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Minutes: July 18 and 19, 2002
Cardiovascular and Renal Drugs Advisory Committee
Holiday Inn, Bethesda, MD

Issues:
July 18th, A.M. Session: ATACAND (candesartan cilexetil) Tablets, NDA 20-838/S015, AstraZeneca LP, labeling change (see below)
July 18th, P.M. Session: pravastatin sodium/aspirin combination product, NDA 21-387, Bristol-Myers Squibb Company, new product (see below)
July 19th Session: VANLEV (omapatrilat), NDA 21-188, Bristol-Myers Squibb Company, new product (see below)

Prior to the meeting, the members and the invited guest had been provided the background material from the FDA and from the sponsors. On both days, the meeting was called to order by Jeffrey Borer, M.D. (Committee chair); the conflict of interest statement was read into the record by Jayne Peterson (Acting Executive Secretary). On both days, there were approximately 200 persons in attendance. There were no speakers for any of the three Open Public Hearing sessions.

Attendance:
Cardio-Renal AC Members Present (July 18th): Jeffrey Borer, M.D (Chair), Susanna Cunningham, Ph.D. (Consumer Representative), Blasé Carabello, M.D., Steven Nissen, M.D., Paul Armstrong, M.D., Thomas Fleming, Ph.D., Michael Artman, M.D., Beverly Lorell, M.D., and JoAnn Lindenfeld, M.D.
(July 19th): Jeffrey Borer, M.D (Chair), Susanna Cunningham, Ph.D. (Consumer Representative), Blasé Carabello, M.D., Steven Nissen, M.D., Paul Armstrong, M.D., Thomas Fleming, Ph.D., Michael Artman, M.D.,

Cardio-Renal AC Guest (July 18th and 19th): Thomas Pickering, M.D. (hypertension specialist)

Cardio-Renal AC Members Absent (July 18th): Allen Hirsch, M.D. **(July 19th)** Allen Hirsch, M.D., Beverly Lorell, M.D., JoAnn Lindenfeld, M.D.

FDA Participants (July 18th and 19th): Douglas Throckmorton, M.D., Robert Temple, M.D.

July 18th, A.M. Sesson:

NDA 20-838/S015, ATACAND® (candesartan cilexetil) Tablets,
AstraZeneca LP, for a proposed claim of comparative efficacy of candesartan cilexetil and losartan in hypertension.

Sponsor's Presentation

Regulatory Introduction Cindy M. Lancaster, MS, MBA, JD

	AstraZeneca
Comparison of the Antihypertensive Efficacy of Candesartan Cilexetil and Losartan	Vasilios Papademetriou, MD, DSc, FACC, Georgetown University
Epidemiologic and Clinical Significance of Incremental Changes in Blood Pressure	William B. Kannell, MD, MPH, FACP, FACC Boston University School of Medicine
Summary	Cindy M. Lancaster, MS, MBA, JD

Questions:

The Cardio-Renal Advisory Committee is asked to opine on the relative antihypertensive efficacy of a regimen containing candesartan and a regimen containing losartan. Specific guidance is sought on how to describe any relevant differences in labeling and on the adequacy of the advice that we have given sponsors to guide future development programs. There is little published experience or relevant guidance, but this issue is briefly addressed in ICH guidance E-10 (*Choice of Control Groups and Related Issues in Clinical Trials*).

In the past, the Agency has told sponsors that demonstrating superiority to another antihypertensive medication on blood pressure lowering, when both were appropriately dosed, was a relevant clinical benefit, and that such a claim required the following data:
1) Evaluation of the antihypertensive effects of the respective drugs at the highest approved doses. If the comparison was not done with the approved product, bioequivalence of the study formulation and the approved product must be demonstrated. Our recommendation has been that this evaluation should include at least two forced-titration trials to adequately assess the drug's relative antihypertensive effects. We have also said that, unless a placebo group is included in the trials, no information about absolute antihypertensive efficacy can be inferred, only comparative antihypertensive effect.
2) Data comparing the safety of the two agents, providing evidence that the 'superior' agent is not inferior with respect to safety.

The present sponsor has provided data from three randomized trials, including two forced-titration trials. These were conducted comparing candesartan force-titrated to a dose of 32 mg per day and losartan force-titrated to a dose of 100 mg per day. The Agency and the sponsor agree on the numerical results of the efficacy analyses for the three trials. At the end of 8 weeks, candesartan 32 mg reduced blood pressure by around 3/2 mmHg more at trough than did losartan 100 mg, when both were given once per day.

1. Which of the following are necessary or sufficient to establish a claim of relative superiority for an antihypertensive?
   1.1. Diastolic pressure at trough?
   1.2. Systolic pressure at trough?
   1.3. Diastolic pressure throughout the dosing interval?
   1.4. Systolic pressure throughout the dosing interval?
   1.5. 24-hour mean ABPM?
   1.6. Other measures of effectiveness?

