Food and Drug Administration
Center for Drug Evaluation and Research

Best Western Washington Gateway Hotel, 1251 W. Montgomery Avenue, Rockville, Maryland

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting on April 18, 2007.

On April 18, 2007, the committee discussed supplemental new drug application (NDA 20-758/S-037), Avalide (irbesartan plus hydrochlorothiazide), Bristol-Myers Squibb Company. The sponsor is seeking approval for first-line use in severely hypertensive patients. The Advisory Committee will be asked to consider what constitutes adequate data to support such a claim and how the information can be most usefully displayed in labeling.

These summary minutes for the April 18, 2007 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on Friday, April 20, 2007.

I certify that I attended the April 18, 2007 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/S/_____	_____/S/_____ 4/20/2007
Cathy A. Groupe Miller, M.P.H., R.N.	Robert A. Harrington, M.D. Date
Designated Federal Official	(Acting) Chair

A verbatim transcript will be available in approximately two weeks and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder07.htm#CardiovascularRenal

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 18, 2007 at the Best Western Washington Gateway Hotel, Rockville, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and the sponsor (BMS). The meeting was called to order by Robert A. Harrington, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Cathy Groupe Miller, M.P.H. (Designated Federal Official). There were approximately 100 persons in attendance. There was one speaker for the Open Public Hearing sessions.

Issue: The committee discussed supplemental new drug application (NDA 20-758/S-037), Avalide (irbesartan plus hydrochlorothiazide), Bristol-Myers Squibb Company. The sponsor is seeking approval for first-line use in severely hypertensive patients. The Advisory Committee will be asked to consider what constitutes adequate data to support such a claim and how the information can be most usefully displayed in labeling.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
Steven D. Findlay, M.P.H.; Robert A. Harrington, M.D., F.A.C.C.; Abraham Michael Lincoff, M.D., F.A.C.C.; Emil P. Paganini, M.D., F.A.C.P., F.R.C.P.; Lynn L. Warner Stevenson, M.D.; John R. Teerlink, M.D.

Special Government Employee Consultants (Voting):
Jason Hsu, Ph.D.

Non-voting Participants:
Steven W. Ryder, M.D. (Industry Representative)

Cardiovascular and Renal Drugs Advisory Committee Members Not Present:
William R. Hiatt, M.D.; John M. Flack, M.D., M.P.H.; Ronald J. Portman, M.D.; David L. DeMets, Ph.D.; Frederick J. Kaskel, M.D., Ph.D.; John Neylan, M.D. (Industry Representative)

FDA Participants (Non-Voting):
Robert Temple, M.D.
Norman Stockbridge, Ph.D., M.D.

Designated Federal Official:
Cathy A. Groupe Miller, M.P.H., R.N.

Open Public Hearing Speaker:
Thomas Giles, M.D.

The agenda was as follows:

Call to Order and Introductions	**Robert A. Harrington, M.D., F.A.C.C.** (Acting) Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	**LCDR Cathy Groupe, M.P.H., R.N.** Designated Federal Official Cardiovascular and Renal Drugs Advisory Committee

Introduction and Background	**Norman Stockbridge, M.D., Ph.D.** Director, Division of Cardiovascular and Renal Products FDA Center for Drug Evaluation and Research
	Open Public Hearing

Sponsor Presentation – Bristol-Myer Squibb Company:

Introduction	Anthony Waclawski, Ph.D. Vice President, Global Regulatory Sciences Bristol-Myers Squibb
Unmet Need in Severe Hypertension	William Weintraub, M.D. John H. Ammon Chair of Cardiology and Director Christiana Center for Outcomes Research
Discussion of Avalide Registrational Program	Pablo Lapuerta, M.D. Executive Director, Global Medical Affairs Bristol-Myers Squibb
Benefit/Risk Profile	Michael Weber, M.D. Professor of Medicine SUNY Downstate Medical Center College of Medicine
Conclusion	Anthony Waclawski, Ph.D.
	Questions from the Committee
	Break
	Committee Discussion
	Lunch
	Committee Discussion
	Questions to the Committee
	Adjournment

Questions to the Committee:

The Advisory Committee is asked to opine on the basis for granting first-line use to combination antihypertensives, and to apply the principles to AVALIDE (irbesartan/HCTZ). For the most part, combination antihypertensive products, formulations of two or more drugs for hypertension, have been given an indication for second-line use, similar to what AVALIDE now has:

"INDICATIONS AND USAGE

> "AVALIDE (irbesartan-hydrochlorothiazide) Tablets is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION)."
>
> "DOSAGE AND ADMINISTRATION
> "To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.
> "The side effects (see WARNINGS) of irbesartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of irbesartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects."

Labeling also typically notes that one can substitute the combination for the individually titrated components or that one can switch to a dose of the combination from some dose of one component.

The general principle of this "stepped-care" approach was that someone should not accept the risk of "dose-independent" adverse events associated with a second drug until he had wrung what value was possible with the first drug.

