13 October 2005

Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS SEPTEMBER 2005

The Uniform Formulary Beneficiary Advisory Panel commented on the DoD Pharmacy & Therapeutics Committee recommendations that resulted from the August 2005 meeting.

1. Angiontensin Converitng Enzyme Inhibitors: The P&T Committee recommended that moexipril, perindopril, quinapril, and ramipril be classified as non-formulary and that benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril be classified as formulary on the UF. The Committee recommended a 120-day implementation period.

Summary of Panel Comments:

- The Panel voted 5-2 (one abstained) to ***non-concur*** with the P&T Committee recommendation for ACE Inhibitors. The non-concurring panel members voted unanimously that their non-concurrence was because the P&T Committee recommendation that ramipril (Altace) be placed in the non-formulary tier.
- The Panel requests that the ability to look at the recommendations on individual agents be re-looked. This issue may have resulted in the majority non-concurrence vote.
- The process of notifying patients and providers led to a non-concur vote on the implementation period. The word is not being disseminated in an effective manner either to providers or to beneficiaries.
- The generic quinapril is actually being dispensed at the $3.00 co-pay; however, the recommendation treats the drug as though it were a brand name drug.
- The Panel would like a cost comparison between the drugs going on the non-formulary to the nearest drug (in cost) that is on the formulary, rather than comparing the least expensive to the most expensive.

Director, TMA: BW

☑ These comments were taken under consideration prior to my final recommendation.

2. Calcium Channel Blockers: The P&T Committee recommended that the following changes be made to the Uniform Formulary with a 150-day implementation period:

1) Dihydropyridines: Isradipine IR and CR, nicardipine IR and SR, and amlodipine be classified as non-formulary, with nifedipine IR, nifedipine CC/XR/ER, felodpine, nimodipine, and nisoldipine classified as formulary on the UF.

2) Verapamil: verapamil extended release (Verelan), verapamil extended release for bedtime dosing (Verelan PM and Covera HS) be classified as non-formulary, and verapamil IR and verapamil SR be classified as formulary on the UF.

3) **Diltiazem**: diltiazem LA be classified as non-formulary, and diltiazem IR, diltiazem SR, and diltiazem CD/XR/XT be classified as formulary on the UF.

Summary of Panel Comments:

- The panel voted 8-0 in favor of the P&T Committee's recommendation.
- The Panel did not vote for nifedipine immediate release to be a cardiovascular agent.
- Communications about formulary changes remains a huge concern of the panel, given the large number of beneficiaries affected by this recommendation. The Panel placed special emphasis on reaching out to TRICARE Reserve Select and TRICARE for Life beneficiaries.
- The committee needs to consider how to address agents with multiple indications.

Director, TMA,: BW

☑ These comments were taken under consideration prior to my final recommendation.

3. Alpha Blockers for Benign Prostatic Hypertrophy: The P&T Committee recommended that tamsulosin be classified as non-formulary, and that alfuzosin, doxazosin, and terazosin be classified as formulary on the UF. The P&T Committee recommended 120-day implementation period.

Summary of Panel Comments:

- The Panel voted 8-0 to concur with the P&T Committee recommendations.

Director, TMA: BW

☑ These comments were taken under consideration prior to my final recommendation

4. Prior authorization for pramlintide (Symlin): The P&T Committee recommended that a PA for be required for pramlintide because of safety concerns.

Panel Comment:

- The Panel voted 8-0 to concur with the P&T Committee recommendations.
- The Panel applauded the P&T Committee for its fast action in this matter.
- The panel notes that beta blockers can mask the signs of hypoglycemia and asks that this be taken into account.

Director, TMA: BW

☑ These comments were taken under consideration prior to my final recommendation

Uniform Formulary Beneficiary Advisory Panel

Meeting Summary
September 28, 2005
Washington, D.C.

Panel Members Present:

- Sydney Hickey, Chair
- John Class
- Deborah Fryar
- Marshall Hanson
- Rance Hutchings
- Lisa Le Gette
- Jeffrey Lenow
- Charles Partridge

The meeting was held at the Naval Heritage Center Theater, 701 Pennsylvania Ave., N.W., Washington, D.C. Major (MAJ) Travis Watson, the Designated Federal Officer (DFO), called the proceedings to order at 8:00 A.M.

Opening Comments

After reviewing the layout of the facility for those present, MAJ Watson summarized the agenda, introduced the panel members present and identified the objectives of the meeting:

- Discuss recommendations of the DOD P&T Committee meeting, 17-19 August 2005, in San Antonio, TX.
- Discuss drugs in the therapeutic classes of:
  -- Angiotensin Converting Enzyme (ACE) Inhibitors
  -- Calcium Channel Blockers
  -- Alpha Blockers for Benign Prostatic Hypertrophy.
- Discuss prior authorization requirements for pramlintide injection
- Review Committee recommendations, make comments, and forward to the Director, TRICARE Management Activity (TMA), for final decision to approve, disapprove, or modify the recommendations

MAJ Watson then reviewed some rules for today's meeting: (1) only the Panel will participate in the meeting; (2) only the Panel may address questions to the briefers; (3) audience comments and interaction must be confined to the time allotted on the agenda (0830-0930) and then only to individuals designated and approved to address the Panel as private citizens; and (4) private citizen comments may be submitted in writing.

MAJ Watson noted that the minutes of the meeting are being recorded and will be reduced to writing. All comments made here today are for the record and will be published.

MAJ Watson announced that no private citizens had requested to address the Panel in advance of the meeting. He then asked if there were any private citizens present who wished to offer comments. There were none.

The Chairperson, Ms. Hickey, began the Panel proceedings by thanking MAJ Watson and Rich Martel for their support of the Panel. She then noted that, per advice from the Panel's Counsel, all discussions among Panel members related to the subject matter under discussion must be public and must be recorded. The Panel can discuss among themselves the matters brought before it so long as the discussions are public and recorded.

Ms. Hickey next spoke to the other Panel Members about a certain class of beneficiary. She noted that the Panel's previous discussions had revolved around beneficiaries having to pay higher co-payments for those drugs that go on non-formulary status. She said there is one class of beneficiary who does not have the freedom to get a non-formulary drug: active duty service members. These beneficiaries must obtain a medical necessity before they can obtain a non-formulary drug. Active duty family members overseas enrolled in a Military Treatment Facility are another group of people who may be financially penalized by not having the option of obtaining drugs at a retail pharmacy. Non-formulary drugs cannot be carried in the MTF, so unless the individual has medical necessity established the financial penalty would amount to an initial fee of $500 and a 50 percent co-payment. Further, regarding active duty service members, Title 10 of the United States Code at Section 1074g (a) (8) that the Secretary shall ensure that an eligible covered beneficiary may continue to receive coverage for any maintenance pharmaceutical that is not on the Uniform Formulary and that was prescribed for the beneficiary prior to October 5, 1999. She reads this to mean that any active duty service member who was receiving maintenance medication on October 5, 1999, who is still on active duty and still on that maintenance medication should be able to receive that medication without going through medical necessity if it is non-formulary. Ms. Hickey said she doesn't know how the Department is going to do that, but she asked Counsel to verify the statement.

MAJ Watson further clarified the matter of discussions among Panel Members by indicating that Members shouldn't discuss deliberations or proceedings among themselves during the breaks or outside the meeting.

MAJ Watson next introduced Lieutenant Colonel (LtCol) Dave Bennett, Director of Clinical Operations at the Pharmacoeconomic Center (PEC) to make the presentations to the Panel.

Presentation on ACE Inhibitors

[Insert script pages 1 through 12]

Panel Questions On ACE Inhibitors

At the conclusion of the PEC presentation the subject was opened for questions from the Panel Members.

Mr. Partridge commented that the decision to exclude ramipril from the formulary seems to have been based on the fact that the number of active duty personnel who use it is small and, therefore, the benefit to the active duty force would be less than to the other beneficiaries. Ms. Allerman said the P&T Committee looked at the patient population for the active duty, the retail and the mail order points of service. She said it is a key point. The patient population that gets the real benefit of ramipril is a very small population. The Committee felt that these patients could be handled through the medical necessity process. The typical patient is using ramipril for hypertension and doesn't have any of the other factors mentioned that make them a very high risk. For hypertension, the patients can use one of the other medications because they all work the same for hypertension.

Mr. Class asked what the definition was meant by "a few." Ms. Allerman said that the system has 670,000 patients using ACEs in general. Of those, ten percent fit the criteria for the HOPE trials whereas over thirty-three percent are using ramipril for hypertension.

Mr. Class asked if that meant about 60,000 patients fit the high risk category.

Ms Allerman said the answer to the question is "no." Of the 670,000 ACEs users, 67 percent are using lisinopril. The vast majority of the patients are not on ramipril.

Ms. Hickey noted that she thought the figure given for those on ramipril was 115,000 and that 33 percent of those were on it for high blood pressure only, leaving 76,000 who are receiving the drug for other reasons.

Maj Tiller replied that the PEC did a retrospective analysis, looking at the patients who were taking ramipril. If they were on no other cardiovascular, heart medication, diuretic, or a diabetic medicine, the PEC assumed that the patients were probably taking the medicine for just hypertension. That amounted to about 33 percent. What they were not able to show is that the other patients had the high cardiovascular risk. The PEC is not saying that the remaining 67 percent have cardiovascular diseases.

Ms. Hickey asked whether the PEC is saying that it doesn't really know whether the 76,000 patients are or are not using ramipril for cardiovascular problems.

Maj Tiller responded that ten percent of patients who have or have had cardiovascular problems have the specific conditions for which ramipril would be appropriate.