   The Committee considered Items 1.1 through 1.4 essential; most also stated that 1.5 would be necessary. Other measurements discussed that the committee noted would provide helpful information were pulse pressure and effect on target organs.

2. The sponsor compared once-daily dosing for both products, although both products are labeled for once- or twice-daily dosing. Is a once-daily comparison a legitimate basis for a superiority claim?

   Yes, but the consensus of the committee was that the only valid superiority claim could be QD dosing of candasartan to QD dosing of losartan.

3. Which of the following are necessary or sufficient to establish a claim of relative superiority for a once-daily antihypertensive?
   3.1 Beating the comparator's highest approved once-daily dose?
   3.2 Beating the comparator's most effective approved regimen?
   3.3 Beating the comparator when it is dosed to its maximum effect, perhaps outside the approved dose range?
   3.4 Beating the comparator when used with other approved agents (e.g., diuretics, beta blockers)?
   3.5 Beating the comparator in special populations (e.g., blacks, elderly)?

   The committee's general consensus was that Item no.s 3.1, 3.2, 3.4 and 3.5 would be necessary/sufficient to establish a relative superiority claim.

4. Is it possible to claim superiority if…
   4.1.1. … the comparator has other outcome benefits not demonstrated by the test drug …
   4.1.2. … on clinical endpoints in hypertensive patients (*e.g.*, stroke reduction)?
   4.1.3. … in other populations (*e.g.*, heart failure, post-MI, diabetic nephropathy)?
   4.1.4. … the comparator has fewer potential pharmacokinetic interactions such as CYP 2D6 or CYP 3A4 inhibition?

   In general, the committee was in agreement that the tested product could claim superiority in lowering blood pressure, if so demonstrated. However, if the comparator drug has proven clinical endpoint data, the test product label must include label language spelling out a lack of demonstrated clinical endpoint effect.

5. In most cases, comparative data have not revealed differences between pharmacologically similar drugs. Should the Division encourage more comparative studies?
   The committee endorsed the idea.

6. Overall, candesartan reduced diastolic BP by around 2 mmHg more at trough than did losartan, an effect size that would be sufficient for approval if a drug were compared with placebo.
   6.1. Is this difference clinically meaningful for a comparison between two antihypertensives? ***Yes: 9 No:0***
   6.2. Are the comparative safety data submitted by the sponsor sufficient to show that the expected reduction in cardiovascular risk would not be offset by other risks of candesartan?
   Yes: 9 No: 0
   6.3 Would your answer regarding the need for comparative safety data be different if the two drugs were from different drug classes (e.g., calcium-channel blocker and diuretic)? *The majority of the committee commented that comparing effects across different drug classes would be difficult.*
   6.4 Is the comparison between candesartan and losartan *fair*, as defined by ICH E-10?
   Yes: 9 No: 0

7. Do you recommend approval of candesartan for superior antihypertensive efficacy when compared with losartan?

   Yes: 9 No: 0

If so, how should the findings of these trials be included in the approved labeling…
… of candesartan? *Complete and relevant study design and study result information should be provided.*
… of losartan? *Findings should not be required to be included.*
… of combination products containing candestartan or losartan? *Findings should not be required to be included.*

July 18th, P.M. Session

NDA 21-387, Pravastatin/Aspirin Combination Product, Bristol-Myers Squibb Company (BMS), proposed for long-term management to reduce the risk of cardiovascular events (death, nonfatal myocardial infarction, myocardial revascularization procedures, and ischemic stroke) in patients with clinically evident coronary heart disease.

Sponsor's Presentation

Introductory Remarks	Todd Baumgartner, MD Vice President – Regulatory Sciences, Life Cycle Management, BMS

Pravastatin/Aspirin: Safety and Dosing Considerations	Rene Belder, MD Executive Director – Clinical Design and Evaluation, Metabolics, BMS
Summary Overview	Fred Fiedorek, MD Vice President – Clinical Design and Evaluation and Exploratory Development, BMS

Questions:

The Cardio-Renal Advisory Committee is asked reconsider the co-packaged product of pravastatin and ASA, based on the additional materials and references provided by the sponsor.
This product was previously presented to the Advisory Committee on 18 January 2002. At that meeting there was general agreement that a population could be defined for which the co-packaged product would be indicated. There was also general agreement that the sponsor's meta-analysis of the five lipid lowering studies in a secondary prevention population (PLAC I, PLAC II, REGRESS, LIPID and CARE) demonstrated that both pravastatin and aspirin individually contributed to the beneficial cardiovascular outcomes seen in the separate trials. The Advisory Committee also endorsed the choice of the two doses of aspirin (81 and 325 mg).

