Questions

Irbesartan/HCTZ
April 18, 2007

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory 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?
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?

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

    Have such findings been adequately excluded for AVALIDE?
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?
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?
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.
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.
- 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.