Mr. Hanson observed that looking at the total population puts the figures somewhere between the 60,000 figure, mentioned by Mr. Class and 76,000. He said it would be statistically inappropriate to apply the ten percent figure to the total population taking ramipril and say that only ten percent of them fit within the HOPE criteria. There is a

reason that 17 percent of the overall population is getting that drug. Perhaps 33 percent is high, but there seems to be a correlation between the difference of ramipril and the overall ten percent of the general population. His reading is that somewhere between 55,000 and 75,000 patients may have needs beyond hypertension.

Ms. Allerman said the PEC asked the providers how frequently they come across a patient who would fit the criteria of the HOPE trial. The P&T Committee members who are providers – internists -- said they never see patients who are this severely ill. In terms of the overall DOD population, the providers do not see these patients that frequently. She also said another reason why the use of ramipril is so high (17 percent) is that when the HOPE trials came out, ramipril actually was on the DCF along with lisinopril. It was subsequently removed from the DCF in July 2004. A lot of providers said that the reason for why there was such a high use of ramipril was that at one time it was available at very low cost. She said that may account for some of the 17 percent usage.

Mr. Class asked whether the PEC representatives had a feel for what the patient base was of the providers on the P&T Committee. He said that if their patients are younger, active duty patients, then he could understand why they don't see many severely ill patients.

Ms. Allerman said the P&T Committee has representatives from all of the major military medical facilities: Brooke Army Medical Center, Bethesda and others. The Committee doesn't just have physicians who are only at small outpatient facilities with no inpatient beds. The clinicians on the Committee reflect a wide range of patients.

Ms. Hickey said she believes that a lot of the providers associated with teaching hospitals do have a wide range of patients, up to the Medicare-eligible population. However, with the growth of the Medicare-eligible population and the reduction of space in teaching hospitals, she believes that group of patients is no longer as well represented as they would have been She asked if any of the providers surveyed were seeing patients in this group in the civilian sector.

Ms. Allerman answered that only Military Health System providers were questioned.

Mr. Hutchings said his organization's experience suggests that the at-risk group being talked about is severely diseased patients. He said there is a very small number of patients who actually meet the 10 milligram criteria. Because of this he can understand why there would be a fairly low number of observations among the providers surveyed. He said he agrees with the medical necessity recommendation.

Dr. Lenow recused himself from making any decisions on this issue. However, he did offer general comments. He said he recognizes the value of collecting data from randomized trials and other means, but is pleased to hear that the Committee surveyed clinicians to obtain their input because their opinion is based on experience. He believes the future of formulary decision making will hinge on that approach. It would be best to be careful not to make too generalized a guess based on the background assumptions used in clinical trials. He also said that the earlier ARB-class drug review in March shows drugs that have been subjected to evidence-based clinical trials get preference in the Military Health System and that preference was also given to agents that met certain

cost considerations. He believes that the weight of clinical evidence should be allowed to stand its ground, even in the face of cost considerations.

Mr. Class raised the issue of cost considerations, which he recognizes as a difficult issue for the Government. He noted that the presentation referred to one group of agents being significantly more costly. He asked again if information could be provided to the Panel to clarify what the word "significantly" means in terms of the cost differential on ramipril.

MAJ Watson said the agency recognizes that the cost component is important and that the information being requested would be valuable to have. He noted again that it is difficult for the Agency to respond to the requests because it is not able to divulge such information in a public forum. The Agency has taken the matter under advisement based on the Panel's earlier requests and is trying to work on ways to deal with the problem.

Mr. Class said that from his viewpoint he isn't looking for specific cost information. He pointed out that the analytical review found that, clinically, ramipril had advantages but the decision to exclude it from the formulary is based on cost and yet no information about cost is available.

One Panel Member noted that it says in the background information that ramipril was tenfold higher than the most cost-effective medication. Mr. Class said it would be more important to know how ramipril compares, cost-wise to the next highest price agent rather than comparing it to the least expensive.

Mr. Hanson agreed, suggesting that the Panel be provided with the delta between the agents in a drug class. He said when the Panel is dealing with drug classes where there are different benefits for different drugs it would be helpful to have a visual display – some kind of a matrix – showing the benefits and cost factors for the different drugs.

Ms. Allerman asked about the usefulness of the information in the handouts from the Power Point slides.

Mr. Hanson said he was most interested in having a matrix that would allow him to make comparisons. He said there appear to be different drugs in the Uniform Formulary that would cover all of the things that ramipril does. He would just like to see this laid out in a matrix.

Dr. Lenow said caution is needed when dealing with the conclusions reached about ramipril. He said this is where the cynicism comes in about trials – some trials stand up better than others. The importance of time-tested quality trials, and their impact from an evidence-based medicine perspective, is a good example of how the argument might be made that "class effect" in a certain category of agents can be disputed owing to solid evidence. Without ramipril, the Formulary basically won't have the medication for the high risk cases without the medical necessity exception.

Ms. Hickey asked how, looking at the criteria used in the past for medical necessity, the system can handle preventive drugs. Dr. Allerman asked whether Ms. Hickey was referring to prevention of renal disease or the high cardiovascular risk. Ms. Hickey said

she was asking about preventing high cardiovascular risk. Ms. Allerman said if the patient is over the age of 55, has a history of stroke, heart attack, peripheral vascular disease, diabetes, hypertension or high cholesterol – the exact criteria of the HOPE trials – these get listed on the medical necessity form. The patient would then meet the criteria in the check-off box, the medical necessity would be approved and the patient could get the ramipril at the lower co-pay. Because the studies have clarified the factors, it will be easier to meet the medical necessity criteria.

Ms. Hickey noted that prevention of diabetes was mentioned in the analysis regarding the relative clinical effectiveness but not in the clinical effectiveness conclusions. She asked if that was because the PEC felt that the HOPE trials were not conclusive on this matter. Ms. Allerman said that the concept of delaying the development of diabetes is still experimental. Nothing has been definitively concluded. It's kind of like a side effect when you look at the HOPE trial. However, the study investigator did not set out to discover this when the study was designed. There are three agents – captopril, enalapril and ramipril – that showed indications; but they don't really know for sure. Ramipril has a trial underway that should be completed in 2008. Until there is better data, the idea is an interesting but unproven concept.

Ms. Hickey said she thought the HOPE II trial, which continues following a significant number of those patients for another two and a half years, showed an increased amount of diabetes prevention. It also looked at a subset in which the drugs were used with aspirin and lipid-lowering drugs and, in that subset, did not show any difference. Ms. Allerman said that in the HOPE II trials the benefits of ramipril were pretty much sustained. But the HOPE II trials also continued the original trial which did not test diabetes from the start of the trail. Results are expected in 2008.

Ms. Hickey said she understood that looking at diabetes prevention was included as a specific objective in the HOPE II group. Dr. Allerman said the investigator has acknowledged that the study wasn't set up ahead of time to look at diabetes prevention. Ms. Hickey opined that the PEC's mix of clinical effectiveness and cost would have changed had the cardiovascular benefits and diabetes prevention been included – diabetes is extremely costly. Dr. Allerman replied that other studies found the same benefit for captopril and enalapril, although, again, it was not set out ahead of the trial to look at these benefits. The Committee did recognize these benefits for the other two drugs (question number nine, page 3 of script).

Ms. Le Gette said that as a clinician, she did not really have any opposition to the P&T Committee's recommendation. She did not understand the clinical value of keeping Mavic (trandolapril) on the formulary when there are so many generic alternatives that are clinically and financially positive. She asked about quinapril products on the market and whether a lawsuit was the reason that this generic product for Accupril was not included in the PEC's analysis. Ms. Allerman said there is generic quinapril and generic moexipril on the shelves. However, the PEC didn't know when the model was set up whether the generics were going to be pulled back because of the lawsuit. She believes that technically the agents should not be out there because of what the lawsuit showed. Maj Tiller added that the PEC used the best information available at the time the model was run. That information suggested that quinapril should not be included. As with any analysis, the PEC can follow the drug class forward and revaluate at a later time. Ms. Le

Gette commented that claims for quinapril products are currently adjudicating on PDTS. She then asked what the copay will be for those products if Accupril becomes non-formulary, given that quinapril was not considered in the overall analysis. A staff member in the audience commented that quinapril products would follow Accupril and process with a non-formulary copay of $22.

Ms. Hickey said the beneficiaries currently getting quinapril are probably paying a $3.00 co-pay. She noted that this seems to be another example where generics are being moved to the third tier, which would affect mail order and retail patients. The problem this will create in this case is that the drug won't be either formulary or non-formulary. A staff member in the audience stated that this matter wasn't addressed because of the pending litigation – drugs were not included in the analysis.

Ms. Hickey said that a patient who presents with a prescription now is being given one of the generics at the $3.00 co-pay, as she understands it. The drugs in question will not be either formulary or non-formulary because they were not looked at due to the lawsuit. Her question is what the patients are going to get when they present a prescription at the retail or TMOP pharmacy for a drug that is no longer listed either on formulary or non-formulary. The BAP is not being presented with a recommendation to move those drugs one way or the other. She would like to know if they would still be treated as generics.

Ms. Hickey also asked if the budget impact analysis included the cost of the additional appointments for the large number of people who will have to either move to another drug or get a medical necessity form. Or was the assumption that these people would have to be seen within the 120 day window anyway?

Maj Tiller said the cost was included in the model and further explained the assumptions used. He emphasized that network providers and MTF providers can be reached very easily.

Mr. Class said there will be a communication problem reaching non-network providers. Even with a 120-day implementation period and with a website available, there is no direct communication with this group.

