

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

Date: **DRAFT***DRAFT***DRAFT 6/19/02**

From: Michael F Johnston, R.Ph. Safety Evaluator
Allen Brinker, M.D, Medical Officer
Division of Drug Risk Evaluation (HFD-430)
Office of Drug Safety

Judy Staffa, Ph.D., Epidemiologist
Jeanine Best, MSN, RN, PNP, Regulatory Health Project Manager
Division of Surveillance, Research, and Communications Support (HFD-410)
Office of Drug Safety

Through: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation (HFD-430)
Office of Drug Safety

Anne Trontell, M.D., Director
Division of Surveillance, Research, and Communications Support (HFD-410)
Office of Drug Safety

To: Douglas Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110

Subject: REVIEW OF RISK MANAGEMENT PLAN FOR OMAPATRILAT (RMPO)
(BMS-186716-01, IND 48,035, Serial Nos. 468 and 474; Bristol-Myers Squibb)

EXECUTIVE SUMMARY

The Office of Drug Safety (ODS) has reviewed the Risk Management Plan for Omapatrilat (BMS-186716-01, IND 48,035, Serial Nos. 468 and 474; Bristol-Myers Squibb Pharmaceutical Research Institute).

In controlled hypertension trials submitted in the original NDA filed in 1999, eight patients were hospitalized for omapatrilat associated angioedema. Four of these patients experienced life-threatening events requiring intubation/ tracheostomy. BMS has recently submitted results of the OCTAVE Trial in which 25,000 hypertensive patients were randomized to either omapatrilat or enalapril. Two patients developed life-threatening angioedema on omapatrilat in this study. The risk of angioedema was 2-3 times greater in black patients (relative to non-black patients) and in current smokers (relative to former or non-smokers). On May 8, 2002 BMS submitted a proposal for risk management strategies to be implemented during marketed use of omapatrilat. A meeting with DCRDP and ODS representatives on May 16 prompted BMS to submit a revised

proposal on June 11. The cornerstone of these proposals is that angioedema lends itself to management through education of the patient, prescriber and pharmacist. This review discusses BMS' risk management proposals in light of this premise.

Despite the use of a lower starting dose (10 mg), exclusion of patients with previous allergic and anaphylactic responses to medications, and a protocol specified 2-hour observation period, life-threatening angioedema was observed in the OCTAVE trial. Blacks and current smokers are at the highest risk of angioedema, but non-black patients and non-black, non-smokers are also at increased risk. Thus it should be assumed that all patients prescribed omapatrilat are at some risk for the development of angioedema.

We believe that education will not prevent cases of angioedema but may reduce poor outcomes associated with severe angioedema such as endotracheal intubation and death. This assumption greatly depends on whether angioedema is a condition that is amenable to self-diagnosis by a patient who has not experienced it before, and whether there is sufficient time to intervene once symptoms have begun.

ODS notes that drug products with high frequencies of anaphylaxis and hypersensitivity reactions, namely intravenous contrast agents and iron products, are typically administered in supervised medical settings prepared to handle airway compromise. In the situation where patients self-manage anaphylaxis or angioedema outside of a medical setting - in the context of known hypersensitivity reactions to insect stings - the patient has had previous experience of life-threatening allergic symptoms to guide self-care.

We believe that additional evidence is needed to assure that patient education regarding risks of angioedema will be uniformly effective in mitigating severe outcomes. While it is plausible that some patients may benefit from education and counseling, it is not known which patients will benefit most. It is possible that some patients will overutilize healthcare systems for nonserious events that are likely to resolve on their own. Conversely, underutilization of healthcare services may result since education may not reach or persuade all individuals at risk. Apart from dialing 9-1-1, there are no proposed systems approaches to ensure that timely medical attention will be given to those patients with rapidly progressive angioedema symptoms.

ODS notes several shortcomings of the proposed postmarketing surveillance plan. Systems approaches and methods to assess the effectiveness of risk management strategies for omapatrilat need further development. Based on the information available, we doubt whether severe angioedema associated with omapatrilat can be adequately managed by a program primarily focused on education. We believe it is unlikely that the proposed risk management plan will reduce the risk of severe omapatrilat associated angioedema to a level generally observed with currently marketed ACE inhibitors.

INTRODUCTION / BACKGROUND

Omapatrilat is the first of a new class of medications, the vasopeptidase inhibitors, under study for the treatment of hypertension and chronic heart failure. The vasopeptidase inhibitors block the actions of angiotensin-converting enzyme and neutral endopeptidase providing dual effects on the physiologic systems for regulating sodium and fluid homeostasis resulting in inhibition of the renin-angiotensin-aldosterone system and producing vasodilation.

Bristol-Myers Squibb (BMS) submitted NDA 21-188 to FDA's Division of Cardio-Renal Drug Products (DCRDP) in late 1999 for the use of omapatrilat in patients with hypertension. In controlled hypertension trials submitted in NDA 21-188, eight patients experienced omapatrilat associated angioedema requiring hospitalization (6 black, 2 non-black patients). Of these eight cases, four (2 black, 2 non-black patients) progressed to require intubation/ tracheostomy. These four cases occurred among 6,662 patients within two weeks of taking a starting dose of 20 mg daily; all recovered. Concerns related to the severe angioedema seen during the initial clinical trials, resulted in a March 17, 2000 meeting between BMS and DCRDP. At this meeting, Dr. Raymond Lipicky, then DCRDP Director, informed BMS that in light of the fact that none of the ACE inhibitors displayed angioedema of this severity in the pre-approval stage, BMS needed to find a way to "make this problem go away" or the approval of omapatrilat was at risk.

