The data base contains blood pressure response over nearly a log-range of doses (20-160 mg/day). Placebo-subtracted supine diastolic pressure over the entire dose-range is statistically different from placebo, with a placebo-subtracted effect of approximately 5-8 mm Hg. There, however, is only a modest trend at best to increasing effect with increasing doses.

Figure 2

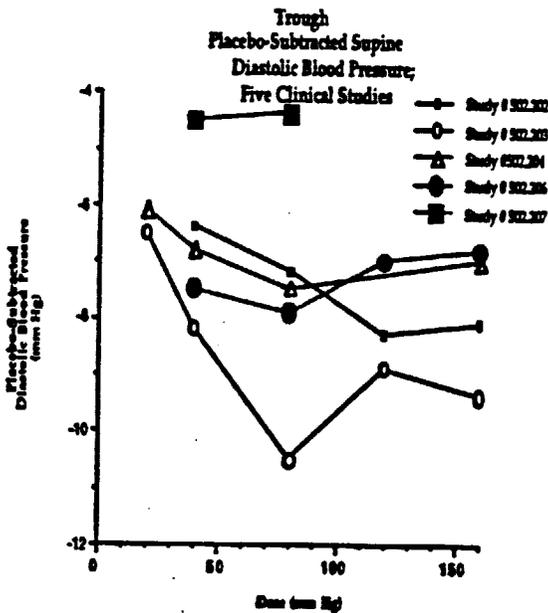
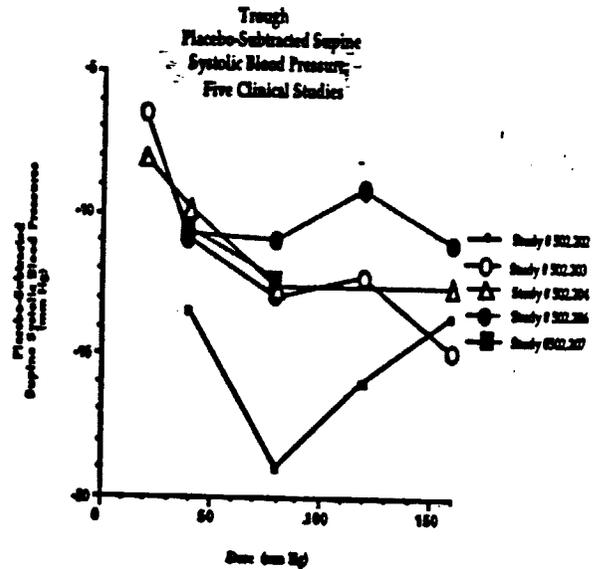


Figure 3



Supine systolic blood pressure responses, over the entire dose-range of telmisartan (20-160 mg/day), also significantly differed from placebo. There appears little additional systolic blood pressure effect at doses above 40 mg./day. The 20 mg dose, however, appears to reflect the shoulder of the dose response curve. The placebo-subtracted effect of telmisartan at ≥ 40 mg on supine systolic blood pressure is approximately 10-15 mm Hg.

Duration of Effect: Despite the large variation of plasma concentrations of telmisartan during the interdosing interval (see Table 1 and 2), blood pressure is maintained after the once daily dose.

The effects of telmisartan are more complicated than a simple plasma concentration-effect relationship. The blood pressure and heart rate response to repeated doses of angiotensin II infusion is diminished by a single dose of telmisartan at doses of 20-80 mg (study #502.103). Peak plasma concentrations of telmisartan at the 80-mg dose were approximately 110 ng/ml at 1.5 hours and decreased to approximately 15 ng/ml at eight hours. Despite approximately 7-fold changes in plasma concentrations, the inhibition of angiotensin II vascular responses were relatively constant during this time. Plotting concentration versus percent inhibition of angiotensin II response demonstrates a clear hysteresis response (see Table 4 of Dr. Fadiran's review).