Ms. Hickey read the following paragraph from the Final Rule in the *Federal Register*: "The intent of this transition period is to allow sufficient time for education and communication of this formulary status change, enabling coordination between beneficiaries and providers on whether to submit documentation of clinical necessity, continue therapy at the non-formulary tier, or modify therapy." She said the document further states: "The Department will incorporate the communication of formulary information into TMA's extensive marketing and education program that employs both electronic and print media." Ms. Hickey said this document can be found on the TRICARE web page.

She noted such marketing material doesn't say anything about why drugs were put on the formulary or the non-formulary. You will only find out which ones did. She said it is very apparent that the news releases are the only mechanism used. They are very general and don't get wide circulation. Whether the local newspapers will have any information is very problematic. It is clear to her that the dissemination of information using these

media is not very wide, and hundreds of thousands of patients are affected by the classes being discussed today. Whether the move is right, wrong or indifferent, these patients will be faced with choices. She said she believes that without adequate education about why the changes are being made as well as early education about what changes are being made, the system's reputation for being a world class operation will suffer. She doesn't want that to happen.

Ms. Hickey added she doesn't know how the Panel can force or encourage more education. She cited the advertising campaign for Levitra at a local MTF as an example of being proactive with the patient population, although she noted several gaps in the information provided. She said she realizes that the Panel has talked about this before, but she wants to raise the issue again, particularly since the patient population involved here is so large.

Mr. Hutchings commented that it looks like it would be an easy switch to say that generic medications are on the formulary and that brand name medications are not. He asked if that was considered. Maj Tiller said the cost-effectiveness is different for different agents. Whether or not the drugs are generic is not part of the decision process. Each agent is looked at individually in terms of the weighted average cost and effect. In the case of trandolapril, there was clinical evidence behind it. While it was more expensive than some of the other generics, the P&T Committee recommended that it be included on the basis of both cost and effect.

Dr. Lenow said he endorses Ms. Hickey's comments about communications. He asked if there was a budget for PR communications and if there was a unit responsible for crafting patient-friendly explanations of why actions were taken.

MAJ Watson said they go through the centralized Communications Division at TMA, which has a budget for marketing. He also said ESI has been reaching out to beneficiaries by sending out individual letters informing them of the change.

Ms. Hickey said she applauds ESI for doing that but the individuals affected by changes in the classes discussed previously were receiving their drugs through TMOP or the retail network for the most part. Very low numbers were receiving their drugs through the MTF. This time, the problem is reversed. ESI will not reach out to those people; it is up to the system to reach out to them. Also to providers.

MAJ Watson said his organization is developing a one-page monograph. They recognize that MTFs are a very important part of the marketing process.

Maj Tiller said the PEC has developed what they call "push out" documents. These are one-page documents that are intended for use by MTF providers and MTF pharmacies to help them implement Uniform Formulary decisions at the MTF.

Ms. Hickey suggested that someone should be working with the marketing people at TMA to develop something for the beneficiaries. It would let them know what they need to talk to their provider about. She offered the Panel's help in getting that done.

Ms. Fryar asked for clarification on about whether the Panel has to vote on the recommendations as a package deal, i.e. all or nothing. MAJ Watson answered that the Panel's comments relate directly to the recommendations from the P&T Committee, so the Panel can formulate its comments however it wants to as long as they relate to the recommendations.

Ms. Fryar asked whether the Panel could, if it wanted to, pull one agent out for a separate vote. MAJ Watson said the Panel can comment on the recommendations and handle its preferences that way. Ms. Fryar asked if this meant the Panel has to concur or non-concur on the whole package. MAJ Watson answered affirmatively. It was further clarified that the Panel may not vote on the drugs in a class individually, but it is free to offer comments on the recommended formulary status of any of the drugs included in the recommendations.

Ms. Fryar also asked about ramipril and the other drugs that are not available in generic form. She asked what happens when generics are developed for these drugs – whether the brand names go back on the formulary or will be left on the non-formulary. Lt Col Bennett replied that the PEC has the option of looking at the classes whenever something happens within it that would affect the dynamics. He said ramipril is scheduled to go generic in 2008 and that would probably be a good time to re-open this class, depending on what happens with the price. He noted that about 20 percent of the drugs drive about 80 percent of the system's cost. Consequently, the PEC wants to look often at the higher cost drugs before they even get to some of the bottom classes that might affect only a small percentage of total cost. This class is in the top ten of drug expenditures, so if something happens in it there is a high likelihood that it will be looked at again within a couple of years.

Mr. Hutchings asked when ramipril goes generic what will happen with the copay. Maj Tiller said that whether brand name or generic the agent keeps its non-formulary status until it is looked at again.

Ms. Hickey clarified that when the panel votes it is voting on "ramipril" rather than on its brand name.

<u>Panel Discussion of the ACE Inhibitor Drug Class</u>

The Panel then discussed the recommendations of the P&T Committee regarding this drug class.

Mr. Hanson said the structure of how the vote is going to be taken is frustrating. He said he will vote to not concur. He thinks it would expedite the process to be able to break out individual drugs and vote on them. The way things stand, if there is a problem with an individual drug that a Panel Member doesn't think is at the right level or if there is a problem with the recommendations regarding brand name versus generic, these issues can create a non-concurring vote. He believes the concurring process should be re-examined to provide a broader approach to making recommendations in the future.

Mr. Partridge said he, too, intends to vote not to concur. As a beneficiary and as a layman, the material presented makes it clear that ramipril is the drug he would want if he had a problem with his heart, and the discussions only reinforce that impression.

Mr. Hutchings feels it gets sticky when comments are added. He is leaning toward concurring. He believes the information provided outlines fairly well why certain decisions were made. He is concerned that ramipril has become the main question. For the beneficiaries he represents, his organization will be able to get information to the providers prior to the drug moving to non-formulary status. He thinks it would be beneficial to have a process in place to identify what ramipril should be used as a treatment for. He also has a problem with quinapril. It is being dispensed now at the $3.00 co-pay level and he believes it should be left there.

Mr. Class said he is leaning toward non-concurrence because he believes too much dependence is being placed on medical necessity and the effect of that on the patients. He also has a problem with not being able to get to the standard providers. He doesn't see how information is being communicated to the rest of the country, even after visiting the website. He is also concerned about the change proposed for ramipril. There is a separation and if more studies need to be done to determine whether it is or is not more effective, he would lean toward leaving it on the formulary until it is proven that it isn't. There are reasons why people are going on it.

Ms. Fryar said she is struggling with not being able to separate out one of the drugs. She recognizes that ramipril has a higher cost but it seems to be especially appropriate for some patients.

MAJ Watson indicated that there is nothing to prevent the Panel from inserting specific comments about a particular drug not being appropriate for non formulary status to explain a non-concur vote if that's what the Panel wants to do. However, the P&T Committee's recommendation will be sent forward as it is.

Ms. Hickey said she understands that if the Panel votes to non-concur with the Committee's recommendation, it can state the reason for the non-concurrence. If it votes to concur, the Panel can also say it has a concern about the recommendation for a particular drug. MAJ Watson agreed with these statements.

Mr. Hanson said the last two meetings of the Panel have led him to believe that a vote to non-concur carries more of a message than a vote to concur with an expression of concern.

Panel Vote on Formulary Recommendation for ACE Inhibitors

The Chairperson called for a vote on the Uniform Formulary recommendation for this drug class:

"Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ACEs, and other relevant factors, the P&T Committee recommended that moexipril, perindopril, quinapril and ramipril be

classified as non-formulary under the UF and that benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril be classified as formulary on the UF."

The Panel voted as follows:

- Concur (2) – Ms. Le Gette and Mr. Hutchings
- Non-concur (5) – Mr. Partridge, Ms. Fryar, Mr. Class, Mr, Hanson and Ms. Hickey
- Abstain (1) – Dr. Lenow

Panel Discussion of Implementation Plan for ACE Inhibitors

Ms. Hickey asked if there was any discussion of the proposed 120-day implementation plan.

Mr. Hutchings said his vote to concur would have included a comment that the implementation date should be moved out beyond 120 days. There is a significant lag time between the time people find out and when the notification is made. His particular concern is with ramipril. He believes it will be possible to move patients off ramipril if the system provides for a 180-day implementation time.

Ms. Fryar noted that the Panel has asked the question in its previous meetings "What is the standard policy for implementation?" Both 90 days and 120 days have been mentioned. It is important to make it easier for those who need to notify the beneficiaries and the providers. She would like to have an answer to the question.

Panel Vote on the Implementation Plan for ACE Inhibitors

The Chairperson next called for a vote on the implementation plan:

"The Committee voted to recommend an implementation period of 120 days."

The Panel voted as follows:

- Concur (1) – Ms. Le Gette
- Non-concur (6) – Mr. Partridge, Ms. Fryar, Mr. Class, Mr, Hanson, Mr. Hutchings and Ms. Hickey
- Abstain (1) – Dr. Lenow

Panel Comments

Ms. Hickey said the Panel comments include:

- The process of not being able to look at the recommendations on individual drugs may have resulted in the majority non-concurrence vote. The Panel requests that this matter be looked at again.

- The process of notifying patients and providers led to a non-concur vote on the implementation period. The word is not being disseminated in an effective manner either to providers or to beneficiaries.
- The generic quinapril is actually being dispensed at the $3.00 co-pay and yet the recommendation treats the drug as though it were a brand name drug.
- The Panel would like a cost comparison between the drugs going on the non-formulary to the nearest drug that is on the formulary rather than comparing the least expensive to the most expensive.

Mr. Hutchings added that it would be very helpful to see what the least expensive drug would be to replace ramipril. Mr. Partridge noted that the Panel didn't have information about how frequently the least expensive drug is used. The Panel generally agreed that more detailed cost comparison information is needed while leaving proprietary information where it needs to be.

