Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, MD

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting for June 15, 2005.

On June 15, 2005, the committee discussed class labeling of antihypertensive drugs based on the proximity of their data to outcome trials.

These summary minutes for the June 15, 2005 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on June 27, 2005.

I certify that I attended the June 15, 2005 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Groupe, R.N., B.S.N.
Executive Secretary

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Steven E. Nissen, M.D.
Chair

Quick Minutes
Cardiovascular and Renal Drugs Advisory Committee Meeting
June 15, 2005

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder05.html#cardiovascularRenal.
Slides of the meeting will be available at least 2 days after the meeting.
All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (voting):
Steven Nissen, MD (Committee Chair)
Blasé Carabello, MD
Susanna Cunningham, PhD
William Hiatt, MD
Frederick Kaskel MD, PhD
Thomas Pickering, MD, DPhil
Ronald Portman, MD
John Teerlink, MD

Cardiovascular and Renal Drugs Advisory Committee Consultants (voting):
Jonathan Sackner-Bernstein, MD
Thomas Fleming, PhD
Henry Black, MD
Michael Proschan, PhD

Patient Representative (voting):
Joseph J. Knapka, PhD

Anesthetic and Life Support Drugs Advisory Committee Industry Representative (non-voting):
Charles H. McLeskey, MD

Guest Speakers:
Stephen MacMahon, MD
Jay Cohn, MD

Cardio-Renal Advisory Committee Members Absent:
Beverly Lorell, MD
David Demets, PhD
Lynn L. Warner Stevenson, MD
John F. Neylan, MD

FDA Participants:
Robert Temple, MD
Norman Stockbridge, MD

Executive Secretary:
Cathy A. Groupe, RN, BSN

Open Public Hearing Speakers:
Charles Pamplin, MD – King Pharmaceuticals

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The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 15, 2005, at the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Steven Nissen, M.D. (Committee chair); the conflict of interest statement was read into the record by Cathy Groupe, RN, BSN (Executive Secretary). There were approximately 75 persons in attendance. There was one speaker for the Open Public Hearing sessions.

Issue: The committee discussed class labeling of antihypertensive drugs based on the proximity of their data to outcome trials .

Quick Minutes
Cardiovascular and Renal Drugs Advisory Committee Meeting
June 15, 2005

The agenda was as follows:

Call to Order and Introductions	**Steven E. Nissen, M.D.** Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	**LT Cathy Groupe, B.S.N.** Executive Secretary Cardiovascular and Renal Drugs Advisory Committee
Welcome Recognition of Retiring Cardiovascular and Renal Drugs Advisory Committee members	**Norman Stockbridge, M.D.** (Acting) Director Division of Cardiovascular and Renal Drug Products FDA Center for Drug Evaluation and Research

FDA Review Division Presentation:

Introduction	**Robert J. Temple, M.D.** (Acting) Director Office of Drug Evaluation I FDA Center for Drug Evaluation and Research
Applicable Outcomes Claims For Antihypertensive Drugs	**Stephen W. MacMahon, B.Sc., Ph.D., M.P.H., F.A.C.C**. Principal Director Professor of Cardiovascular Medicine and Epidemiology The George Institute for International Health The University of Sydney
Differences in Outcomes Claims For Different Drug Classes	**Stephen W. MacMahon, B.Sc., Ph.D., M.P.H., F.A.C.C**.
Deciding Whom to Treat For Hypertension	**Jay N. Cohn, M.D**. Professor of Medicine and Director Rasmussen Center for Cardiovascular Disease Prevention University of Minnesota
When to Initiate Successive Antihypertensive Drugs	**Henry R. Black, M.D.** Chairman and Associate Vice President for Research Rush University Medical Center
Can One Sustain an Outcome Claim Based on an Active Controlled Study? Introduction	**Pfizer, Inc.** **Lance Berman, MD** Medical Director – U.S. Team Leader Pfizer, Inc.
Methodology and Analysis [Overview]	**Michael Gaffney, Ph.D.** Senior Director – Statistical Research and Consulting Pfizer, Inc.

Quick Minutes
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Agenda (Continued):

	Break
Does the Pattern of Blood Pressure Effects During a Day Matter?	**Thomas G. Pickering, M.D., Ph.D., F.R.C.P.** Director – Integrative and Behavioral Cardiology Program The Zena and Michael A. Wiener Cardiovascular Institute Mount Sinai Medical Center
Does the Benefit Associated with Treating Hypertension Apply to Children?	**Ronald J. Portman, M.D.** Professor of Pediatrics and Director of the Division Pediatric Nephrology and Hypertension University of Texas – Houston Medical School
	Committee Discussion
	Lunch
	Open Public Hearing
	Committee Discussion and Questions
	Break
	Adjournment

Questions to the Committee:

The Advisory Committee is asked to opine on class labeling for antihypertensive drugs. The Agency requested of the committee, a complete and robust discussion of the issues outlined in the 'Questions to the Committee'. Although the committee participants were encouraged to use these questions to help structure their discussion, the Agency did not request a vote on any of the questions presented. While certain key points are identified below, in the context of the open dialogue amongst the committee members, please refer to the transcripts for a complete and detailed account of the committee discussion.