Manual cuff measurements were performed hourly for 12 hours and at the end of 24 hours. Both systolic and diastolic blood-pressure response are fairly stable during the dosing interval (study # 502.202- see Figure 202.4.1-iii of Dr. U's review). In addition, for study 502.204 the placebo-subtracted blood-pressure response at three hours post-dose was not different from the placebo subtracted response at trough³.

In summary, there are more than adequate data that telmisartan is an active antihypertensive in the dose range of 20-160 mg. Blood pressure response is sufficiently stable during the interdosing interval to recommend dosing once daily.

Safety: Telmisartan appears to be safe, Dr. U has completed his review of the original safety data of the NDA as well as the safety update. The update adds approximately 10% additional exposures (336 patients) to telmisartan and increases the mean duration of those already exposed an additional three months from the data base in the original NDA.

There were a total of 3781 unique patients (3,445 patients in the original NDA data base), who were treated with telmisartan either alone or in combination (with

³ Peak:trough ratios in this study were calculated by subtracting both peak placebo and peak treatment from their corresponding baseline (trough) measurements with subsequent subtraction of the placebo 'peak' values from the treatment 'peak' values.

hydrochlorothiazide), in either double-blinded or open-labeled studies.

Placebo-controlled data was available for 1455 patients. These patients received either telmisartan as monotherapy or in combination with hydrochlorothiazide (6.25-25 mg daily), in fixed-dose parallel-group or dose-titration studies (#502.202, #502.203, #502.204, #502.206, #502.207 and #502.208).

In fixed dose, placebo-controlled studies, subjects were treated with between 20-160 mg daily of telmisartan, with exposure ranging between 4-12 weeks. Patient exposures to telmisartan in positive-controlled, uncontrolled or long-term open-labeled extension studies make up the residual data bases. The exposure for these patients was generally between 26-52 weeks.

Overall duration of exposure to telmisartan was 8.7 months (5.7 months in the original NDA safety review). There were 1937 patients exposed to telmisartan for six months or longer (1400 in the original NDA data base) and 1360 patients exposed to telmisartan for greater than one year (415 in the original NDA data base). Most subjects were treated with either telmisartan at a dose of 40 or 80 mg daily (mean duration of exposure 303 and 297 days, respectively; this excludes those treated in combination with HCTZ), with a substantial number of patients exposed to telmisartan at the 160-mg dose (396 patients with a mean exposure 139 days).

According to Dr. U's review, neither discontinuations, serious adverse events, overall adverse events nor laboratory adverse events appeared to be telmisartan related. Overall adverse events did not appear dose related.

Not surprisingly, orthostatis particularly in combination with a diuretic was more frequent in telmisartan-treated patients than placebo patients.

In summary, there was adequate patient exposure to telmisartan during the clinical development program. There were no alarming safety issues.

cc: NDA 20-850
HFD-110-File
HFD-110 AKarkowsky/KBongiovanni

NOV 10 1992

EXCLUSIVITY SUMMARY FOR NDA # 20-850

SUPPL # _____

Trade Name Micardis

Generic Name telmisartan

Applicant Name Boehringer Ingelheim HFD # 110

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? *not specified*

e) Has pediatric exclusivity been granted for this Active Moiety?

no

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

4. If yes, explain: _____

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES / / ! NO / / Explain:

!
!

Investigation #2

IND # YES / / ! NO / / Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / / Explain ! NO / / Explain

Investigation #2

YES / / Explain ! NO / / Explain

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / /

If yes, explain: _____

/S/

Signature

Title: Reg. Hlth. Project Mgr

Date

11-5-98

/S/

Signature of Office/
Division Director

Date

11/10/98

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

13.0 PATENT INFORMATION

Required Information

- (i) Applicable Patent Numbers and Expiration Date of Each U.S. Patent No. 5,591,762
January 7, 2014
- (ii) Type of Patent drug, drug product and method of use
- (iii) Name of Patent Owner Dr. Karl Thomae GmbH
- (iv) Entity authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R §§ 314.52 and 314.95
Boehringer Ingelheim Pharmaceuticals, Inc.(the applicant), which has its place of business at 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877

Original Declaration with respect to a formulation, composition or method of use patent

The undersigned declares that Patent No. 5,591,762 covers the formulation, composition, and/or method of use of telmisartan tablets that is the subject of this application and for which approval is being sought.