After the March 2000 meeting and in response to Dr. Lipicky's request, BMS initiated the larger (n = 25,302), double-blinded Omapatrilat Cardiovascular Treatment Versus Enalapril (OCTAVE) clinical trial in which omapatrilat was compared to enalapril in a 24 week study in uncontrolled hypertensive patients. This multi-center, multi-country trial specifically excluded patients with a history of angioedema, anaphylaxis, contraindication or hypersensitivity to ACE inhibitors or Angiotensin II receptor blockers, drug-related urticaria or chronic urticaria, or a history of rash in response to two or more drug classes. The omapatrilat starting dose was also reduced to 10 mg daily with subsequent increases to 20 mg, 40 mg, and 80 mg at two-week intervals. Enalapril was started at 5 mg daily and titrated up to 40 mg. All patients were observed for two hours following study drug initiation and titration to the second dose level (omapatrilat 20 mg or enalapril 10 mg). OCTAVE investigators were provided instructions from enalapril product labeling as a guide to angioedema treatment. Treatment facilities were not required to have onsite resuscitation support/equipment but had to be located within an hour of such support. An Adjudication Committee of experts external to BMS reviewed all possible cases of angioedema in blinded fashion.

In OCTAVE, patients randomized to omapatrilat experienced a 3-fold higher rate of angioedema than those taking enalapril (2.17% vs. 0.68%). Angioedema with omapatrilat was most often characterized by swelling of the lip (53%), face (32%), tongue (28%), neck (21%) and eyelids (16%), a pattern similar to that of enalapril. Symptoms associated with the swelling included flushing or facial redness (22% with omapatrilat, 28% with enalapril), difficulty swallowing (15% with omapatrilat, 9% with enalapril), and difficulty speaking (12% with omapatrilat, 6% with enalapril). In the OCTAVE trial, there were two cases of life-threatening airway obstruction, both on the omapatrilat arm (n=12,609). One case occurred in a black female who presented after 10 weeks of therapy (at a daily dose of 80 mg) and progressed over several hours to the need for intubation / tracheostomy. The second case was in a non-black female and

current smoker who experienced an anaphylactic reaction with airway compromise within 15 minutes of receiving the first 10 mg dose of omapatrilat but responded to subcutaneous epinephrine. In addition to these two life-threatening cases, 17 patients on the omapatrilat arm were hospitalized for severe angioedema as compared to two patients on enalapril. These patients did not require mechanical ventilation.

The time course of evolution of angioedema symptoms was variable, but tended to occur earlier in omapatrilat-treated patients than in enalapril-treated patients. Of the 274 angioedema events occurring on omapatrilat, a third or 88 occurred on the first day of therapy; nearly two-thirds of these within the first two hours. Of the 86 angioedema events occurring on enalapril, only 3 occurred on the first day, with one of these occurring in the first two hours. *At a meeting on June 18, 2002 BMS indicated that the majority of patients developed symptoms outside of the doctor's office and sought medical attention within hours of symptom onset. BMS has committed to submit additional information regarding the time course of severe angioedema events with omapatrilat from its clinical trials experience.* Angioedema events on both drugs occurred throughout the 24 week period of the study. There did not appear to be an increased risk of angioedema with dose titration for either drug.

In order to address this repeated result of higher incidence and greater severity of angioedema with omapatrilat, on May 16, 2002 BMS presented to members of the DCRDP, Office of Drug Safety (ODS), and Division of Drug Marketing, Advertising, and Communication (DDMAC) their proposal for a risk management plan for omapatrilat. This plan proposes, through education of the patient, prescriber, and pharmacist, to minimize the incidence of severe angioedema. Pages 16-17 of the BMS May 8, 2002 meeting submission (prepared for the May 16, 2002 meeting) note that the effectiveness of the plan is based upon the following principles:

1. Angioedema, due to its symptoms and characteristic presentation, lends itself to management through education of the patient, prescriber, and pharmacist;
2. The time course, symptomatology, risk factors and treatment for angioedema have been identified. Two groups (blacks and smokers) have been clearly identified as higher risk;
3. BMS is committed to "establishing awareness of angioedema and to implementation" of the plan as an integral part of the marketing and launch of omapatrilat;
4. BMS has proposed research plans to assure key messages concerning risk of angioedema are understood by patients, prescribers, and pharmacists;
5. Post-marketing surveys of the plan's effectiveness, surveillance programs, and post-marketing studies will assure that the risk management plan works in the "real world"; and,
6. "System approaches are widely considered required elements of risk management. Specifically, the FDA has encouraged stakeholders to devise and participate in programs that incorporate checks and balances, redundancies, and other systems approaches to assure products are used appropriately."

In response to comments from DCRDP and ODS at the May 16, 2002 meeting, BMS submitted a revised risk management plan on June 14, 2002 (document dated June 11, 2002). This submission makes modifications to the original plan and changes the name of the plan to the “Risk Management Plan for Omapatrilat” (RMPO).

Per BMS, the Risk Management Plan for Omapatrilat ensures that the following goals are adopted for marketed use (pages 5-6 of the May 8 submission and expanded on page 4 of the June 11 submission):

1. Omapatrilat is used only in patients for whom drug is indicated/ appropriate;
2. Prescribing physicians and dispensing pharmacists have adequate knowledge of the benefits and risks of omapatrilat, and are capable of counseling patients effectively and recognizing angioedema;
3. Omapatrilat is administered and patients are followed in a way that minimizes the rate and severity of angioedema;
4. Patients who are prescribed omapatrilat are knowledgeable of the importance of blood pressure normalization, treatment compliance, and are aware of the signs and symptoms of angioedema and will take appropriate action if these signs and symptoms occur; and
5. Effectiveness of the plan will be monitored, specifically in regard to the occurrence of angioedema and compliance measures implemented.