Exceptions to recommending single-drug initial therapy are:

- Capozide (captopril/HCTZ) was approved for first-line therapy because it reduced the need to dose from two or three times per day to once a day.
- ZIAC (bisoprolol/HCTZ) earned a first-line claim through demonstration that one got better blood pressure reduction with low doses of the drugs in combination than one got with single agents at high doses, *and* had less of either individual agent's principal adverse effects.
- HYZAAR (losartan/HCTZ) earned a first-line claim by demonstrating that the combination was effective and well-tolerated in a patient population with extremely elevated blood pressures, very unlikely to reach a blood pressure goal on either drug alone and in a population where a delay of control was most likely to lead to adverse outcomes even during short periods of inadequate blood pressure control. By agreement with the Division, "very unlikely to reach goal" was defined as <10% reaching goal on monotherapy. For showing this, HYZAAR got a limited first-line indication: "This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients."

It was this latter pathway that was followed for AVALIDE (irbesartan/HCTZ). The study easily showed better blood pressure control on the combination than on monotherapy, and the combination regimen was well tolerated. However, irbesartan alone was effective in achieving goal in 33% of these subjects; thus, this population failed to meet the "very unlikely to reach goal" criterion.

The Division recognized that there were many problems with the current basis for a achieving first-line claim, and invited SPONSOR to make a case for altering the paradigm. Among the issues are:

- The arbitrariness of the blood pressure goals.
- Failure to take into account different goals that might be appropriate based on risk factors (e.g., diabetes).
- The arbitrariness of the "very unlikely" criterion.
- The actual risks of "dose-independent" adverse events.
- The ambiguity in what constitutes tolerability to starting two drugs.
- The fact that most hypertensive patients are on multiple drugs.

- The fact that many people need multiple drugs at the time of initiating treatment.
- However the inclusion criteria are defined, one can always identify subsets of subjects "unlikely" to reach goal.

For drug combinations with no special ZIAC-like claim, the Cardio-Renal Advisory Committee is asked to consider the following alternatives to obtain a first-line claim:

- Identify a population with a demonstrably low rate of adequate response to single agents and show that the response rate on the combination is improved with little adverse effect on tolerability ("Hyzaar method").
- Characterize the tolerability and likelihood of achieving various blood pressure goals as a function of baseline blood pressure, using the factorial trial intended to show that both components contribute to the combination's antihypertensive effects or a special study in severe hypertension, as was done with Avalide ("Full Disclosure method").

In considering whether one of these alternatives is more medically and scientifically sound, in general or in specific cases, the following questions are posed:

1. The vast majority of the studies demonstrating the benefit of antihypertensive drugs in the prevention of cardiovascular events incorporated a stepped-therapy approach using single drugs at low doses with titration to the maximum tolerated dose prior to adding a second and third medication. How does that affect your thinking about the preferred approach to a claim for first-line use for combinations?

There was general agreement amongst the committee that reducing BP with anti-hypertensive drugs improves cardiovascular outcomes (reference last year's committee meeting). The committee was comfortable with notion that reducing blood pressure with combination therapy likely will result in improved cardiovascular outcomes, but also discussion the need for careful evaluation of individual components of combination for specific blood pressure effects and risks.

(See transcripts for detailed discussion)

2. Please comment on the following factors that might commend initial or early use of antihypertensive combinations:

- Treatment goals change. While a study may be designed around a specific goal, the practicing physician may be considering different goals.
- Even at the time of initial diagnosis, most patients require more than one antihypertensive product to control blood pressure.
- Lower blood pressure, at least until hypotension becomes symptomatic, is associated with a lower risk of cardiovascular events.
- Antihypertensive drugs are, for the most part, very well tolerated.
- Some drugs (e.g., ACE inhibitors and ARBs) have minimal dose-dependent and dose-independent adverse effects.
- Are there other factors to consider?

The committee generally agreed that all these factors are important considerations. Some commented that we should align the 'message' (i.e. JNC7 recommendations) in the labeling. They recognized that getting to some sort of blood pressure goal is the critical issue and realize that a majority of patients will take more than one drug to get there. There was some additional discussion about issues related to considerations among patient subsets (age and race) and co-morbid conditions (chronic kidney disease, congestive heart failure, coronary artery disease and diabetes mellitus).

(See transcripts for detailed discussion)

3. What is the role of a study targeting a severely hypertensive population, like the one done with Avalide?
    - Is it necessary? Would the usual factorial study have been sufficient?
    - In what population would it be most appropriate to assess the safety consequences of initiating therapy with more than one drug? Should it, for instance, be enriched in elderly patients, who, one might expect, would be less tolerant of excessive pharmacological effect?

Studies with Avalide were acknowledged by the committee to be well done and helpful in sorting through the issues. There was also acknowledgement that targeting the extreme of blood pressure, while possible in studies, may be increasingly difficult. The committee commented that these studies need to include active control as was done with Avalide. Broader studies (larger range of blood pressure) can be informative, including 'moderate' hypertension. The committee commented that they would like more information in elderly, particularly those > 70 or 75 years to explore risks more fully. Additional comments from the committee included pointing out that the duration of the study is not optimal for looking at safety data.