By:


Alan Stempel

Capacity: Applicant's Agent (Representative)
 Applicant's Attorney

Date:

Sept. 16, 1997

CONFIDENTIAL

patent.doc/Page 1
08/27/97

Original Application - NDA 20-850

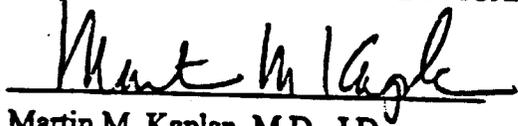
Page

EXCLUSIVITY INFORMATION

- 1) The applicant, Boehringer Ingelheim Pharmaceuticals, Inc., believes that after approval of the New Drug Application, the new drug which is the formulation of telmisartan tablets that is the subject of this application and for which approval is sought will be entitled to a period of marketing exclusivity under the provisions of 37 CFR 314.108, and is, therefore, claiming exclusivity.
- 2) Reference is made to 37 CFR 314.108(b)(2) to support the applicant's claim to exclusivity for the new drug which is the formulation of telmisartan tablets which is the subject of this application and for which approval is sought.
- 3) The applicant claims exclusivity under 37 CFR 314.108(b)(2), and accordingly must submit information to show that, to the best of the applicant's knowledge or belief, a drug has not previously been approved under section 505(b) of the Federal Food, Drug and Cosmetic Act containing any active moiety in the drug for which the applicant is seeking approval. This information is as follows: The sole active ingredient in the drug for which the applicant is seeking approval is telmisartan, the chemical name for which is 4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazole-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid or 4'[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl-[1,1'-biphenyl]-2-carboxylic acid 2-b:2',3'-e][1,4]diazepin-6-one). To the best of the applicant's knowledge and belief, no drug containing telmisartan as an active moiety has previously been approved under section 505(b) of the Federal Food, Drug and Cosmetic Act.

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

By:


Martin M. Kaplan, M.D., J.D.

Title: Director, Drug Regulatory Affairs

Date:

9/18/97

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-850

Supplement # _____

Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD: 110 Trade and generic names/dosage form: Micardis (+lmsisctm) Tab Action: AP AE NA

Applicant Beechinger Ingelheim Therapeutic Class IS

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate inadequate

Proposed indication in this application treatment of hypertension

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No
(Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? Yes No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Team Leader (e.g., medical review, medical officer, team leader)

/S/
Signature of Preparer and Title

8/6/98
Date

cc: Orig NDA/BLA # _____
HF _____ /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Telmisartan Tablets, 40 mg and 80 mg
(BIBR 277 SE)

NEW DRUG APPLICATION
Boehringer Ingelheim
Pharmaceuticals, Inc.
Ridgefield, CT 06877

CERTIFICATION: DEBARRED PERSONS

CERTIFICATION REQUIREMENT

SECTION 306(k)(1) OF THE ACT
21 U.S.C. 355a(k)(1)

The undersigned certifies, that, to the best knowledge and belief of the undersigned, Boehringer Ingelheim Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)], in connection with Telmisartan (BIBR 277 SE) Tablets.