In a teleconference on June 14, 2002 between Dr. Anthony Waclawski of BMS and ODS staff, the scope and focus of BMS’ presentation at the July Advisory Committee was briefly discussed. At that time, BMS provided ODS with a three-page draft version of their description of the RMPO to be included in an Appendix to their Advisory Committee Briefing Document. It was agreed that only a limited presentation of the RMPO would be made at the upcoming Advisory Committee meeting with references made to future development of the components of the risk management program being a cooperative effort between BMS and the FDA.

RELEVANT PRODUCT LABELING

Proposed angioedema-related wording for omapatrilat (Vanlev®) from draft labeling dated December 12, 2001 is included as Appendix (1). BMS noted in their May 8, 2002 meeting package “final labeling will be completed following upcoming discussions with the FDA Cardio-Renal Division, and will be intended to both optimize benefit and minimize risk.” This labeling should be considered an early draft at this time.

EVALUATION OF ANGIOEDEMA RISK IN OCTAVE TRIAL

BMS’ evaluation of angioedema risk revealed a 2-3-fold increase in risk for black patients (relative to non-black patients) and for current smokers (relative to former and non-smokers). A

1-2-fold increase in risk was also identified for female patients, patients with seasonal allergies, and former smokers.

Allen Brinker, M.D., developed the following table based on the OCTAVE dataset (as supplied by Norman Stockbridge, M.D., DCRDP) to assess the risk of omapatrilat associated angioedema in other subsets of patients (i.e., non-black patients and non-black non-smokers).

	Enalapril (OCTAVE – all patients)	Omapatrilat (OCTAVE – all patients)	Omapatrilat (OCTAVE – non- black patients only)	Omapatrilat (OCTAVE – only non-black, non-smokers*)
Relative Risk for Angioedema - All Severities (frequency)	1.0 (88 / 12,557)	3.1 (272 / 12,609)	2.6 (201 / 11,101)	2.0 (130 / 9,152)
Relative Risk for Angioedema - Hospitalized only (frequency)	1.0 (2 / 12,557)	9.5 (19 / 12,609)	7.4 (13 / 11,101)	4.8 (7 / 9,152)

*Includes both non-black never (n=5,780) and former (n=3,372) smokers

As shown in this table, the risk for angioedema of all severities with omapatrilat decreases from 3.1 to 2.0 in comparison to enalapril with restriction to (1) non-black patients and (2) non-black, non-smokers. For the subset of hospitalized cases of angioedema, the relative risk only falls from 9.5 to 4.8. Thus, despite restriction to only non-black non-smokers, we could expect angioedema-related hospitalizations to occur some 5-fold more frequently in association with omapatrilat in this subset as compared to enalapril.

Based on OCTAVE, omapatrilat-associated angioedema is both more frequent (relative risk of 3) and associated more frequently with severe outcomes (relative risk of 9) in comparison to enalapril. However, there is no evidence to date of hyperacute angioedema with omapatrilat (as per N. Stockbridge). In other words, the initial presentation appears similar for both drugs, but omapatrilat-associated angioedema appears to progress more frequently to a stage requiring hospitalization. This suggests that omapatrilat-associated angioedema may be either more rapidly aggressive and/or resistant to therapy than angioedema seen with enalapril. If this is true, it becomes even more critical for patients prescribed omapatrilat, compared to ACE inhibitors, to recognize symptoms early and seek prompt medical attention. BMS has committed to provide additional information on the time course of angioedema for omapatrilat compared with other anti-hypertensives from its clinical trials experience.

As BMS expects that omapatrilat “may eventually be used by hundreds of thousands of patients” (page 41 of the May 8 submission), angioedema rates from OCTAVE (in the preceding table) were transformed to assess their impact following drug launch. The table below represents cases of angioedema expected in a hypothetical population of 100,000 under the hypothesis that the OCTAVE results are generalizable.

N = 100,000	Enalapril (all patients)	Omapatrilat (all patients)	Omapatrilat (non-black only)	Omapatrilat (only non- black, non- smokers*)
Expected number of patients with angioedema – All severities	701	2,157	1,811	1,420
Expected number of patients with angioedema - Hospitalized only	16	151	117	77

*Includes both non-black never and former smokers

EVALUATION OF PATIENT EDUCATION

The RMPO will provide patient education brochures for use by healthcare professionals to convey important risk information to patients. These materials will be tested to ensure patient comprehension. In addition, a Patient Package Insert (PPI) that will follow the Q&A Medication Guide format will be developed and tested for comprehension. The PPI will be contained within sample and trade packages of omapatrilat. A novel pharmacist-to-patient counseling program is also proposed (June 11, 2002 submission). Patients would call a toll-free number to receive counseling by a pharmacist who would reinforce information provided by the physician regarding the signs and symptoms of angioedema. Upon completion of this activity, the counseling pharmacist will provide the patient with a code number. The patient must present the code number to the retail pharmacist and the pharmacist must verify the number at the time the prescription is filled. Jeanine Best contributed the following comments.

- **Managing Risk of Angioedema via Patient Education**

Risk Factor Awareness. BMS has not provided a complete message regarding the risks of angioedema with omapatrilat in the draft Patient Package Insert submitted to date. Based on OCTAVE, BMS documents five key risk factors for angioedema with omapatrilat: black race, current or former smoking, female gender, and seasonal allergies. BMS proposes cautionary language for only two of these risk factors, current smoking and black race. These two factors were selected based on BMS's definition that a 2-fold elevation in the risk of angioedema is "clinically meaningful". ODS notes that even though the other risk factors for angioedema (e.g., female gender, seasonal allergies, former smoking) do not elevate risk by more than 100%, they do elevate risks by approximately 50% (range 47-52%; see page 14 of the May 8, 2002 BMS meeting package). As such, efforts to prevent the occurrence of angioedema by advising cautious use in blacks and current smokers incompletely capture the populations identified as having an increased risk of this event with omapatrilat.