Mr. Hanson said he agrees with Mr. Hutchings on the implementation period. A 90-day implementation period gives providers only a two-week period to work with because of the lag time in the system. There should be a "true" 90-day implementation period allowed.

Dr. Lenow said he had a broader question concerning what impact, if any, the Panel's comments had on the final decisions made as a result of the first two meetings. MAJ Watson said Dr. Winkenwerder considered all of the BAP comments prior to making his decisions. The concept of including a cover sheet with the Panel's comments has been discussed.

Ms. Hickey said all of the P&T Committee's recommendations regarding the previous drug classes have been signed off on. She noted that the Final Rule clearly states that Dr. Winkenwerder does not have to explain to the Panel why he made his decisions. He doesn't have to respond back to the Panel because he is not subject to the Panel's jurisdiction.

Dr. Lenow said that from the standpoint of quality analysis or process improvement, it would be beneficial if the Panel could get some insight into what impact its concerns may have. It goes to the question of why the Panel sits.

Mr. Class said he agrees with Dr. Lenow. The Panel puts a lot of thought into the process and doesn't have the benefit of a lot of the information available. He sees it as a simple matter of professional courtesy. Without that input the Panel has no understanding of why it isn't included in the decision. The Panel's discussions are public and yet the public has no indication of why its recommendations are or are not accepted.

Mr. Partridge stated that his non-concurrence is because ramipril is not listed as a formulary drug. Mr. Marshall, Mr. Class, Ms. Fryar and Ms. Hickey all concurred in this statement as being the reason for their non-concurrence.

Ms. Hickey said that Dr. Winkenwerder should be made aware that the education of both beneficiaries and providers is a concern of the highest magnitude to the members of this

Panel. Also of concern is the extent to which formulary decisions are being made on the basis of cost.

Presentation on Calcium Channel Blockers

Ms. Allerman presented the findings of the P&T Committee on the Calcium Channel Blocker drug class to the Panel.

[Insert script, pages 13 through 24]

Panel Questions on Calcium Channel Blockers

Ms. Hickey began the questioning by asking for a clarification of whether diltiazem SR is included as a formulary drug. She said one read-ahead included it and one did not. After some discussion of the tables provided in the read ahead materials, Ms. Allerman replied that diltiazem IR, SR and ER (NOTE: ER not in script) are recommended for inclusion in the formulary.

Ms. Hickey also asked about nifedipine immediate release, which the read ahead says is no longer used for cardiovascular conditions due to a high incidence of reflux tachycardia leading to mortality. She noted that it is recommended for inclusion on the formulary and asked for clarification. Ms. Allerman said nifedipine immediate release is not used for hypertension but for premature labor. Where it is used, physicians do not see an increased incidence of death. There are only a small number of patients on it and it is not being used for cardiovascular conditions.

Ms. Hickey said the problem is that the Panel was told that the review was only going to look at the efficacy of these drugs as far as cardiovascular conditions were concerned. This moves the analysis into another direction. She does not want to deny anybody a drug, but she doesn't want the system to look foolish by recommending a drug that has a high mortality for inclusion in the formulary for cardiovascular medicines. Further discussion among the Panel clarified that the drug is being kept on the formulary for reasons that aren't included in the read-ahead material.

Ms. Hickey said it would make her uncomfortable to vote on something that has a high mortality rate without any explanation as to why. She asked if it would be appropriate for the Panel to clarify that the drug is being left on the formulary for pregnancy reasons and those alone. Mr. Burleson of the Office of General Counsel said that the wording or scope of the P&T Committee's recommendations can't be changed at this point. The Panel has to deal with the recommendations as they stand. However, he advised the Panel that it can make whatever comments and express whatever concerns it may have about this therapeutic class.

Dr, Lenow said he also agrees with the Chairperson that the matter was intended to be a cardiovascular discussion. In looking at the purpose of this class review the wording clearly states that it was to look at the safety, effectiveness and clinical outcomes of calcium channel blockers when used for cardiovascular conditions. He said he thinks the

Panel's comments should point out that the Committee recommended the inclusion of the agent in a cardiovascular context. Mr. Hutchings noted that the material referred to is in the backup information. The recommendation itself makes no reference to cardiovascular. He said he could concur based on the language that's been presented.

Ms. Allerman said that the PEC develops one- or two-page papers to send out to the medical community. In this case, the papers can include a statement indicating that the medication, while on the Uniform Formulary, should not be used for hypertension or angina or cardiovascular conditions but was included because of its minor role in treating other conditions.

Mr. Hanson observed that the Uniform Formulary recommendations include five or six drugs that have generic equivalents. He asked if the names used here are drug names or names that would be specific to the formulary. Lt Col Bennett agreed that the class was a mixture of types. He said there are generic equivalents for verapamil, but there are a number of agents that are brand name agents which do not have generic equivalents because of their release mechanism. In those cases, brand names are used. He said that for the Uniform Formulary, there are generic equivalents for all the drugs that are included except for Sular. Generic equivalents are available for verapamil and diltiazem. The Formulary will use the best price for whichever is available.

Mr. Hanson asked what would happen to the generics if the Panel concurs with the recommendation, i.e. does the system consider verapamil to be a generic term or is it a specific sub-group that excludes the generics. Mr. Hutchings said the Panel would be voting to accept inclusion in the formulary of the brand name verapamil. Mr. Hanson asked if that action would result in inadvertently moving the generic groups from tier one to tier two. Ms. Allerman said that would not be the case. Maj Tiller said the drug would still be available at the $3.00 co-pay, if that is the concern.

Dr. Lenow acknowledged his understanding that the recommendations are drug-class focused and not clinically focused. But he noted that the verapamil and diltiazem cost-effectiveness discussions are presented in the context of hypertension and angina. He asked again whether the recommendations are meant to be considered in the context of the whole therapeutic class or on how the agents are used within that therapeutic class. He said when a drug has multiple uses – like migraine or pregnancy – if the analysis doesn't include all of those in the discussion of the class, he would believe that it really was focused on cardiovascular issues alone. If that was the case, then the Panel should also make its judgment based on cardiovascular consideration and not on things outside that use.

Lt Col Bennett replied that the process is still evolving. One of the problems the PEC has is that it can't put drugs in more than one category. Because of this, a clinical judgment was made about where to put items that were in overlapping categories. The particular agents that were competed in this class will not be competed in another class.

Dr. Lenow said he assumes the drugs will be appropriately labeled as to indications. Dr. Allerman agreed that they would. She also said that somewhere down the road the PEC would need to find a drug class they would fit in. Dr. Lenow said he understood. However, he remembers hearing nightmare stories about quick release nifedipine and is

concerned that the issues be properly dealt with. He is reluctant to sign off on including the drug without some admonitions.

Ms. Hickey asked if in future cases when there is a drug like this the Committee could recommend that a drug be included on the formulary for other than cardiovascular uses and non-formulary for cardiovascular uses. She is trying to figure out how this dilemma can be avoided in the future. She said that for today, if the Panel decides to concur in the Committee's recommendations, she would like the comments to be very clear that the Panel is not concurring that this drug should be used for cardiovascular conditions.

Mr. Class agreed and said the discussion raises the question of whether there are other uses for anything else being considered. He doesn't see how it would work to say that a drug is on formulary for one use and not on formulary for another use. He also asked about all of the things that the Panel has looked at in the past. His question is whether something has been put on non-formulary that should not have been put there because of its other uses.

Ms. Allerman said there is nothing in the drug classes considered earlier that would fit in this multiple-use category. She also noted that in the past the P&T Committee has gone back and clarified its minutes. The next Committee meeting is in November and the question can be raised at that time.

MAJ Watson said that TMA will take the issue raised under advisement.

Mr. Hanson asked a question about the recommended 150-day implementation time. He noted that the explanation given was the large number of patients now using drugs that will be in a non-formulary status and more time will be needed to move these patients to new drugs. He said this looks to him like trying to change the method of prescribing by using the Formulary as a sledge hammer to force something that could actually be accomplished through better education with the providers. He cited the chart at page 7 and said amlodipine, recommended as non-formulary, is the most frequently prescribed medication in this class. The next four agents underneath it are all formulary items. It emphasizes that there is a lot of use of the number one product and that a lot of habits – both for the provider and the patient – will have to be changed.

Mr. Hutchings said his view is that the change is long overdue for this medication. He said there has been very good marketing for amlodipine and that it has affected the way a lot of providers write prescriptions. He sees changing the co-pay as a good way to drive change.

Mr. Class said it sounds like we're putting the patients in a position where they might need to question the providers' decisions about what to prescribe. He said the implication is that when his physician says he's going to prescribe something he would have to do all the homework to say whether one drug is better than another. He said he didn't go to medical school and isn't equipped to do this, so he has a lot of problems with putting the responsibility on the patient.

Mr. Hutchings said in this case, the physician informing the patient that the drug is being moved to non-formulary should ring a bell. Mr. Class said the patient doesn't go back to

the doctor to ring a bell. The patient will go to the pharmacy and find out his medicine now costs $22.00. Now he has to go back and question the provider about the efficacy of the medicine when he's the one who originally prescribed it. He thinks that puts too much emphasis on the beneficiary.

Dr. Lenow said what is happening in the world of primary care medicine supports that. The American Academy of Family Practice commissioned a white paper two years ago called "The Future of Family Medicine." It was done because the primary care industry started to feel nervous that residents were drifting away from primary care medicine back to specialties. It is a powerhouse paper. It says that the world of primary care medicine, through which drugs like this are pretty much driven, is moving to a mode of patient self-determination and patient empowerment. All residents are now being trained this way and board re-certification will also hinge on this approach. Patients are being asked to be more responsible for their own care and for working with their primary care doctor to take a lot more control of their own care. It is how future physicians will be trained. He believes formulary decision making will have to recognize that the focus of primary care medicine and other specialties is changing.