Signature



Name of the Applicant:

Martin Kaplan, M.D., J.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Mailing Address:

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

CONFIDENTIAL

FEB 3 1998

MEMORANDUM

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

DATE: FEB 3 1998

FROM: ^{ADFC.} Albert DeFelice, Ph.D., Team Leader (Pharmacology)
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Hepatic Clinical Chemistry/Histopathology Profiles in Pre-Clinical
Toxicity Tests of Seven NDA "Sartan" Compounds

TO: File - NDAs 20-386, 20-665, 20-738, 20-757, 20-838,
and ~~20-838~~
Through: Robert Fenichel, M.D., Ph.D., Deputy Director ^{RAF}
Division of Cardio-Renal Drug Products, HFD-110

Summary:

Animal toxicity test results of each of the seven approved or pending "sartans" were re-visited by certain of the Division's review pharmacologists (Drs. A. Proakis, J. Koerner, G. Jagadeesh, T. Papoian, and myself) to look, only, for any histologic or clinical chemistry evidence of hepatotoxicity. Data base included a) 14 lifetime rodent studies (mice and rats) done at up to max. tolerated dosages, b) 6 more chronic (6-12 mo.) rodent studies; c) 5 oral dog studies (4 3-12 mo. studies; 1 1-mo. study) at doses affording 10-50X human AUC plasma exposure, d) 2 intravenous dog studies (1-day; 30 days) at up to 50X human plasma exposure, and e) 5 oral monkey studies (3 6-12 mo.; 2 1-3 mo.) done at up to 50X human AUC plasma exposure. My scrutiny of losartan (orig. reviewers: Drs Proakis and Jagadeesh) included examining the trajectory of clin. chemistries for individual animals in chronic studies with a serial bleed design.

Despite unblinded review of the data - and foreknowledge that these agents may damage human liver - neither the individual evaluations, nor my overview of them, perceived any concentration or duration-related hepatotoxicity in rodents, dogs, or monkeys - as concluded in the original reviews of these studies. Where individual animal data were available, the occasional 2-4 fold increase in ALT value over basal level was confined to either dog or monkey (not both in a given sartan) and, furthermore, were not accompanied by AST, AP, bilirubin, or liver histology change in that animal. Perhaps compellingly, there was no excess liver histopathology in tumorigenicity assays performed at lifetime exposure of mice and rats at up to maximum tolerated (or otherwise acceptable) dosages of each of the sartans.

A summary of the scope, and duration, of animal toxicity studies which monitored both clinical chemistries and histology follows:

TASOSARTAN :

Chronic oral studies:

52 wk. mouse and rat: No signif incr. in AST, ALT, or AP at up to 100 mg/Kg vs. concurrent control group. Max. exposure vs. human: 30X.

2-yr. rodent tumorigenicity : No excess liver histopathology vs concurrent control in either species at up to approx. Max. Tolerated Dose in either species (ca. 30X human exposure).

13 and 26 week monkey: No clin. chem. or histologic evidence of hepatotoxicity at up to approx. 70X human exposures.

52 wk. monkey: A transient 3-fold increase in one, and a sustained 2-fold in a second, of 4 females at 15 mg/Kg without change in AST, AP, bilirubin, or liver histology. No liver changes at higher dose (45 mg/Kg) in 4 other females and 4 males.

EPROSARTAN :

Chronic oral studies:

13-week mouse: No evidence of hepatotoxicity at up to 2000 mg/Kg.

6-month rat: At 1000 mg/Kg, mean ALT and AST in females are 1.5 X concurrent control. No associated liver histopath.

2-year mice/rat: No histologic evidence of hepatotoxicity at up to approx. max. tolerated dosage.

12- month dog.: At up to 1000 mg/Kg, no clin. chem. or histologic evidence of any hepatotoxicity (dose is 100x dog efficacious dose; affords 10 x human blood levels).

Single iv dose, dog ALT, AST, and AP raised 2-5 fold 3 days post 300 mg/Kg iv. Mild multifocal cholangiitis only liver histopath. Dosage affords 1000X human free drug level.

VALSARTAN:

Chronic oral studies

3-12 mo rat: No clin. chem. (ALT, AST, AP, bilirubin) or histologic evidence of hepatotox. at up to 600 mg/Kg/ 3-mo. (which affords 100 X human free drug AUC) or 200 mg/Kg/year. (which affords 35X human free drug AUC).