Antihypertensive drugs, with few exceptions, have no outcome claim in their labeling. This is inconsistent with their approval based on the surrogate of blood pressure and with the advice given to practitioners. This meeting is to consider how, if at all, labeling should address the relationship between blood pressure and outcome.

1. Since outcome data come from studies of drug regimens and not single agents, what can one determine about the effects of individual agents or drug classes? Is it appropriate to generalize any observed benefits to all agents or classes, or should one conclude that one does not know enough about most single agents?

The committee agreed that not having outcome data available in the label was an important issue; knowledge about antihypertensives is extensive but there is little said in the labels. Members agreed that an opportunity exists to refocus the attention of the practitioner through education, continue to shape the pharmaceutical industry and address the therapeutic substitution problem that currently exists.

Members added that, while such initiatives are important, we should state what we know, with care not to overstate. Members agreed that lowering blood pressure is one of the best surrogates we currently have on outcomes but there is much we do not understand. Additionally, the committee cites that there is a need for safety and post marketing data to capture adverse outcomes of "unintended consequences".

The committee industry representative cautioned the committee that there may be a disincentive to the pharmaceutical industry and the scientific community, to engage in future clinical trials, depending on labeling changes considered.

Finally, the committee recommended that labeling statements not conflict with the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) and the American Diabetes Association, guidelines. ***(See transcripts for detailed discussion)***

2. A variety of benefits are associated with drugs that reduce blood pressure.
    - Reduction in the risk of ischemic stroke
    - Reduction in the risk of hemorrhagic stroke
    - Reduction in the risk of myocardial infarction
    - Reduction in the risk of cardiovascular mortality
    - Reduction in the risk of mortality from any cause
    - Reduction in the risk of other manifestations of coronary disease
    - Reduction in the risk of end-stage renal disease
    - Other

    2.1. Which items in the above list…

        2.1.1. …are attributable to blood pressure reduction—and would be expected of any drug that lowers blood pressure?

        2.1.2. …apply to most antihypertensive agents, with clear exceptions noted?

        2.1.3. …are benefits associated with specific classes of drugs?

After considerable discussion, the committee agreed that stroke, myocardial infarction and cardiovascular mortality are most clearly attributable to blood pressure reduction, and to a lesser degree, renal disease. The committee thought that a new drug seeking an indication for hypertension should not automatically receive all of the above indications, however, it would be "generally expected" for a drug to affect these diseases if it lowered blood pressure. With regard to class effect of drugs, the committee was able to identify a class effect with some drugs and determined that more data is needed with regards to other drugs. ***(See transcripts for detailed discussions).***

2.2. For the purposes of this discussion, are ACE inhibitors and angiotensin receptor antagonists the same class?

The committee discussed this issue, in the context of Dr. MacMahon's presentation, citing a 5-fold difference identified comparing ACE Inhibitors and ARB drugs, with no bradykinin effect present in ARBs. There was general agreement that it is a mistake to say that these are the same class of drugs and they should not be treated the same.

2.3. Are the magnitudes of the benefits the same among members of a class?

The committee pointed out some of the major differences between classes and agreed that the benefits are not the same among members of a class.

2.4. Are there other important distinctions among drugs in a class?

The committee deferred to earlier conversation on this issue, citing important distinctions among drugs in a class depends on whether the data can make a claim.

2.5. How are the benefits affected by age, gender, diabetes, or other risk factors?

While providing considerable discussion on this issue, the committee decided that these decisions are best served by the writers of the guidelines affecting hypertension and diabetes. Specifics should not be included in the label but patients and physicians should be directed to follow the standard guidelines. ***(See transcripts for detailed discussion)***

3. Most modern labels for non-antihypertensive drugs describe the supporting data under Clinical Trials and then cite the specific benefits of treatment in the Indications.
   3.1. Should labels for antihypertensive drugs follow this pattern?

Discussion included the challenge of where on the label this would be placed; the 'Indication' section was suggested as a possibility. The committee discussed language provided in the four examples included in the Agency background document for this meeting.

3.2. Should labeling distinguish drugs on the basis of whether the specific agent or the specific class contributed to the available outcome data?