A Panel member asked about bedtime dosing. Ms. Allerman said there is nothing special about bedtime dosing. The patient could just as well be given the medication in the morning. Verelan and Verelan PM are the exact same purple capsule. The labels are different. The issue is whether the compliance is better in the morning or in the evening. If a patient only has to take something once or twice a day, the instruction is based on when the patient is most likely to remember.

Ms. Le Gette noted that when Express Scripts was reviewing this class of drugs, they analyzed a large client's claims data to determine how many patients receiving Norvasc actually had drug markers for heart failure. The percentage was low, only 6.2% of patients using Norvasc. Ms. Le Gette asked the presenters if DOD had done similar analysis. Ms. Allerman noted that they had done this analysis, and that only about 5% of Norvasc users in the MHS actually had drug markers for heart failure.

Ms. Hickey asked about the pediatric use of amlodipine. She asked if the PEC expects that this drug will still be used for the pediatric population and if the medical necessity would be written differently for the pediatric population than for the adult population. Ms. Allerman said there are two pediatric specialists on the P&T Committee. Verapamil is included on the Uniform Formulary and there was a lot of discussion about pediatric use. Patients will be able to get Norvasc under the generic co-pay. There will not be a separate medical necessity form for pediatric patients. The general medical necessity form will be used, which is an automatic "yes." It will be available in retail and TMOP also.

Panel Discussion of Calcium Channel Blocker Recommendations

Ms. Fryar expressed concern about the implementation plan. She noted that this is a different time frame than the other classes – 150 days. She said she believes that 180 days should be the standard for any drug to allow for adequate education.

Ms. Hickey said she agreed and asked whether there is a reason for the number of days allowed for implementation other than the number of beneficiaries affected by the decision. Commander (CDR) Jill Pettit, a contracting officer's representative for the retail pharmacy, said there was a lot of discussion about implementation time frames. One reason is that the different time frame allows for a staggered start. Making all of the changes standardized at any number – 180 days, 150 days or any other time frame – would cause a lot of disruption with the contractors as well as with the beneficiaries. The reason 120 days was chosen for the first drug class is that the easiest way for the MTFs to communicate about the change is to put a "stuffer" into the bag when the prescription is refilled. Since most refills are for a 90-day supply, a 120-day transition period would give the MTF an opportunity to get a refill "stuffer" into the bag in time to effect a change before the next prescription or to get a medical necessity. With the calcium channel blockers the idea was to go through at least one refill cycle. So the implementation plan considers not just the MTFs but also the contractors.

Mr. Hanson said the concern is with how long it actually takes to get the word out. He said the 150 days actually works out to be 75 days of actual process time. If the need is to impact a 90-day refill cycle, the system should be allowing a 180-day implementation period at a minimum. To get 150 days actual time, the implementation period would have to be something more like 210 days. Ms. Hickey commented that by law and by federal rule the transition period has to be no more than 180 days. Mr. Hanson was asked to explain why what he said would be the case.

Mr. Hanson used the actual experience with erectile dysfunction drugs as an example. The Committee recommended a 90-day cycle, which was approved. By the time everything worked through the process there was only about two weeks available to make the change. Mr. Hutchings said there was actually a seven-week delay in getting the information on the decisions from the March meeting. In the end, his health plan had only two and a half weeks to implement the change. CDR Pettit asked whether that was a DOD issue or an issue with the health plan. Ms. Hickey said it was largely a DOD issue because a lot of the public stuff was not put out. The information from Dr. Winkenwerder's office was significantly delayed. The staff noted that the implementation date starts when Dr. Winkenwerder signs the recommendation, so they will try to make sure they get the information out as quickly as possible.

Ms. Hickey said she is aware that the TMOP and retail contractor were notified right away. She thinks there needs to be a method that provides for the timely notification of the Department's other partners, including the Uniformed Services Family Health Plan.

Dr. Lenow asked for additional clarification of the issue of off-label uses of drugs. He asked whether it is even appropriate for off-label uses to be considered. He is concerned because of the stories in the news. The Inspector General's number one target is off-label marketing as a side promotion. The approach used here almost tacitly endorses off-label uses. He wondered whether it is appropriate for the P&T Committee to even be looking at off label uses.

A staff member replied that the Code of Federal Regulations allows DOD to use off-label drugs provided that there is reliable evidence supporting their safety and efficacy. What they can look at in this regard are randomized control trials, published review literature in

American journals, statement of professional organizations and similar things. If there is no reliable evidence, the off-labels uses are taken off the table. With the Phosphodiesterase-5 (PDE-5) inhibitors, off label uses were taken off the table. With this class of drugs, an off-label use was also taken off the table. There is a process and the Committee is very careful about sticking to the regulation.

Mr. Hutchings commented that he thinks the recommendations of the P&T Committee are very valid and he intends to vote in favor of them.

Panel Vote on Calcium Channel Blockers Formulary Recommendation

The Chairperson read the P&T Committee's formulary recommendation for this drug class:

"Considering the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the calcium channel blockers, and other relevant factors, the P&T Committee recommended that:

1) DHP: Isradipine IR and CR, nicardipine IR and SR, and amlodipine be classified as non-formulary, with nifedipine IR, nifedipine CC/XR/ER, felodipine, nimodipine, and nisoldipine classified as formulary on the UF.

2) Verapamil: Verelan (verapamil extended release), Verelan PM and Covera HS (verapamil extended release for bedtime) be classified as non-formulary, and verapamil IR and verapamil SR be classified as formulary on the UF.

3) Diltiazem: diltiazem extended release for bedtime dosing be classified as non-formulary; and diltiazem IR, diltiazem SR and diltiazem CD/XR/XT be classified as formulary on the UF."

The Panel voted as follows:

- Concur (8) – Ms. Le Gette, Mr. Hutchings, Dr. Lenow, Mr. Partridge, Ms. Fryar, Mr. Class, Mr. Hanson and Ms. Hickey
- Non-concur (0)
- Abstaining (0)

Panel Vote on Calcium Channel Blockers Implementation Plan Recommendation

The Chairperson read the P&T Committee's implementation plan recommendation for this drug class:

"The Committee voted to recommend an implementation period of 150 days."

Panel Discussion on Calcium Channel Blockers Implementation Recommendation

Mr. Hutchings stated that he understands the reason for staggering the implementation times and agrees with it. He thinks the majority of patients will be notified rapidly through ESI.

The Panel voted as follows:

- Concur (8) – Ms. Le Gette, Mr. Hutchings, Dr. Lenow, Mr. Partridge, Ms. Fryar, Mr. Class, Mr. Hanson and Ms. Hickey
- Non-concur (0)
- Abstaining (0)

Panel Comments on Calcium Channel Blockers Recommendation

Ms. Hickey said that a comment would be included to state that the Panel did not vote for nifedipine immediate release to be a cardiovascular agent.

Dr. Lenow requested that the P&T Committee be asked to carve out discussion time in its review when faced with agents having multiple uses in the future. He would like it made clear to everybody what the Committee intends regarding alternative uses. He said he can see lots of examples down the road where multiple uses will become an important question. He would like the commentary and recommendations to include appropriate details about these.

Ms. Hickey said the comments should also express the Panel's concern about the need to communicate with beneficiaries about what is on the Uniform Formulary, what is non-formulary and the reasons why. The larger the number of beneficiaries, the greater the need for a more accurate and timely education program.

Mr. Partridge said the comments should indicate that notification should go out immediately once Dr. Winkenwerder signs off on the decision. We not only have the MTF and the Family Health Plan, we have TRICARE Standard and the TRICARE Reserve Select group.

Mr. Class said there are plans for a standard newsletter to go to beneficiaries but, right now, communicating to TRICARE Standard beneficiaries is not done.

Ms. Hickey said the Panel probably needs to make a special point about communicating with the TRICARE Reserve Select group. Many of those people are not used to our system and they are scattered all over the country. TRICARE For Life people are also scattered all over the country but many of them tend to be clustered.

MAJ Watson asked for a clarification from the Panel on their comment regarding immediate release nifedipine. The question is whether the Panel non-concurred that it was included with the cardiovascular portion of the review or that the Panel wanted to recommend that it be a non-formulary medication. Ms. Hickey said the Panel concurred with the P&T Committee recommendations. The Panel unanimously agreed to include a comment that the particular drug was not for use with cardiovascular conditions.

Ms. Allerman added that the P&T Committee understands the risks here and believes that the drug nifedipine IR will actually be used for a very small number of patients.

Presentation on Alpha Blockers for Benign Prostatic Hyperplasia

Maj Tiller next gave a presentation on alpha blockers to the Panel.

[Insert Script pages 25 through 29]

Panel Questions on Alpha Blockers

Dr. Lenow noted that the presentation mentioned there was a dramatic cost difference when adjustments were made for the cost of adverse events associated with non-selective alpha blocker treatment. He asked what made the dramatic difference in the analysis. Maj Tiller replied that it was partly due to documented medical costs of the adverse effects of patients using second-generation alpha blockers. He also looked at a four-year record which showed that if someone experienced an adverse drug reaction to the second-generation alpha blockers in the first 90-180 days, it is more than likely that the provider would not continue them, but would switch to third-generation alpha blockers, which are more expensive.

Dr. Lenow said that giving the provider a choice of using either selective or non-selective alpha blockers is important. He asked if the PEC ever considers the preference of the prescribing physician in making its analysis.

Maj Tiller said that does occur. For this drug class, provider input shows that physicians are migrating to the third-generation alpha blockers. That means they need to have at least one of them available on formulary.