As documented in Dr. Brinker's section above, the risk for angioedema in patients without risk factors of black race and smoking remains elevated above that of enalapril. Thus, patient educational materials should emphasize that all patients prescribed omapatrilat are at risk for angioedema, but that this risk is higher for some patients than others.

Risk Prevention versus Mitigation. BMS's risk management program is best described as a risk mitigation program. Their program, if successful, may reduce severe and life-threatening outcomes of angioedema once it occurs by educating patients to seek prompt medical attention. The program will not likely prevent the occurrence of angioedema itself. This is analogous to alerting patients to the early signs and symptoms of liver injury from drugs in order to prevent progression to liver failure; by stopping drug treatment and instituting corrective therapy early in the course of injury, severe outcomes are hoped to be prevented.

Key to any risk mitigation strategy is the assumption that there is sufficient time and adequate means to intervene between early signs and symptoms and the occurrence of severe injury. A second and related assumption is that patients can be adequately educated to quickly and accurately self-diagnose early symptoms of angioedema.

In the case of angioedema associated with omapatrilat, there may not be sufficient time to intervene between the onset of symptoms and life-threatening respiratory compromise. The OCTAVE study data indicate in a first-dose setting that angioedema occurs more commonly and quickly with omapatrilat (64% of cases within 2 hours of dosing) than with enalapril (33% of cases in the same time period). One omapatrilat patient developed respiratory compromise within minutes of her first dose of 10 mg, presumably during a protocol-specified 2-hour observation period. She responded to subcutaneous epinephrine and avoided intubation. Had the patient not been observed during the event it is possible that she would have done less well. It is also uncertain what value education would have played in this case; if her symptom course had been rapidly progressive, there may not have been sufficient time to intervene. These concerns are valid whether omapatrilat associated angioedema occurs with the first dose or with some later dose. BMS has committed to submit additional information regarding the time course of severe angioedema events with omapatrilat from its clinical trials experience.

Based on available data, there appears to be no clear relationship between the severity of symptoms and the time course during which symptoms evolve (per Dr. Stockbridge, DCRDP). Thus, it is not possible to predict the time course for medically significant angioedema in a given patient who develops it in association with omapatrilat use. A potential consequence of this is that many more omapatrilat patients will seek medical attention for nonserious events than is probably necessary. Conversely, patients may choose to ignore symptoms and delay therapy.

Critical to the determination of whether there is adequate time to intervene between symptom onset and progression to severe angioedema is the question of whether patients who have never before experienced angioedema can be adequately educated to reliably self-diagnose the early symptoms of angioedema. With rapidly progressing and potentially fatal events, there may be little if any time for patients to check different sources of information to validate their experiences. BMS should provide data to demonstrate that patient education and counseling can ensure the ability to self-diagnose and appropriately manage a previously unknown, rapidly developing, potentially life-threatening event. In particular, this ability needs to be demonstrated in a diverse population, particularly in individuals with low literacy, before proceeding. Alternatives to reach low or illiterate populations (such as video or audio materials) may merit exploration.

Drug products with high frequencies of anaphylaxis and hypersensitivity reactions, namely intravenous contrast agents and iron products, are typically administered in supervised medical settings prepared to handle airway compromise, and/or carry labeled warnings that they should be used in settings where epinephrine is immediately available (e.g., iron dextran injection). The only known situation where patients self-manage anaphylaxis or angioedema outside of a medical setting is in the context of known hypersensitivity reactions (e.g., to insect stings). In these instances, the reactions are due to uncontrollable exposures (not routine drug administration) and the patient has previous experience of life-threatening allergic symptoms to guide self-care.

In summary, ODS believes that all patients prescribed omapatrilat are at some risk for the development of angioedema and that this risk is higher than for currently marketed ACE inhibitors. It is unlikely that the RMPO will reduce the risk of omapatrilat associated angioedema to a level generally observed for these other agents. Additional evidence is needed to assure that patient education regarding risks of angioedema will be uniformly effective in mitigating severe outcomes. While it is plausible that some patients may benefit from education and counseling, it is not known which patients will benefit most. It is possible that some patients will overutilize healthcare systems for nonserious events that are likely to resolve on their own. Conversely, underutilization of healthcare services may result since education may not reach or persuade all individuals at risk. Apart from dialing 9-1-1, there are no proposed systems approaches to ensure that timely medical attention will be given to those patients with rapidly progressive angioedema symptoms.

- **Patient Package Insert**

Notwithstanding concerns that the risk of severe angioedema is unlikely to be mitigated sufficiently by patient education, there are also concerns with the proposal to use a PPI rather than a Medication Guide for patient education. Medication Guides are appropriate to the potential seriousness of the angioedema, their distribution is legally required, and the effectiveness of their communication format has been established through extensive research and experience. Medication Guides also guarantee parity of generics manufacturers and innovators in patient education.

Severe angioedema is a serious and significant risk to public health and so meets at least the first of the 3 triggering criteria for a Medication Guide [21 CFR § 208.1(c)(1)(2)(3)]:

- (1) “The drug product is one for which patient labeling could help prevent serious adverse events.”
- (2) “The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients’ decision to use, or continue to use, the product.”
- (3) “The drug product is important to health and patient adherence to directions for use is crucial for the drug’s effectiveness.”

In addition, the second criterion may be met in consideration of the many therapeutic options available to treat hypertension. The risks of omapatrilat relative to its benefits merit discussion in the context of alternative medications within the ACE inhibitor class and others to treat

hypertension. Such products do not carry the same risk of angioedema seen with omapatrilat in clinical trials.

Medication Guides are required by law to be distributed at the time of dispensing. This requirement does not apply to PPIs. A Patient Package Insert packaged in unit-of-use packaging and formatted like a Medication Guide may operate effectively as a Medication Guide, but it will not have the force of the law and could present problems when or if generics enter the market. PPIs are discretionary. Proper formatting, font size, and mandatory distribution could not be assured for a generic manufacturer of omapatrilat unless the innovator had a Medication Guide.