The consensus of the committee was that labeling should distinguish drugs on the basis of whether the specific agent or class contributed to the available outcome data. ***(See transcripts for detailed discussion***

4. Various draft statements have been included in the background package. Rather than trying to edit them, please identify which of the following should be elements of labeling?
   4.1. The specific benefits thought to apply

The committee was in complete agreement about inclusion of specific benefits in the labeling.

4.2. The magnitude of those benefits

Some members thought it risky to make this claim, citing that it may depend on the specific risk – high risk versus low risk (i.e. 4mm blood pressure reduction). Many members thought supportive generalities based on what we know, only, should be included. There was additional discussion about the comparison of epidemiological study results with clinical trials results and how they differ in terms of decisions need to be made about labeling. ***(See transcripts for detailed discussion)***

4.3. The relationship between blood pressure and risk

The committee consensus was that this is epidemiologic data and should be left to guideline writers.

4.4. The interaction among cardiovascular risk factors

The committee agreed that there is a need to focus on these risks co-existing but there was uncertainty about inclusion in the label. Again, they emphasized that 'we shouldn't say more than we know.'

4.5. The specific drugs with a primary role in outcome trials

The agency clarified that this would mean for any drug label, naming the source of the outcome data/naming the drug in the trial. Many members agreed that more compelling evidence could be illustrated in a MacMahon-type data meta-analysis.

4.6. The drug classes with a primary role in outcome trials

There was somewhat more consensus amongst the committee of accepting this in the labeling.

4.7. Whether this specific drug has outcome data

Discussion included clarification about specific outcome data being included in the label, along with specifically indicating when there is not outcome data. There was considerable concern expressed by the committee Industry

Representative, that this may appear punitive to industry and that performing a study to prove such may not be feasible.

4.8. Whether the specific drug's class has outcome data

Many members support this statement and emphasized that it may be useful as new classes of antihypertensives come along. There should be a distinction between classes we know something about and those we do not. This information recognizes the levels of extrapolation based on outcome data and reflects that truth, along with the level of its reliability. *(See transcripts for detailed discussion).*

4.9. Factors to consider in choosing a drug class
- 4.9.1. Other established claims in heart failure or renal disease
- 4.9.2. Risk of hypokalemia
- 4.9.3. Other considerations

Some members expressed concern that, while these factors may be important in labeling, too much information may dilute the overall effectiveness and create a disincentive for practitioners to read the data. *(See transcripts for detailed discussion).*

4.10. Other elements of a cardiovascular risk reduction program (control lipids, stop smoking, lose weight, get exercise, etc.)

The committee agreed that it is important, to a certain extent, to recognize risk factors and how they interact. *(See transcripts for detailed discussion).*

4.11. The importance of blood pressure control throughout the inter-dosing interval

Many committee members felt there is not enough known about inter-dosing [limited outcome data] to make such claims, although this is important and relevant to clinicians. There was additional discussion about circadian rhythm differences amongst blood pressure medications. (See transcripts for detailed discussion).

4.12. The importance of blood pressure control at various times of day.
4.13. Other elements

There were few additional comments on these factors. *(See transcripts for detailed discussion)*

5. Labeling for lipid-lowering drugs is quite explicit in recommending an approach to treatment—when to initiate treatment, what the goals are, etc. Currently, labels for antihypertensive drugs do not say whom or how to treat for hypertension. How should physicians be instructed to assess blood pressure with respect to…
   5.1. …what to measure (systolic, diastolic, pulse pressure)?

The committee thought that information regarding what to measure can be obtained through other sources and not necessarily be placed in the label.

5.2. …how many times to make the measurement during a visit?

Some members recognized that these readings are often times inconsistent and the question was raised, as to whether we can believe these blood pressure readings, but adding that taking a single measure does not provide the complete picture. Members agree, though, that despite this clinical inconsistency, it is not a problem that can be remedied in a label.

5.3. …what period of time or over how many visits?
5.4. …what time of day to make measurements?
5.5. …timing with respect to the last dose?

The committee had minimal discussion about these timing considerations.

5.6. …the risk of developing a cardiovascular event over the next few years?

There was discussion of the Framingham Risk Assessment and the difficulty in getting people to implement.

5.7. …what goals to seek? Are the goals lower in high-risk patients?

The committee agreed that this is a guideline issue.

5.8. …how closely to monitor during and after up-titration

There is concern that multiple drugs may be necessary to achieve control – Titrating up too fast could be a problem. Suggestions included titrating up in one week intervals and link a statement about the possible need for multiple drugs, in order to achieve control.

5.9. …which drug classes are appropriate for initial therapy and which should be used second or later?

The committee agrees that the most conclusive data suggests starting with diuretics and this is also cited in the guidelines. There was discussion about the challenge in labeling any of the three drugs included in ALLHAT. At the end of the day, all three drugs are indistinguishable and none should be first line preference. It was added that a meta analysis is difficult to duplicate. Members comment that they are comfortable not trying to declare any particular class superior. Many committee members felt that, with the exception of when we know there is a real difference, this should be left to the guideline writers, rather than labeling.