Ms. Hickey asked what the response was of the Military Health System providers. Maj Tiller said they didn't get a large response but, in general, the MHS providers who responded said they didn't care whether they had a second- or third-generation alpha blocker as long as they have one of them available.

Panel Vote on Alpha Blockers Recommendation

The Chairperson read the P&T Committee's formulary recommendation for alpha blockers for benign Prostatic Hypertrophy:

"Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee recommended that tamsulosin be classified as non-formulary, and that alfuzosin, doxazosin, and terazosin be classified as formulary on the UF."

Panel Discussion on Alpha Blockers Recommendation

There was no Panel discussion on this recommendation.

The Chairperson then called for a vote on the formulary recommendation. The Panel voted as follows:

- Concur (8) – Ms. Le Gette, Mr. Hutchings, Dr. Lenow, Mr. Partridge, Ms. Fryar, Mr. Class, Mr. Hanson and Ms. Hickey
- Non-concur (0)
- Abstaining (0)

Panel Vote on Alpha Blockers Implementation Plan Recommendation

The Chairperson read the P&T Committee's implementation plan recommendation for alpha blockers for Benign Prostatic Hypertrophy:

"The P&T Committee recommended an effective date no later than the first Wednesday following a 120-day implementation period."

Panel Discussion on Alpha Blockers Implementation Plan Recommendation

Mr. Hanson reiterated his earlier concern that the process time is about 50 days. If the system wants to go through a 90-day prescription cycle for this class, more time will be needed – 140 days instead of the 120 recommended.

Ms. Hickey said this is a case where the majority of the patients are getting their drugs through the mail order and retail pharmacy. They have been very helpful in the past so, in this case, she will accept the 120 days in this instance. Mr. Hutchings agreed that the 120 days should be adequate.

The Chairperson called for a vote on the implementation plan recommendation. The Panel voted as follows:

- Concur (8) – Ms. Le Gette, Mr. Hutchings, Dr. Lenow, Mr. Partridge, Ms. Fryar, Mr. Class, Mr. Hanson and Ms. Hickey
- Non-concur (0)
- Abstaining (0)

Panel Comments on Alpha Blockers Recommendation

The Panel made no comments regarding the alpha blocker recommendations.

Ms. Fryar observed that table 7 of the handout – the Uniform Formulary Implementation Plan Summary – provides very useful phase-in information. She said she would encourage the inclusion of additional information indicating the date on which the decision was signed to provide a frame of reference.

Presentation on Prior Authorization Requirements for Pramlintide

Lt Col Bennett made the presentation to the Panel on "Prior Authorization Requirements for Pramlintide." He began by noting that Pramlintide is a new drug and that was reviewed at the May meeting of the P&T Committee and about which the Committee had some concerns about safety. Accordingly they made recommendations about prior authorization requirements for this new drug.

[Insert script, pages 30 and 31]

Panel Questions on Pramlintide Prior Authorization Requirements

The Chairperson said kudos are due to the P&T Committee for moving so rapidly on this new drug. She noted that it was only approved in March 2005. It obviously has severe side effects so moving rapidly was important and helps the beneficiaries.

Mr. Class said he hasn't been involved much in prior authorization. He asked about why prior authorization is required and what the criteria are. Mr. Hutchings replied that a lot of times things like this that are supposed to be done by specialists get into general practice. The risk is that the drug will be prescribed by somebody who isn't familiar with it. The purpose of prior authorization is to prevent patients who shouldn't be using the drug from taking it. The idea is to stop bad effects before they happen. Lt Col Bennett added that prior authorization ensures that the safety and tolerability criteria are being met.

Mr. Burleson (Office of General Counsel) noted that the regulation is not clear and consistent in any case. But it does say that prior authorization is used to determine whether something is even covered under TRICARE.

Mr. Hutching asked whether hypoglycemia was discussed, because beta blockers mask the signs. Ms. Allerman said she wasn't sure how that was handled. Ms. Hickey said that she hopes diabetic educators are aware that beta blockers mask the hypoglycemia.

Dr. Lenow asked how prior authorizations are enforced. He asked whether there is a check list that prescribers have to fill out to validate and verify. Ms. Allerman said that is the case.

Panel Vote on Pramlintide Prior Authorization Requirements Recommendation

The Chairperson read the P&T Committee recommendation, which is to require prior authorization for pramlintide using the following criteria:

"Coverage is provided for the use of pramlintide as an adjunct treatment in type 1 and type 2 diabetic patients 18 or older who use mealtime insulin therapy and who meet all of the following criteria:

- are currently on insulin
- have an HbA1c $\leq 9\%$
- are monitoring blood glucose levels frequently (at least 3 or more times per day)
- have failed to achieve adequate control of blood glucose levels despite individualized management of their insulin therapy

- are receiving ongoing care under the guidance of a health care provider skilled in use of insulin and supported by the services of a diabetic educator.

Coverage is not provided for patients who:

- have poor adherence to their current insulin regimen or blood glucose monitoring
- have a HbA1c > 9%
- have experienced recurrent severe hypoglycemia requiring assistance within the past 6 months
- have a confirmed diagnosis of gastroparesis or require the use of drugs to stimulate gastrointestinal motility."

The Panel voted as follows:

- Concur (8) – Ms. Le Gette, Mr. Hutchings, Dr. Lenow, Mr. Partridge, Ms. Fryar, Mr. Class, Mr. Hanson and Ms. Hickey
- Non-concur (0)
- Abstaining (0)

Panel Vote on Pramlintide Implementation Plan

The Chairperson next called for the Panel vote on the P&T Committee recommendation to:

"Have an effective date no later than the first Wednesday following a 30-day implementation period. Patients who received pramlintide from a DOD pharmacy point of service prior to the PA effective date should be allowed to continue to receive pramlintide."

The Panel voted as follows:

- Concur (8) – Ms. Le Gette, Mr. Hutchings, Dr. Lenow, Mr. Partridge, Ms. Fryar, Mr. Class, Mr. Hanson and Ms. Hickey
- Non-concur (0)
- Abstaining (0)

Panel Comments on Pramlintide Prior Authorization Requirements Recommendation

Ms. Hickey asked that two comments be included with the Panel's vote to concur. One is that the Panel applauds the P&T Committee for its fast action in this matter. The other is that the panel notes that beta blockers can mask the signs of hypoglycemia and asks that this be taken into account.

Closing Remarks

MAJ Watson remarked that the minutes will be reviewed prior to their publication on the website. He asked that the Panel provide a 48-hour turnaround time on the minutes. If

corrections or clarifications are needed after the minutes get posted, they should be sent to MAJ Watson no later than one month after the posting.

Ms. Hickey thanked the presenters on behalf of the Panel. She also thanked MAJ Watson and Rich Martel for their support.

She announced that the next meeting of the Beneficiary Panel is scheduled for December 16 at 8:00 AM at the Naval Heritage Center in Washington, D.C. She said this presents a bit of a tight timeline in getting the read-ahead materials to Panel members, but asked that the materials be provided no less than one week before the meeting.

She said the March meeting might be an appropriate time to look at the results of the original drugs going on to the Uniform Formulary.

The Chairperson adjourned the meeting at 2:50 PM.

Brief Listing of Acronyms Used in This Summary

Abbreviated terms are spelled out in full in this summary; when they are first used, the acronym is listed in parentheses immediately following the term. All of the terms used as acronyms are listed below for easy reference. The term "Panel" in this summary refers to the "Uniform Formulary Beneficiary Advisory Panel," the group whose meeting is the subject of this report.

- ACE and ACEI – Angiotensin converting enzyme inhibitor (a drug class)
- ARBs – Angiotensin receptor blockers (a drug class)
- ASCOT – Anglo-Scandinavian Cardiac Outcomes Trial (a drug trial)
- BAP – Uniform Formulary Beneficiary Advisory Panel (the "Panel" referred to above)
- BIA – Budget Impact Analysis
- BPH – Benign Prostatic Hyperplasia
- CAMELOT – Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (a drug trial)
- CC – Core coat (a drug formulation)
- CCB – Calcium channel blocker (a drug class)
- CD/XR/XT – Diltiazem extended release preparations
- CEA – Cost-effectiveness analysis
- C.F.R – Code of Federal Regulations
- CEA – Cost-Effectiveness Analysis
- CMA – Cost-Minimization Analysis
- CR/XL – Osmotic pump formulations (for the CCB drug class)
- CR – Controlled release (a drug formulation)
- CV – Cardiovascular
- DFO – Designated Federal Officer
- DHP – Dihydropyridines (a sub-class of the CCB drug class)
- DOD – Department of Defense
- EUROPA – European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (a drug trial)
- FDA – U.S. Food and Drug Administration
- HbA1c – A type (A1c) of hemoglobin (Hb)
- HCTZ – Hydrochlorothiazide (an anti-hypertension drug)
- HOPE & HOPE II – Heart Outcomes Prevention Evaluation Study (a National Cancer Institute drug trial)
- IR – Immediate release (a drug formulation)
- MHS – Military Health System
- MI – Myocardial infarction
- MTF – Military Treatment Facility
- MTOPS – Medical Therapy of Prostatic Symptoms Study
- OTC – Over the counter
- PA – Prior Authorization
- PAH – Pulmonary arterial hypertension

- P&T Committee – DOD Pharmacy and Therapeutics Committee
- PEACE – Prevention of Events with Angiotensin Converting Enzyme Inhibitors (a drug trial)
- PEC – DOD Pharmacoeconomic Center
- PRAISE – Prospective Randomized Amlodipine Survival Evaluation (a drug trial)
- SR – Sustained release (a drug formulation)
- TMA – TRICARE Management Activity
- TMOP – Tricare Mail Order Pharmacy
- UF – DOD Uniform Formulary
- U.S.C. – United States Code
- VA – U.S. Department of Veterans Affairs

The following script was provided by Lt Col Bennett, Pharmacoeconomic Center. Lt Col Bennett and his staff read from this during the meeting, as indicated in the minutes.