(See transcripts for detailed discussion)

4. What findings would support a more cautious approach to combination therapy?
    - Symptomatic hypotension or syncope
    - Hypokalemia
    - Are there other adverse consequences to consider?

The committee's comments included also considering 'worsening renal function' in supporting a more cautious approach to the combination therapy along with hypotension/syncope and hypokalemia..

Have such findings been adequately excluded for AVALIDE?

Taking all data into consideration, the committee felt that these adverse risks have been reasonably excluded for this specific combination. They emphasize that this point to the value of large, extensive experience with components of the combination.

(See transcripts for detailed discussion)

5. Demonstrating blood pressure effects in clinical trials requires many subjects, many replications, and carefully controlled conditions unlike clinical practice. Is there a value in terms of expected clinical outcomes to reducing the number of titration steps a physician is expected to make?

There was general consensus among the committee that there is value. They pointed out that this still step therapy but is a 'bigger' first step. The committee was impressed with Dr. Weber's presentation illustrating that getting earlier control of blood pressure may well translate into better longer term control.

(See transcripts for detailed discussion)

6. Is there a quantitative risk-benefit assessment that provides credible support for the initial use of AVALIDE? If so, should initial use be limited to a specific population?

The committee felt that the data, (blood pressure lowering balanced against risks), seem consistent across range of blood pressures studied with Avalide. The assessment requires a number of extrapolations and does not necessarily help pick out a specific population. Limitations include small group of elderly and little comorbidities. The committee would not recommend limiting to a specific population.

(See transcripts for detailed discussion)

7. On the basis of available data, should AVALIDE be approved for first-line use? Please vote. If you do not believe the data are adequate to support approval, describe what additional data would be needed.

YES: 7 ***NO: 0***

(See transcripts for detailed discussion)

8. If AVALIDE were approved for first-line use, should it have an INDICATION with constraints similar to those for HYZAAR or is it possible to give better advice? A major element of better advice is a better description of the expectations of using irbesartan alone and in combination.

    - The placebo effect observed in controlled clinical trials has at least two components. Please comment on whether either component is relevant to clinical practice.
        - Regression to the mean
        - Accommodation to the clinical setting
    - Should the description in the label be based on placebo-subtracted data?
    - Should the description take into consideration the likelihood of getting to goal on each component alone, or just irbesartan?
    - Did subgroup analyses show other factors—like age or race—that should be considered?
    - Should the description take into consideration the dose of each component, or just a dosing strategy?
    - Should the description focus on systolic pressure, diastolic pressure, or both simultaneously?
    - Please identify any data presentation you saw that you felt best communicated the necessary information in a manner understandable by a practicing physician.

The committee agreed that regression to the mean and accommodation to the clinical setting are relevant and help explain the effects. The committee agreed there is a need to present the placebo corrected data. They agreed that the data are generally consistent and benefit appeared to be equivalent regardless of race, but subgroups need to be interpreted cautiously. The committee favored simply informing about the dosing strategy used in the study. The committee recommended that description focus on both systolic and diastolic pressures and recommend a presentation of the percentage who achieved goals (JNC7) in different groups. Most of the committee favored the 2-dimensional graph rather than the 3-dimensional (i.e. Sponsor slide 39, 176: Influence of Baseline Blood Pressure.

    - Please comment on wording for a possible INDICATION statement. Some versions to consider are:
        - Current HYZAAR: This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.
        - Alternative proposal: AVALIDE is also indicated as initial treatment when hypertension is sufficiently severe that rapid control of blood pressure (within days to weeks) is of primary clinical importance
        - Sponsor's proposal: AVALIDE is also indicated as initial treatment for severe hypertension.

The committee favored the Agency's "full disclosure" of data and allowing clinicians to make decisions. The committee was split 3/3 in favor of Alternative proposal #2 versus the Sponsor's proposal #3 with recommendations for changes to the language in the these proposals as follows:

- *Alternative proposal:*

-AVALIDE is also indicated as initial treatment when hypertension is sufficiently severe that control of blood pressure is unlikely to be achieved with a single drug (refer to Figures that would help with this assessment)

-Suggestion not to refer to specific guidelines but rather a functional definition "unlikely to achieve desired goal"… or "sufficient likelihood of failing…"

-Change 'severe' to 'moderate to severe'

- *Sponsor's proposal:*

-Add language such as "unlikely to achieve goal on a single therapy

-Add 'moderate to severe'

There as additional discussion about whether statements such as these should also be included in monotherapy labels indicating when one would want to start with two drugs: "most patients do not get to goal on a single agent..." Suggestions were made to add in general statements about outcomes.

The committee adjourned at approximately 3:30 P.M.

(See transcript for detailed discussion)