In their most recent submission, the sponsor has proposed a “Q&A” Medication Guide format for their PPI. In light of data supporting the effectiveness of the Medication Guide format, ODS recommends that all PPIs be placed in Medication Guide format. The Medication Guide format may be modified with appropriate data to justify doing so. Promotional language should be removed and full review of content for comprehension by low literacy populations would be required for approval of either a Medication Guide or a PPI for omapatrilat.

EVALUATION OF POSTMARKETING SURVEILLANCE PROPOSAL

BMS has proposed a three-pronged postmarketing surveillance program for omapatrilat. These approaches were expanded in the June 11, 2002 submission and are currently under review. Briefly these approaches are:

- 1) Intensive surveillance of a national hospital and emergency department database to estimate the relative frequency of life-threatening angioedema (i.e., resulting in intubation or death);
 - 2) A prospective cohort registry study in 10,000 patients to assess whether the frequency of less severe angioedema is similar to that observed in the OCTAVE trial; this venue would offer the opportunity to periodically survey patients regarding their angioedema events and whether physician or pharmacist efforts to educate them were effective; and,
 - 3) Evaluation of spontaneously reported adverse events using specific data collection forms to retrieve important clinical information, including pharmacotherapy, intubation/tracheostomy, hospitalization or death.
- **Epidemiologic Assessment of Severe Angioedema (Case Control Study)**

Judy Staffa, Ph.D., has provided the following comments on this component of the proposed surveillance program.

BMS has stated that they will use Premier Inc’s hospital database to conduct surveillance of emergency room visits and hospital admissions for severe angioedema to determine the proportion of angioedema associated with omapatrilat and ACE inhibitors. Further, they will use these data in conjunction with IMS HEALTH data to examine nationwide exposure to

omapatrilat and ACE inhibitors in relation to the proportion of angioedema cases related to omapatrilat or ACE inhibitor use, in an ecologic analysis. BMS also proposes to conduct a pilot study to evaluate the Premier dataset for the surveillance of angioedema. This study is designed to capture angioedema cases in the Premier dataset between 1999-2001 and characterize them by demographics, encounter type (emergency department vs. inpatient) and severity (pharmacotherapy, intubation or death). A sample of cases will undergo medical record review to verify diagnosis and ascertain drug exposures, prior history of angioedema, allergies, smoking status, diabetes, race, age and gender. The pilot study would offer the opportunity to evaluate a process for rapid case ascertainment (avoiding data lags) and document the data flow process including time at which data subsets will be available.

The rationale behind these proposed studies is unclear to ODS. BMS states, “the primary goal of the post-marketing surveillance will be to ascertain the rate of angioedema observed during actual use of omapatrilat in the market place”. However, it would seem more appropriate if the purpose of using these data was to determine whether the risk management program is effective. If so, then a set level of “acceptable risk” for angioedema associated with omapatrilat should be negotiated with FDA and the studies powered to detect these levels. Without a baseline assessment of some type, though, it would be difficult to attribute any success to the program itself, unless the assumption is made that the risk would be at the level seen in the OCTAVE trial. This is a questionable assumption, since it is well known that adverse reactions occur in real world settings at a higher frequency than in clinical trials of select patient populations. Thus, the rate of angioedema during actual use of omapatrilat would be expected to be even higher than that seen in the trials. Determining the rate of angioedema would also mandate the use of numerator and denominator data from the same source, such as in a cohort or registry, rather than an “ecologic analysis” of numerators from Premier and denominators from IMS HEALTH, as was proposed.

We agree that the Premier data are of high quality, and that it is likely possible to identify emergency room visits and admissions for angioedema within a short time period (e.g., the 2-3 weeks referred to in the proposal). Our major concern with this strategy is that the sample size of several hundred hospitals is too small to pick up a sufficient number of angioedema cases attributed to one specific cause, such as omapatrilat, for which prevalence of use will not likely be high in the population. This may lead to underestimation of the true incidence of angioedema associated with omapatrilat.

In addition, although the numbers of discharges for the most common principal diagnoses associated with hospitalization in Premier hospitals can be nationally projected, and match up favorably with data from the National Center for Health Statistics’ National Hospital Discharge Survey, we are not aware of any evidence to suggest that diagnoses stratified by specific cause will also reliably project. For example, it may be possible to project total hospitalizations for angioedema from the Premier hospital sample to all U.S. hospitals, but that does not mean it is possible or wise to attempt to project the subgroups of angioedema due to different causes. We believe that there are many factors that undermine this subgroup projection, including geographical differences in patterns of drug use, third-party payor influence on prescribing practices and differences in patient demographics throughout the country. These factors may impact on the representativeness of Premier hospitals in relation to the approximately 5,000

hospitals throughout the U.S. with regard to the prevalence of use of various ACE inhibitors, including omapatrilat, in the hospitals' catchment area. Therefore, we do not agree that this proposed strategy would effectively monitor for all, or even most, cases of severe angioedema associated with omapatrilat.

In summary, the rationale, methods, statistical power and biases of the proposed Premier, Inc. studies suffer from numerous deficiencies in assessing real-world rates of angioedema with omapatrilat. Full and accurate ascertainment could be better served using a patient registry with periodic follow-up for adverse event detection.

- **Assessment and Reporting of Spontaneous Reports of Angioedema**

BMS plans to systematically collect data on angioedema cases and has drafted a questionnaire to be used by staff at the BMS AE Call Center (Appendix 4 of the June 11, 2002 submission). Data elements targeted for collection include race, smoking status, gender, relevant history, duration of therapy, and detailed descriptions of the adverse events in terms of severity and outcomes. BMS proposes to report all serious cases of angioedema in omapatrilat users to the FDA on an expedited basis (i.e., fatal, life-threatening, hospitalized and medically serious cases). BMS will also provide estimates of drug use and summaries of nonserious cases with a frequency to be determined upon further discussion with FDA.