AGENDA
BENEFICIARY ADVISORY PANEL

Good Morning,

I'm Lt Col Dave Bennett: Director of Clinical Operations at the PEC. Today, fellow PEC Clinical Operations staff members join me: Angela Allerman Staff Clinical Pharmacist, and Maj Wade Tiller Pharmacoeconomic Analyst.

The DoD Pharmacoeconomic Center (PEC) supports the DoD P&T Committee by conducting the relative (relative meaning in comparison to the other agents defined in the same class) clinical-effectiveness analyses and relative cost-effectiveness analyses of drug classes under review and consideration by the DoD P&T Committee for the Uniform Formulary (UF).

Angela Allerman, Maj Tiller, and I are here to present an overview of the analyses presented to the DoD P&T Committee. 32 Code of Federal Regulation (C.F.R.) establishes procedures for inclusion of pharmaceutical agents on a Uniform Formulary based upon both the relative clinical-effectiveness and the relative cost-effectiveness. The goal of this presentation is not to provide you with the same in depth analyses presented to the DoD P&T Committee but a summary of the processes and analyses presented to the DoD P&T Committee which include:

1) A brief overview of the relative clinical-effectiveness analyses considered by the DoD P&T Committee.
2) A brief general overview of the relative cost-effectiveness analyses. This overview will be general in nature since we are unable to disclose the actual costs used in the economic models. This overview will include the factors used to evaluate the costs of the agents in relation to the safety, effectiveness, and clinical outcomes.
3) The DoD P&T Committee's Uniform Formulary recommendation based upon its collective professional judgment when considering the analyses from both the relative clinical and relative cost-effectiveness evaluations of the Angiotensin Converting Enzyme Inhibitors (ACE inhibitors), Calcium Channel Blockers, and Alpha-Blockers.
4) The DoD P&T Committees recommendation as to the effective date of the agents being changed from formulary tier to the non-formulary tier of the Uniform Formulary. Based on 32 C.F.R. 199.21, such change will not be longer than 180 days from the final decision date but may be less.

ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACE) DRUG CLASS REVIEW

Relative Clinical Effectiveness:

Background: The relative clinical effectiveness of the ACEs takes into consideration their relative safety (likelihood to do no harm), tolerability (likelihood to be taken), and efficacy (likelihood to work).

There are ten ACEs marketed in the US, five are available in generic formulations, and five are only available in branded formulations. (See table 2 in your handout). The five generic ACEs are benazepril, captopril, enalapril, fosinopril, and lisinopril. The five branded ACEs are moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace) and trandolapril (Mavik). Moexipril and quinapril used to be available in generic formulations, however litigation has resulted in removal of the generics from the market. Generic competition for ramipril is not expected until 2008. Seven ACEs are available in combination with the diuretic hydrochlorothiazide, and these were included in the evaluation. The ones that are not available in combination with hydrochlorothiazide are perindopril, ramipril and trandolapril. The ACEs that are available in combination with calcium channel blockers were not evaluated at this meeting.

Generic Name	Brand Name	Available in Combo with HCTZ
Benazepril	Lotensin; generics	Yes
Captopril	Capoten; generics	Yes
Enalapril	Vasotec; generics	Yes
Fosinopril	Monopril; generics	Yes
Lisinopril	Prinvil, Zestril; generics	Yes
Moexipril	Univasc	Yes
Perindopril	Aceon	No
Quinapril	Accupril	Yes
Ramipril	Altace	No
Trandolapril	Mavik	No

Relevance to MHS and Utilization: The ACEs currently rank #10 in terms of Military Health System (MHS) drug class expenditures. (Look at figure 1 in your handout). In FY 2004, $75.5 million dollars was spent in all three points of service (retail, mail order, and military treatment facility – MTF) on ACEs. Lisinopril is the most popular ACE inhibitor in the MHS; it is ranked #1 in utilization (number of prescriptions) at all three venues (MTF, mail order, and retail network). Ramipril is #2 in utilization at all three venues. There are 670,000 unique utilizers of ACEs in the MHS; 67% of patients receiving an ACE in the MHS are receiving lisinopril, while 17% are receiving ramipril.

FDA Indications: All ten ACEs are approved for treating hypertension. (Refer to table 3 in your handout).

In addition to hypertension, some of the ACEs have additional indications such as recent Heart Attack (captopril, lisinopril, ramipril, trandolapril); Heart Failure {captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril, trandolapril} and Type 1 Diabetic Renal Nephropathy (kidney

disease in diabetic patients needing insulin) {captopril}. Two of the ACEs are indicated for use in patients who are at high risk for future cardiovascular events; ramipril is indicated to reduce the risk of cardiovascular death, heart attack and stroke; perindopril received approval in August 2005 to reduce the risk of death, heart attack and cardiac arrest, but the benefit was primarily due to a reduction in heart attack.

Based on the relative clinical effectiveness review the DoD P&T committee concluded the following nine points:

1) There is no evidence to suggest that any one ACE inhibitor is associated with a lower risk of serious complications than any other ACE.
2) All 10 ACEs have similar relative (relative meaning in comparison to the ACEs with indications for hypertension) clinical effectiveness for treating hypertension.
3) In patients who have high cardiovascular risk, ramipril 10 mg is the only ACE that has been shown to reduce death and other cardiovascular events (heart attack and stroke). Perindopril reduces the risk of heart attack, but was not shown to reduce the risk of death. Trandolapril was not shown to reduce the risk of death or cardiovascular events (such as heart attack or need for repeat heart surgery) in one large trial.
4) In patients who have recently experienced a heart attack, a reduced risk of death has been shown with captopril, lisinopril, ramipril and trandolapril.
5) In patients with chronic heart failure, a reduced risk of death has been shown with captopril, enalapril, lisinopril, ramipril, and trandolapril.
6) In patients with type 1 diabetic renal disease (kidney disease in diabetic patients receiving insulin), captopril reduces the risk of death and the need for kidney dialysis or kidney transplant.
7) In patients with type 2 diabetic renal disease (diabetics who do not need insulin and can take oral medications), enalapril, benazepril, ramipril, lisinopril, quinapril, and trandolapril have been shown to have a benefit on various lab tests for kidney disease, but have not been shown to reduce the risk of death, or the need for kidney dialysis or kidney transplant.
8) In patients who have kidney disease that is not caused by diabetes (non-diabetic nephropathy), captopril, enalapril, benazepril, and ramipril reduce the need for kidney dialysis or kidney transplant.
9) Current studies suggest that enalapril, captopril, and ramipril may delay or prevent the development of diabetes, but further research is needed to confirm this beneficial effect. A large trial is underway with ramipril to evaluate whether ramipril will reduce the risk of developing diabetes.

The DoD P&T Committee's conclusion was determined after answering the following key questions based upon the Relative Clinical Effectiveness Review:

Key Questions:

1) Are there differences in the safety and tolerability profiles of the ACEs?
2) Are there any differences in the efficacy of the ACEs used for treating hypertension?
3) Are there any differences in the efficacy of the ACEs used to prevent death, heart attack, or stroke in patients who are at high risk of cardiovascular events.

4) Are there differences in the efficacy of the ACEs used for treating patients who recently have had a heart attack (myocardial infarction)?
5) Are there differences in the efficacy of the ACEs used for treating chronic heart failure?
6) Are there differences in the efficacy of the ACEs used for treating patients with renal disease due to type 1 diabetes
7) Are there differences in the efficacy of the ACEs used for treating patients with renal disease due to type 2 diabetes
8) Are there differences in the efficacy of the ACEs used for treating patients with renal disease due to conditions other than diabetes?
9) Are there differences in the efficacy of ACEs to either prevent or delay the development of diabetes?

(Data Source): To answer these key questions the ACE inhibitor relative clinical effectiveness analysis evaluated information from randomized, clinical trials (which were used to produce the ACE inhibitor class review). Additional published clinical trials were found using a Medline Search, searching major medical journals table of contents, and manufacturer press releases. Proceedings from the major Cardiology group meetings (American Heart Association, American College of Clinical Cardiology, and the European Society of Cardiology) were also reviewed to find published clinical trials. And the FDA website was monitored for new indications.

(Key question #1) Are there differences in Safety and Tolerability profiles of the ACEs: The Committee concluded that there is no evidence that any one ACE is preferable to the others with respect to safety or tolerability profiles. The most common adverse events are low blood pressure (hypotension), dry cough, swelling of the throat and mouth (angioedema) which can cause death, increased potassium (which can cause heart rhythm abnormalities and death), and kidney function impairment. High doses of captopril (>100 mg/day) can cause taste disturbances and low white blood cell count (which increases the risk of infection).

Head to head trials of the ACEs in hypertension, heart attack, and heart failure reported the percentage of patients stopping therapy due to adverse effects as ranging between 0% and 39%, but there were no differences between any one ACE inhibitor. All the ACEs should be used with caution in the 1st trimester of pregnancy, but none of the ACEs are recommended for use in the 2nd and 3rd trimester of pregnancy, due to birth defects

Conclusion: The DoD P&T Committee agreed there is no evidence that any one ACE is preferable to the others with respect to safety and tolerability.

Key question #2 (Efficacy for Hypertension): Differences in efficacy of the ACEs when used for treating hypertension were reviewed by the DoD P&T Committee. No clinically relevant differences in blood pressure reduction are seen when the ACE inhibitor doses are adjusted to reach target blood pressure goals. Head to head trials comparing one ACE inhibitor with another have not shown that one ACE is better than another at reducing blood pressure.