5.10. …when to add a second drug? Note that labeling currently usually says to start a second drug only after a single drug has proven inadequate at its highest tolerated dose.

The committee discussed the importance of looking at the methods used to achieve this and these methods cannot substitute for clinical judgment – some patients get dose limiting toxicity at lower doses than others while others tolerate a moderate dose of an ace inhibitor. Because clinicians need to make decisions such as these, depending upon the speed with which it is considered necessary to achieve blood pressure control, it would be difficult to convey this in labeling. This information will not apply equally, to every drug. *(See transcripts for detailed discussion)*.

6. How, if at all, and in which labels, should one describe the results of an active-controlled study in which the various regimens were not distinguished for their primary end points?

Dr. Stockbridge added clarification to this question's purpose, an example: Which labels should have some mention of the results of ALLHAT? If one has a high confidence interval/precise estimates, then the results should be described in the label. The committee agreed that, in a well sized study such as ALLHAT, contributing to a more global understanding, information belongs in the label. If there was considerable insight about relative efficacy on clinical endpoints (from a trial such as ALLHAT), giving substantive information about the efficacy of a specific product, a description of those results should be seen in the label.

Members recognized that, given the large trial size of ALLHAT, drugs involved in the trial deserve something in their label. Data in this trial, members said, provides some of the best data clinicians are going to get. They point out, however, that there is a difference between a large trial that shows significant differences and smaller trials that lack the power to show significance and we should take care, not to overstate the claims made. *(See transcripts for detailed discussion)*.

7. If there are differences among drug classes, should the classes with fewer or less well established claims get labeled as second-line?

The Agency was satisfied that answers to this question were adequately addressed throughout the meeting and did not require additional discussion. *(See transcripts for detailed discussion).*

8. Consider the ramifications of revised labeling on…
   8.1. …pediatric studies. The Agency can require studies of antihypertensive drugs in children prior to approval for use in adults. The Agency can also promote studies in children by granting additional exclusivity for assessing the effects of antihypertensive drugs in children.
      8.1.1. Should it do either of these?
      8.1.2. Is study of effects on blood pressure adequate?

The committee consensus was, following the theme of Dr. Portman's earlier presentation, that the Agency should not require studies of antihypertensive drugs in children prior to approval for use in adults. Members felt, however, that the Agency should promote studies in children by granting additional exclusivity for assessing the effects of antihypertensive drugs in children. They added that information is needed other than blood pressure as an outcome such as biomarkers of LDH, microalbuminuria and also areas such as physical growth/development. In discussing the challenge of placebo trials in children, there was some disagreement about the inability to design a study effectively, with some comfort level, of 1-3 month treatment with a placebo, as opposed to randomized withdrawal.

Additionally, a suggestion was made to add transition studies (Pediatric-Teen-Adult), where additional outcome data would become available in 5 years, opening up an area of study for practitioners. *(See transcripts for detailed discussion).*

   8.2. …a drug for another indication also happens to reduce or to increase blood pressure. Should class labeling extend to it? Does it matter…
      8.2.1. …if the drug is for intermittent or short-term use?
      8.2.2. …if the effects on blood pressure are not sustained through the interdosing interval?
      8.2.3. …how large is the effect on blood pressure?

Discussion included identification of certain non-cardiovascular drugs and their effect on the central nervous system, and subsequent disagreement about how important those blood pressure changes are, questioning whether these observations should lead to further long term studies. Additionally, members point out that the answer to this question is affected by whether the drug increases or decreases the blood pressure. The Chair encouraged committee discussion of the difference in the two directions.

The committee agreed that it is difficult to extrapolate this data (increase versus decrease of blood pressure) due to the lack of outcome data. Though the issue is relevant, concern was expressed about setting a regulatory standard for labeling, especially without direct evidence. Members further identified the challenge in teasing out relative risk increase and absolute risk increase due to the fact that many of these drugs are being used in less 'at risk' patients, lowering the baseline risk. The suggestion was made, in this context, to add wording that emphasized the 'additional increase in blood pressure' that can add to risk, in the presence of other risk factors related to hypertension, citing birth control pills as an example.

Members provided summary that this information should be noted as part of the labeling but such information should not be put in the clinical trials or indications section. The committee added that, though this information is relevant, it may be a challenge to provide language, as such, in a label, without 'leaping' to conclusions that are not warranted. Members suggest that the bigger the magnitude and the longer term the use is contemplated for the drug, the more likely it should appear in a warning. *(See transcript for detailed discussion)*

The meeting adjourned at approximately 6:40 PM.

(See transcript for detailed discussion)