BMS also proposes evaluating other adverse events in the context of their background rates. Data from Premier Network, the Veteran's Administration and United HealthCare Network may be utilized depending on omapatrilat use within these systems.

ODS agrees that submission of serious angioedema reports on an expedited basis as 15 day reports may more quickly help to identify additional risk factors which may in turn allow for improved labeling and/or education. In addition, spontaneous reports may be able to detect off-label use or non-compliance with RMPO elements. Current MedWatch reports do not have a field that explicitly captures race. Race information is voluntary. We support BMS' efforts to obtain and report information on race to the extent that this is possible.

THE BMS RISK MANAGEMENT PLAN for OMAPATRILAT / DISCUSSION

The RMPO emphasizes the use of educational programs designed to reach the patient, prescriber, and pharmacist at three stages of the treatment process: pre-therapy, therapy initiation, and during ongoing therapy. Educational materials are under development by BMS and will contain simple graphic/text information designed to teach and reinforce the critical messages concerning the benefits and risks of omapatrilat. BMS plans to include these messages on all trade and sample packaging and in all physician, patient, and pharmacist programs.

The table below lists some of the proposed elements of the sponsor's RMPO with comments/discussion points as collected from ODS staff members.

Proposed RMPO Element	BMS Comments/ Rationale	Office of Drug Safety Comments / Discussion Points
1. Limit use to patients in which omapatrilat is indicated/ appropriate	Use should be reserved for patients in whom benefit/risk is CLEARLY favorable	<ul style="list-style-type: none"> • BMS should specify in what population the risk-benefit is truly favorable for omapatrilat. Is there a treatment-refractory population of hypertensive patients who might merit this drug over other HTN treatment options? • Even with removal of higher risk populations (blacks, current smokers), use of omapatrilat is associated with 2-3 times the angioedema risk of enalapril. • Current draft labeling lists contraindications only for patients with known hypersensitivity to omapatrilat and in patients with a history of angioedema. With regard to blacks and/or current smokers, BMS states, “such patients may benefit from omapatrilat but should be followed carefully”. It must be remembered that patients were excluded from the OCTAVE trial with other risk factors for developing angioedema but treatment in these patients is not contraindicated. • The process of identifying allergies/sensitivities is often difficult and unreliable.
2. Patients, physicians and pharmacists must be familiar with signs and symptoms of angioedema	This knowledge may prevent “some” cases from progressing	<ul style="list-style-type: none"> • Education on the subject of the signs and symptoms of angioedema to patients, physicians and pharmacists will not prevent angioedema but may reduce the severity of outcomes seen (intubation, tracheotomy) if there is sufficient time to intervene. Reducing severe outcomes is greatly dependent on the patient’s ability to self-diagnose angioedema as well as on immediate availability of medical care. • All patients are at risk of developing angioedema, although some are at greater risk than others. • Unlike some other medical conditions (i.e., pregnancy, Q-T prolongation, etc.) in which high-risk populations may be identified prior to initiating drug therapy, no laboratory test or procedure is available to identify patients who may have an elevated risk for angioedema. • Patients prescribed omapatrilat should have no prior history of angioedema, and so it may be challenging to educate them on the rapid recognition of symptoms they have not previously experienced. • Options such as limiting omapatrilat to certain specialty prescribers, although not proposed by BMS, would be problematic because of the primary care nature of treating hypertensive disease. • It is unclear whether BMS intends to limit prescribing by extended health care providers (nurse practitioners, physicians assistants, etc.).
3. Physicians must exercise particular caution when treating blacks and patients with a	Increased risks for angioedema (2-3 fold) over the general hypertensive	<ul style="list-style-type: none"> • Although this statement is true, it seems that “particular caution” must be applied to all patients taking omapatrilat. See Dr. Brinker’s section above. • Particular cautions are not specified in the proposed label so clinicians are left in the dark about what to do in actual practice

Proposed RMPO Element	BMS Comments/ Rationale	Office of Drug Safety Comments / Discussion Points
current smoking history	population. Careful consideration of potential benefit should be undertaken prior to treating each of these high-risk groups.	(e.g., prescribe to these groups only if they have ready access to emergency medical services? etc).
4. Increasing Dose to 20 mg after 10-14 days (then to 40 mg and 80 mg over two week intervals)	Titration method utilized in OCTAVE	<ul style="list-style-type: none"> • Would agree with increasing/ titrating doses as was utilized in OCTAVE, however dose titration is not a formal part of risk-management.
5. Regular contact with patients should take place w/patients reminded of the benefits and risks as well as the actions to take should symptoms occur.	Since risk of angioedema appears to persist (albeit at a low rate)	<ul style="list-style-type: none"> • The June 11 submission suggests that patients would have access to a pharmacist counseling service on an ongoing basis. • Pharmacist counselors could place out-going calls to patients to reinforce awareness of the risk of angioedema. • These activities will help reinforce patient education on signs and symptoms of angioedema. Again, likely won't prevent angioedema but may reduce poor outcomes.
6. Pharmacists should verify that patients have a code number at the time of dispensing (this number signifies that they have undergone pharmacist counseling)	Helps to ensure that the patient is educated about angioedema when the first prescription is filled.	<ul style="list-style-type: none"> • Verification step will increase the burden of the retail pharmacist. • What ensures that verification will be done routinely? • Will prescriptions be denied if the code number is not available or verifiable? • Verification procedure does not occur in the event that the patient is given office samples; angioedema risk is present even with the first dose.