The Advisory Committee, however, felt that the risk/benefit ratio of marketing the co-packaged product was adverse based on the following considerations:

1) The potential for excessive bleeding should the product not be discontinued prior to a surgical procedure.
2) The potential for inappropriate discontinuation of the pravastatin should the patient need to temporarily discontinue aspirin.
3) The use of the single fixed dose of the 40-mg pravastatin dose, where a higher or lower dose of pravastatin would be more appropriate for the individual.
4) The potential for use of this co-packaged product in an inappropriate population such as for primary prevention of cardiovascular events.

Not all members of the advisory committee applied equivalent weight to each of the above concerns.

The sponsor amended their application by a response addressing aspects of these concerns, including the following:

- A proposal to include in the pravastatin/aspirin co-packaged product two new doses of pravastatin 20 and 80 mg in addition to the originally proposed 40 mg dose, to be co-packaged with the 81 and 325 mg doses of aspirin.
- Submission of numerous publications.

1. To what extent has the sponsor's submission addressed your concern regarding…
   1.1 … the potential for excessive bleeding should the pravastatin/aspirin not be discontinued prior to surgery? *The consensus of the committee was that the sponsor*

had not adequately addressed this concern. The committee suggested that: the labeling of the product be explicit and clear that the product is ASA containing; and it include a statement suggesting that the patient inform the physician if surgery is planned.

1.2 … the potential for inappropriate discontinuation of pravastatin during times when aspirin is temporarily discontinued? *The main concern expressed by the committee was with the lack of available information regarding the potential risk(s) associated with discontinuation of a statin product.*

1.3 … the inappropriate use of a lower or higher dose of pravastatin than is necessary or safe for a given patient? *The committee was pleased that the sponsor had made the decision to offer numerous doses of pravastatin in the co-packaged product..*

1.4 … the inappropriate use of the co-packaged product in a non-indicated population?

2. Do you recommend the approval of the co-packaged pravastatin/aspirin as therapy for patients for whom both products are indicated?
Yes: 9 No: 0

July 19th Session

NDA 21-188, VANLEV™ (omapatrilat), Bristol-Myers Squibb Company, proposed for the treatment of hypertension.

Sponsor's Presentation

Introduction	Anthony Waclawski, PhD Director, Global Regulatory Sciences, Pharmaceutical Research Institute, Bristol-Myers Squibb Company
Clinical Efficacy Data	Elliott Levy, MD Vice President, Clinical Development, Pharmaceutical Research Institute, Bristol-Myers Squibb Company
Angioedema: Clinical Overview	Allen Kaplan, MD Professor, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina
Clinical Safety Data Benefit/Risk Considerations	Elliott Levy, MD
OVERTURE	Milton Packer, MD

Clinician's Perspective	Henry Black, MD Chairman, Department of Preventative Medicine, Professor of Internal Medicine, Rush Medical College, Rush University Chicago, Illinois
Conclusion	Anthony Waclawski, PhD

Questions:

The Committee is asked to opine on the approvability of omapatrilat for hypertension. Omapatrilat is an inhibitor of angiotensin converting enzyme and neutral endopeptidase. Reviews of chemistry, pharmacology, toxicology, and biopharmaceutics present no apparent barriers to approval. Omaparilat clearly lowers blood pressure. During its initial development, an increased risk of life-threatening angioedema was noted for patients taking omapatrilat compared with other antihypertensives (including ACE inhibitors). To characterize this safety finding and to gain additional information on the relative antihypertensive efficacy of omapatrilat, the sponsor conducted the OCTAVE trial.

OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) was a randomized, double-blind study in which 25302 subjects with hypertension were randomized to once-daily enalapril or omaparilat and followed for 24 weeks. During the first 8 weeks, subjects were titrated to a maximum dose of 40 mg (enalapril) or 80 mg (omapatrilat) as needed, after which subjects who did not achieve the blood pressure goal could have additional antihypertensive agents added through week 24. At 8 weeks, 41% of subjects in the enalapril group and 33% in the omapatrilat group were on the highest recommended doses. Between weeks 8 and 24, 19 to 36% of the enalapril subjects and 13 to 26% of the omapatrilat subjects added antihypertensive therapies. At 8 and 24 weeks, omapatrilat had a significantly greater effect to lower trough blood pressure compared with enalapril, but angioedema, including serious angioedema, was significantly more common in subjects taking omapatrilat.

GRADE	ENALAPRIL N=12557	OMAPATRILAT N=12609	RATIO
Mild	65	161	2.5
Moderate	19	94	4.9
Severe	2	17	8.5
Life-threatening	0	2	?

With these results and the data from the other trials of omapatrilat, the Committee is being asked

- to characterize the risks of omapatrilat (questions 1 & 2),
- to identify and characterize the benefit to which this risk needs be compared (questions 3 to 5), and
- to discuss whether omapatrilat's benefits outweigh its risks (question 6).