3-12 mo. marmoset: No clin. chem. or histologic evidence of hepatotox. at up to 120 mg/Kg/ 12 mo. (ca. 60X human dose). At \geq 200 mg/Kg/ 3-mo.: 36% incr. in AP; marked lipid vacuolation of liver in 3 animals; 1 animal with mild chronic hepatitis and minimal focal necrosis in liver.

14-day iv.:

Marmoset: No evidence of hepatotoxicity after 60 mg/Kg iv / day / 2 weeks. (dose is estimated to afford ca. 300 X human serum drug levels).

Rat: No evidence of hepatotoxicity after 100 mg/Kg iv / day / 2 weeks. (dose is estimated to afford ca. 500 X human serum drug levels).

TELMISARTAN:

Chronic oral studies:

26-week rat: 2 -fold increase in total bilirubin (but no other clin. chem., or liver histopath.), and 25% decr. in liver wt. at 500 mg/Kg, which affords 200- 300X human free drug AUC exposure. 1 mg/Kg is efficacious dose in this species.

52-week dog: No change in ALT, AST, AP, LDH, or total bilirubin at up to 500 mg/Kg which affords ca. 40X the human AUC exposure to free drug.

Intravenous studies:

4-week rat: Liver wt. decreased 10-15% without histopathology.

30-day dog: At 50 mg/Kg, mean AST, ALT, and LDH in females increased 2, 10, and 2-fold, respectively, vs. baseline, and one male also had 2-fold increase in these enzymes. Liver wts. increased ca. 10-15% in both sexes, with no histopathology. Dosage afforded 52-63X human AUC exposure to free drug. Although exposure was not markedly higher than that achieved in the 1-year oral dog study, liver enzymes were not elevated in the latter.

CANDESARTAN:

Chronic oral studies:

6-mo. rat (10/sex/dose): There was no clin. chem. (including ast, alt, ap, and bilirubin) or histologic evidence of hepatotoxicity at up to 1000 mg/Kg daily in either sex.

52-week dog(4/sex/dose): There was no clin. chem. (include. aminotransferase and bill.) or histologic evidence of hepatotoxicity at up to 300 mg/Kg daily in either sex.

4-week monkey (2/sex/dose): At 300 mg/Kg daily, 2-fold incr. in ALT in 1 male and AST in 1 female at 4 -weeks, with no other enzyme, bilirubin , or liver histology change.

LOSARTAN:

Sub-acute and Chronic oral studies:

Rodent:

14 week rodent (15/sex/dose):

Except for a 40% incr. above control in high-dose males at wk.12, there was no stat. signif. increase in ALT at dosages up to 450 (rat) and 500 (mice) mg/Kg /day/14 weeks. No bilirubinemia or liver histopath. cited. It must be noted that the high dose in this study was lethal to approx. 20% of both sexes of rats

14-week mice: (15/sex/dose). No change in ALT

1-year rat: (30 /sex/dose). No ALT, bilirubin, or liver histopathology. No hemorrhages cited even at high ulcerogenic dosages.

2-year rat tumorigenicity: (30 /sex/dose). : No excess liver histopathology or hemorrhagic deaths cited even at high (ulcerogenic) dosage. Clin. chem. not monitored.

2-year mouse tumorigenicity: (30 /sex/dose): No serum ALT, bilirubin, hepatic histology, or hemorrhagic deaths cited even at the ulcerogenic high dose.

DOG:

1-mo. dog (4/sex/dose): Tested at up to 125 mg/Kg, affording 50X human plasma Cmax. A transient doubling of ALT in one high-dose dog , but stable AST, bilirubin , and albumin in that dog, and no liver histopathology (his blood level was ca. 50X human ther. level) -

3-mo. dog (5/sex/dose): Tested at up to 50 X human Cmax. No change in ALT, AST, bilirubin, or liver histology. Normal ALT values contrast with the positive findings noted below in the 12-month study.