CONCLUSION

BMS is to be commended for undertaking the large multi-center OCTAVE trial in an attempt to evaluate the severe angioedema events seen in earlier (and smaller) clinical trials. The results of OCTAVE reinforce that the problem continues to exist and occurs at all doses. Compared with enalapril, angioedema is more frequent, more severe and occurs sooner in omapatrilat users. Although two at-risk populations (blacks and current smokers) have been identified, we note that a 2-3-fold increase in angioedema with omapatrilat compared to enalapril still appears to exist even after these higher risk groups are excluded. Thus, it should be assumed that all patients prescribed omapatrilat are at some risk for the development of angioedema. Despite the use of a lower starting dose (10 mg), exclusion of patients with previous allergic and anaphylactic responses to medications, and a protocol specified 2-hour observation period, life-threatening angioedema was observed in the OCTAVE trial.

Several questions remain regarding omapatrilat associated angioedema, including:

1. In light of other antihypertensives on the market, what is an acceptable risk for angioedema with omapatrilat? Is the risk of angioedema as observed in the OCTAVE trial acceptable in the marketplace?
2. For what patient population would omapatrilat be considered appropriate therapy?
3. Is angioedema a condition that is amenable to self-diagnosis by patients?
4. Will the RMPO proposed by BMS effectively minimize the risk of severe angioedema to a level generally observed for marketed ACE inhibitors?
5. How will the effectiveness of the RMPO be evaluated? What are the benchmarks of success for a program intended to manage angioedema?

The BMS RMPO attempts to educate patients, prescribers, and pharmacists with the goal of decreasing the incidence of severe angioedema by trying to ensure that angioedema will be recognized early by patients. The program will not likely prevent the occurrence of angioedema itself. Key to the success of the RMPO is the assumption that there is sufficient time and adequate means to intervene between early signs and symptoms and the occurrence of severe injury. A second and related assumption is that patients can be adequately educated to quickly and accurately self-diagnose early symptoms of angioedema.

We believe that the sponsor needs to provide additional evidence to assure that patient education regarding risks of angioedema will be uniformly effective in mitigating severe outcomes. While it is plausible that some patients may benefit from education and counseling, it is not known which patients will benefit most. It is possible that some patients will overutilize healthcare systems for nonserious events that are likely to resolve on their own. Conversely, underutilization of healthcare services may result since education may not reach or persuade all individuals at risk. Apart from dialing 9-1-1, there are no proposed systems approaches to ensure that timely medical attention will be given to those patients with rapidly progressive angioedema symptoms.

The primary care nature of hypertension and its treatments also makes prescriber and pharmacist education a significant challenge and would make it difficult to restrict omapatrilat to specific prescribers or pharmacies, as some recent risk management plans have done.

Based on the information available, the Office of Drug Safety doubts whether severe angioedema associated with omapatrilat can be effectively managed by a program primarily focused on education. We believe it is unlikely that the proposed risk management plan will reduce the risk of severe omapatrilat associated angioedema to a level generally observed with currently marketed ACE inhibitors.

Reviewed By:

Concur:

Michael F. Johnston, R.Ph.

Claudia Karwoski, Pharm.D.

Safety Evaluator

Team Leader

CC: HFD-400 MHimmel/PSeligman
HFD-410: ATrontell/JBest/JStaffa
HFD-430: Drug Files(omapatrilat)/ JBeitz/ATrontell/CKarwoski/MJohnston/SLu/
CKortepeter/PGuinn/SBirdsong
HFD-110: Division File/IND 48,035/NDA 21-288/DThrockmorton/NStockbridge/
CLocicero/JPelayo
HFD-2 MedWatch

Electronic File Name (Final Version): omipatRM06.XX.02.doc

Appendix 1.

Angioedema-Related Wording from Proposed Omapatrilat (Vanlev) Labeling:

1. Black Box Warning at Beginning of Label:

USE IN BLACK PATIENTS
VANLEV can cause an increased incidence and severity of angioedema in black patients compared to non-black patients. The benefits and risks of prescribing VANLEV to black patients should be considered carefully before initiating treatment. See WARNINGS: Angioedema.

2. Contraindications Section:

CONTRAINDICATIONS

VANLEV is contraindicated in patients with a known sensitivity to omapatrilat, or any other component of this formulation, and in patients with a history of angioedema.

3. WARNINGS Section:

WARNINGS:

Angioedema

VANLEV can cause an increased incidence and severity of angioedema in black patients compared to non-black patients. The benefits and risks of prescribing VANLEV to black patients should be considered carefully before initiating treatment.

Angioedema most commonly presents as superficial swelling of the eyelids, face or lips, or may involve the tongue, glottis, and/or larynx. It may occur at any time during treatment. If a patient develops angioedema, VANLEV should be discontinued immediately and appropriate therapy and monitoring should be provided until complete and sustained resolution of the signs and symptoms has occurred.

Rarely, patients treated with VANLEV have developed airway compromise associated with angioedema. Angioedema associated with laryngeal edema can be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway compromise, appropriate therapy such as parenteral catecholamines (e.g. subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), corticosteroids and/or measures necessary to ensure a patent airway (including orotracheal intubation), should be promptly provided.

Administration of VANLEV should be initiated at a dose of 10 mg once daily for 2 weeks and titrated to the maintenance dose to achieve blood pressure control according to the JNC-VI Guidelines. Initiating therapy at a higher dose may increase the risk of severe angioedema, including laryngeal edema and airway compromise.

The incidence and severity of angioedema with VANLEV and enalapril were carefully examined in the 25,166 patient OCTAVE study. VANLEV was administered using a starting dose of 10 mg once daily for 2 weeks. All patients were then titrated to 20 mg once daily for 2 weeks and then electively titrated to 40 and 80 mg once daily. Enalapril was administered using a starting dose of 5 mg once daily for 2 weeks. All patients were then titrated to 10 mg once daily for 2 weeks and electively titrated to 20 and 40 mg once daily. Overall, 12,609 patients received VANLEV in the OCTAVE study, including 1,300 black patients.