1. How should one best characterize the risk of angioedema with omapatrilat?
   1.1 Are the clinical features of the angioedema associated with omapatrilat similar to those associated with approved ACE inhibitors? *The committee agreed that the clinical features were similar.*

   1.2 In the original development program, about twice as many subjects were exposed to omapatrilat 20 mg than to 10 mg, as an initial dose, and the rate of any angioedema was about 3-fold higher in subjects initially receiving 20 mg. OCTAVE's primary safety hypothesis was that starting omapatrilat at a low dose and titrating up would reduce the risk of angioedema of any severity to no more than twice that of enalapril. Was this hypothesis supported by the study? *The committee did not feel that the OCTAVE results supported the sponsor's hypothesis*
   .

   1.3 In OCTAVE, there were 2 cases of life-threatening angioedema among 12000 subjects treated for about 6 months. In the original development program, there were 4 such cases in a population about 1/3 as large. Estimate the risk of life-threatening angioedema to expect post-marketing, and estimate the upper confidence limit for that risk. *The risk estimate of life-threatening angioedema to expect post-marketing: 1.6/10,000. The upper confidence limit for that risk was estimated to be: 5.7/10,000.*

   1.4 The sponsor has proposed a risk management plan focusing on patient education by pharmacists. To what extent can a risk management program based on patient education be expected to reduce the risk of death from angioedema? *The consensus of the committee was that the proposed patient education program would not suffice. Patients should be educated on the signs and symptoms of angioedema, but just as importantly, primary care and emergency room physicians would need to be targeted for education.*

2. The sponsor has shown the results of OVERTURE, a comparison of omapatrilat and enalapril in the treatment of chronic heart failure. If the results of this study are as presented, …
   2.1 … how relevant are these data to the approval of omapatrilat for hypertension? *The committee consensus was that these data are minimally relevant for the purpose of efficacy of the product in hypertension. However, these data do appear to indicate that there is was no new, unexpected harm done to the OVERTURE patients.*
   2.2 … how reassuring are these data with respect to the use of omapatrilat in a hypertensive population? *The committee, in general, gave the data minimal weight; their concern with the associated risk of: angioedema and any possible unknown side effects due to the fact the drug product is the first of a new class.*

3. Consider the antihypertensive effects of omapatrilat relative to other drugs.
   3.1 Is omapatrilat superior to enalapril? What results support this? *The consensus of the committee was that omapatrilat was superior to enalapril based upon the results of the OCTAVE trial.*
   3.2 Is omapatrilat superior to lisinopril? What results support this? *The consensus of the committee was that omapatrilat was superior to lisenopril as*

supported by two active controlled trials included in the application.

3.3 Is omapatrilat superior to amlodipine? What results support this?
The consensus of the committee was that omapatrilat was superior to amlodipine as supported by two active controlled trials included in the application.

3.4 Is omapatrilat superior to losartan? What results support this?
The consensus of the committee was that omapatrilat was superior to losartan as supported by two active controlled trials included in the application.

4. With what potential benefit should the risk of angioedema be balanced? OCTAVE allowed the addition of no new antihypertensive drugs during the first 8 weeks, at which time the blood pressure was about 3/2 mmHg lower on omapatrilat. During the following 16 weeks, other drugs were to be added to meet blood pressure goals, but at the end of 24 weeks, the blood pressure difference was still 3/2 mmHg. What explains the persistence of the differential effect at 24 weeks?

   4.1 Is a regimen including omapatrilat able to lower blood pressure to an extent that combinations of enalapril and other drugs cannot? If so, is the risk-benefit comparison between the risk of angioedema and the expected reduction in cardiovascular events attributable to this blood pressure difference?

   4.2 Is the persistence of a blood pressure difference at 24 weeks a consequence of trial design, e.g., the goal blood pressure, or to the inadequate use of additional drugs? If so, is the risk-benefit comparison between the risk of angioedema and the avoidance of adverse events associated with additional antihypertensive drugs?

   The committee intensely discussed Question No. 4 and it's sub-elements; details can be found in the meeting transcripts.

5. Depending on the Committee's answer in question 4, identify a target population and estimate the magnitude of the expected benefit.
   The committee agreed that a target population might be those patients refractory to blood pressure control. However, because this population was not prospectively defined in the OCTAVE trial, the trial would not support any population other than the general hypertensive patient population.

6. Should omapatrilat be approved for the treatment of hypertension?
   Yes: 1 ***No: 5***

   If so…

   6.1 … in what population should it be indicated?

   6.2 … in what population should it be contraindicated?

   6.3 … what is the starting dose?

   These questions were not answered by the committee since the majority vote for Item 6 was not a recommendation for approval.