12-mo. dog (8/sex/dose): Losartan was tested at up to 50 X human Cmax. Dosages were 5, 25, and 125 mg/Kg p.o. with 4 dogs/sex/dose being sacrificed at 6-months and the remainder continuing on treatment for an additional 6 months.

The trajectory of serum ALT values, including that of 2 dogs sacrificed, as scheduled, at 27 weeks, is shown in Sponsor's table :

TABLE 1281
INDIVIDUAL SERUM ALT (U/L) VALUES, STUDY #90-028-0

Dose mg/kg/day	Pretest -1 week	Drug week					
		4	12	17	25	39	51
25/Male	28	34	73*	83*	99*	-	-
125/Female	36	41	46	49*	167*	86*	199*
125/Female	27	83*	91*	25	37	-	-
125/Male	31	26	43	32	32	49*	46*

* Values outside 95% limits for 3 year control values
-- Sacrificed at interim necropsy

In the course of the study, there were increases in serum ALT values in 4 treated dogs: one mid-dose male dog, one high-dose male, and two high-dose female dogs. The magnitude of the ALT elevation is not obviously dose or time dependent, and is stated as not involving any hepatic histopathology. Positive ALT findings contrast with the absence of findings at comparable intervals and dosages in the 3-mo. study. Although elevations were observed within 4 to 12 weeks in 2 of the 4 presenting dogs of this 1-year study, it is noted that none of the dogs in the 3-month study had elevated ALT levels.

Intravenous studies:

16-day rat (15/sex/dose): At up to 9 mg/Kg/day i.v., no difference in mean ALT or AST vs. concurrent control, or excess liver histopathology.

17 day dog (4/sex/dose): At up to 9 mg/Kg/day i.v., no difference in mean ALT or AST vs. concurrent control, or excess liver histopathology.

IRBESARTAN:

Chronic oral studies:

26-week rat: At up to 1000 mg/Kg (300-1000X efficacious dose), mean serum bilirubin ca. 50% greater than concurrent control at wk. 13 but not 26. No ALT rise, or excess liver histopathology cited.

2-year rat: At 2000 mg/Kg daily in females, AP, ALT and AST were elevated, but no excess liver histopathology even at this maximum tolerated dose.

2-year mouse: No liver histopathology at up to 1000 mg/Kg, an approx. maximum tolerated dosage. (clin. chem. not monitored).

1-year monkey: At up to 500 mg/Kg daily (500 - 1500 X efficacious dose), no clin. chem. or histologic evidence of hepatotoxicity.

cc:

Orig.

HFD-110

HFD-110/Project Manager

HFD-110/ADeFelice

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

SEP - 1 1998

DATE: Tuesday, September 01, 1998

TO: NDA 20-850 File

FROM: Carl J. Berninger, Ph.D., Chemist

SUBJECT: Dosage Issue - Scoring Versus Tablet - Telmisartan

Boehringer Ingelheim has requested registration for 40 and 80 mg tablets, however there is medical need for the 20 and perhaps the 10 mg tablet. The document in the approvable package listing changes in the insert has a 20 mg tablet included. (See approvable memo from Dr. Lipicky dated August 25, 1998).

The decorative score on the 40 mg tablet, which might have provided the 20 mg dosage, is not functional according to the firm.

The use of the scored tablet to provide another strength is problematic because the form of the drug substance, the sodium salt, used in the tablet is hygroscopic. Further, the approved packaging properly states that: "Tablets should not be removed from blisters until immediately prior to administration".

We certainly support the added tablet strengths, but do not feel a tablet score is a viable option for this particular drug product. The firm should be encouraged to develop additional lower strength tablets.

Copies:

Original NDA
HFD-110 Division File
HFD-110 A. Karkowsky
HFD-110 R. Lipicky
✓ HFD-110 K. Bongiovanni
HFD-810 J. Simmons
K. Srinivasachar, TL

/S/

Carl J. Berninger, Ph.D., Chemist

/S/
9-1-98