Incidence

In the OCTAVE study, the overall incidence of angioedema during the 24 weeks of treatment was 2.17% in patients who received VANLEV versus 0.68% in patients who received enalapril. The relative risk for angioedema with omapatrilat compared to enalapril was 3.17 (95% CI 2.52 to 4.12). The incidence of angioedema associated with either treatment was approximately three times higher in black compared to non-black patients (Table 6).

Table 6: Comparative Incidence of Angioedema in the OCTAVE Study

Patient Group	Incidence (%)
Overall	
VANLEV (n=12609)	2.17
Enalapril (n=12557)	0.68
Black Patients	
VANLEV (n=1300)	5.54
Enalapril (n=1237)	1.62
Non-Black Patients	
VANLEV (n=11309)	1.79
Enalapril (n=11320)	0.58

Risk Factors

VANLEV can cause an increased incidence and severity of angioedema in black patients compared to non-black patients. The benefits and risks of prescribing VANLEV to black patients should be considered carefully before initiating treatment. In the OCTAVE study, the incidence of angioedema with VANLEV in smokers was higher than the overall population. Prior treatment with an ACE inhibitor did not appear to affect the risk of developing angioedema with VANLEV. Patients with a history of angioedema of any etiology should not take VANLEV (see **CONTRAINDICATIONS**).

Severity

Rarely, patients treated with VANLEV have developed airway compromise associated with angioedema. There were 2 events of airway compromise in the OCTAVE study, both in VANLEV treated patients. One of the events was an anaphylactic reaction in a non-black patient which occurred shortly after the first dose (10 mg) and responded promptly to treatment with epinephrine (see **WARNINGS: Anaphylaxis**). The other event was a case of progressive oropharyngeal and laryngeal swelling in a black patient that occurred during maintenance therapy with VANLEV 80 mg, and required intubation/tracheotomy prior to resolution.

There was no airway compromise in the remaining events. The most common manifestation for both VANLEV and enalapril treated patients was face or lip swelling. Tongue swelling, difficulty swallowing and difficulty speaking were more common findings in VANLEV treated patients whereas face and eyelid swelling and flushing/facial redness were more common in enalapril treated patients.

Relationship to Dose

Out of 12,609 patients (including 1,300 black patients) who received VANLEV starting at 10 mg in the OCTAVE study, one black patient experienced severe angioedema requiring intubation/tracheotomy. In 3361 patients who received a starting dose of 20 mg once daily in controlled hypertension clinical trials other than OCTAVE, there were 4 cases of severe angioedema requiring intubation and/or tracheotomy, 2 of which occurred in 645 black patients treated. **Administration of VANLEV should be initiated at a dose of 10 mg once daily for 2 weeks and titrated to the maintenance dose to achieve blood pressure control according to the JNC-VI Guidelines. Initiating therapy at a higher dose may increase the risk of severe angioedema, including laryngeal edema and airway compromise.**

After initiation of treatment with VANLEV 10 mg in the OCTAVE study, treatment with higher doses of VANLEV did not significantly increase the risk of angioedema compared to lower doses. If treatment with VANLEV is interrupted for several days or longer, treatment should be reinstated at a dose of 10 mg once daily for 2 weeks and retitrated to the maintenance dose to achieve blood pressure control.

Time Course of Onset

In OCTAVE, the incidence of angioedema during the first day of dosing was 0.70%. Most of these first day events occurred within 4 hours. With chronic treatment, the risk of angioedema decreased sharply over time. The incidence of angioedema for weeks 1-4 was approximately 1.36% compared to 0.10% for weeks 21-24.

Management

If a patient develops angioedema, VANLEV should be discontinued immediately and appropriate therapy and monitoring should be provided until complete and sustained resolution of the signs and symptoms has occurred.

Angioedema associated with laryngeal edema can be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway compromise, appropriate therapy such as parenteral catecholamines (e.g. subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), corticosteroids and/or measures necessary to ensure a patent airway (including orotracheal intubation), should be promptly provided.

Most of the patients who developed angioedema during the OCTAVE study received no treatment or treatment with an antihistamine only. Epinephrine or corticosteroids were provided to approximately 40% of the patients who developed angioedema while receiving VANLEV. With cessation of study therapy and prompt treatment, there were no serious clinical sequelae for any of the events. Approximately half the events associated with VANLEV resolved within one day and 90% resolved within 1 week.

Information for Patients

Patients should be informed about the signs and symptoms of angioedema and instructed to be cognizant of any face or neck swelling while receiving VANLEV. Angioedema may present as superficial swelling of the eyelids, face or lips, or may involve the oropharynx including the tongue, glottis or larynx. The patient should be advised to stop taking VANLEV and notify the physician if superficial swelling involving the eyelids, face or lips occurs. If there is involvement of the oropharynx, including the tongue, glottis or larynx, the patient should stop taking VANLEV, notify the physician, and seek medical attention immediately.

4. In the “Information for Patients” section:

Angioedema

Patients should be informed about the signs and symptoms of angioedema and instructed to be cognizant of any face or neck swelling while receiving VANLEV. Angioedema may present as superficial swelling of the eyelids, face or lips, or may involve the oropharynx including the tongue, glottis or larynx. The patient should be advised to stop taking VANLEV and notify the physician if superficial swelling involving the eyelids, face or lips occurs. If there is involvement of the oropharynx including the tongue, glottis or larynx, the patient should stop taking VANLEV, notify the physician, and seek medical attention immediately.

(see **WARNINGS: Angioedema**).

5. In the “Adverse Reactions” section:

The OCTAVE Study

Other than angioedema (see **WARNINGS: Angioedema**), the tolerability of VANLEV was similar to enalapril.

Angioedema

The incidence and severity of angioedema associated with VANLEV and enalapril were carefully examined in the OCTAVE study (see **WARNINGS: Angioedema**).