Place in therapy for hypertension: A government group of hypertension experts that published guidelines in 2003 for treating high blood pressure recommended that ACE inhibitors should be used first line in patient with hypertension who also have heart failure, have a history of heart attack, diabetes, are at high risk for heart disease, or who have a history of stroke.

Conclusion: The DoD P&T Committee agreed there is no evidence that any one ACE inhibitor is more efficacious than the others for lowering elevated blood pressure.

To answer key questions #3 through 9; the DoD P&T Committee then reviewed the Efficacy of the ACEs for use in conditions other than hypertension (High Cardiovascular Risk, Heart Attack, Chronic Heart Failure or Renal Nephropathy): Evidence for use of the ACEs in these conditions was based on FDA approved indications and clinical trials. For these other indications, the DOD P&T Committee concluded that studies with ACE inhibitors that have shown a benefit in reducing the risk of death due to a cardiovascular cause would be the most important factor in determining efficacy. Studies with ACE inhibitors that have shown a reduction in other clinical outcomes, such as a reduction in heart attack, stroke, hospitalization for heart failure, need for kidney dialysis, or need for kidney transplant are also important factors. Studies that have only shown a beneficial change in lab values would be less important factors when determining efficacy.

Efficacy for patients at high cardiovascular risk (key question #3): This category includes patients who have a history of heart disease (such as heart attack, stroke, or peripheral vascular disease) but who do not have heart failure; these patients are at high risk for having another cardiovascular event. (See Table 4 in your handout). The three ACEs that have been studied in large trials enrolling more than 8,000 patients each are ramipril, perindopril, and trandolapril. Ramipril at a dose of 10 mg was studied in the HOPE trial and was found to reduce the risk of death due to cardiovascular causes, heart attack, and stroke. These results were in addition to any blood pressure-lowering effects. When this study was conducted, patients did not receive what is now considered standard background therapy for heart disease; only 29% were on statin drugs to lower cholesterol, and 76% were on aspirin (which is now standard therapy for heart disease). The patients in this trial had severe heart disease and were considered unstable; additionally, 38% had diabetes, which is a known risk factor for development of cardiac disease. Based on the results of this trial, ramipril has FDA-approval for reducing mortality in these patients. The 10 mg dose of ramipril is important to point out, as two other studies with lower ramipril doses did not show a reduced risk of death (5 mg) or reduced development of heart attack or stroke (1.25 mg).

Perindopril was studied in 12,000 patients in the EUROPA trial. These patients had stable coronary heart disease and were not as sick as the patients in the ramipril study. In this trial, perindopril was not shown to reduce the risk of death alone or cardiac arrest alone, but did reduce the risk of non-fatal heart attack. When the endpoints were combined together (death, heart attack, and cardiac arrest), there was a significant difference compared with placebo. Another difference in the EUROPA trial was that more patients were receiving appropriate background therapy than in the HOPE trial; 58% were receiving cholesterol drugs, while 92% were receiving aspirin.

Trandolapril was studied in 8,200 patients in the PEACE trial. These patients were also less severely ill than in the HOPE trial. Almost ¾ of these patients had undergone some type of heart surgery procedure, such bypass or balloon angioplasty. 70% of these patients were on cholesterol lowering drugs, and 90% were on aspirin. Interesting, in this study, there was no benefit of trandolapril in reducing the risk of death, non-fatal heart attack, or need for a repeat heart surgery procedure.

The results of these studies are the key differentiating factors when we are looking at differences in efficacy for the ACE inhibitors. Why did the results of the ramipril study show a benefit in reducing death, but the studies with perindopril only showed a reduction in heart attack (perindopril) or no benefit at all (trandolapril)? Some experts think that since the perindopril (EUROPA) and trandolapril (PEACE) studies were recently completed, the majority of the patients received standard background therapies that have been proven to reduce death (aspirin and cholesterol drugs), thus, it was less likely to see reduction in death with the ACE inhibitor. Also, the patients receiving trandolapril were likely to have had a procedure (balloon angioplasty or bypass) that is also known to reduce the risk of death. When patients are already receiving procedures or medications known to reduce death, it is less likely that an additional reduction in death will be seen when a study medication is added on.

Another question to answer is "how many patients are there in the DOD who are similar to the patients in the HOPE study." Ideally, patients who meet the criteria of the HOPE study should receive ramipril 10 mg, due to the mortality benefit seen. In the Military Health System, a rough estimate is that 10% of the patients with cardiovascular disease fit the criteria of the patients in the HOPE study.

Conclusion: The DoD P&T Committee agreed that: in patients with high cardiovascular risk, ramipril 10 mg has been shown to reduce mortality, heart attack and stroke; perindopril has been shown to reduce the risk of heart attack and cardiac arrest, but not death; and trandolapril did not show a reduction in death, or heart attack.

Efficacy for recent heart attack (key question #4) Mortality is the most important clinical outcome for heart attack. The American College of Clinical Cardiology and the American Heart Association have published guidelines for treating patients with a recent heart attack. Trials where an ACE was compared to placebo have shown a reduction in mortality with captopril, lisinopril, ramipril, and trandolapril. Enalapril has shown a reduction in hospitalization due to heart failure, but not death.

Conclusion: The DoD P&T Committee concluded that a mortality benefit in patients with a recent heart attack has been shown with captopril, lisinopril, ramipril and trandolapril.

Efficacy for chronic heart failure: (key question #5) For heart failure, the most important outcomes of interest are reduction in mortality, or reductions in hospitalization for heart failure. In patients with heart failure who are older than age 65 years, hospitalization for heart failure is the most expensive disease state for Medicare charges. Once again, the American College of

Clinical Cardiology and the American Heart Association have published guidelines for treating patients with chronic heart failure. A reduction in mortality or hospitalization for heart failure has been shown with captopril, lisinopril, ramipril, trandolapril, and enalapril. Fosinopril and quinapril are FDA-approved for heart failure, but do not have evidence of improved clinical outcomes, just improvement in symptoms. There are no studies with moexipril.

Conclusion: The DoD P&T Committee agreed that mortality benefit in patients with chronic heart failure has been shown with captopril, lisinopril, ramipril, enalapril and trandolapril.

Efficacy for type 1 diabetic nephropathy: (key question #6)
Background: ACE inhibitors are used to prevent the progression of renal disease in diabetics who already have renal impairment, and to prevent the development of renal disease in diabetics who have no evidence of renal impairment. ACE inhibitors have been found to reduce spilling of protein into the urine, which can be measured by a lab test, and which is an early sign of renal damage in diabetics.

Captopril is the only ACE approved for use in patients with type 1 diabetic kidney damage. One study in poorly controlled patients who had had diabetes for over 20 years showed a reduction in death or need for kidney dialysis or kidney transplant. Beneficial changes in lab values have been reported with captopril, enalapril, lisinopril, ramipril, and perindopril, but remember that a reduction in death, need for kidney dialysis, or kidney transplant is more important than beneficial changes in lab values, when we are evaluating these studies.

Conclusion: The DoD P&T Committee agreed that the best evidence for a benefit in clinical outcomes in patients with type 1 diabetes is with captopril, which has been shown to reduce death, need for kidney dialysis, or need for kidney transplant.

Efficacy for type 2 diabetic nephropathy: (key question #7) None of the ACEs are approved for use in patients with kidney damage caused by type 2 diabetes, but they are frequently used in this condition to reduce the progression of renal damage. No studies enrolling large numbers of patients have shown any ACE inhibitor to reduce the risk of death, need for kidney transplant or kidney dialysis. One study with ramipril 1.25 mg did not show a benefit in the need for kidney dialysis or kidney transplant. An Italian trial with benazepril showed a reduction in death, but only 21 patients had diabetic renal disease, thus it is difficult to say if this result would also be seen in a larger trial with more patients. Benefits in terms of a reduction in the amount of protein spilled into the urine has been reported with enalapril, lisinopril, captopril, quinapril, and ramipril, but they have not been studied to see if they will reduce death, need for kidney transplant or kidney dialysis.

Conclusion: The DoD P&T Committee agreed that in patients with kidney damage caused by type 2 diabetes, not ACE inhibitor has been shown to reduce death, need for kidney dialysis, or need for kidney transplant. Beneficial changes in lab values that assess kidney damage have been reported with enalapril, lisinopril, captopril, quinapril, and ramipril.

Efficacy for renal damage due to conditions other than diabetes: (key question #8) A meta-analysis of 11 randomized, controlled trials found that captopril, enalapril, benazepril and ramipril reduced the development of end stage renal disease (need for kidney transplant of kidney dialysis).

Conclusion: The DoD P&T Committee agreed that in patients with non-diabetic renal damage, the best evidence is seen with captopril, enalapril, benazepril, and ramipril in preventing further renal damage.

Efficacy for delaying or preventing the development of diabetes: (key question #9) One area of a lot of interest is whether you can give an ACE inhibitor and actually delay the development of type 2 diabetes, or prevent its development. Sub-analyses of three studies with captopril, enalapril and ramipril have suggested this may be the case, but it has not been adequately studied. A trial is currently underway with ramipril to definitively answer this question.

Conclusion: The DoD P&T Committee concluded the evidence suggests that captopril, enalapril and ramipril may prevent the development of diabetes, but further trials are needed.

Overall Conclusion to Relative Clinical Effectiveness: Two methods were used to determine overall relative clinical effectiveness of the ACE inhibitors. (See page 5 of your handout, at the bottom of the page, where the ACE rankings are discussed). When taking into account existing DOD Military Health System utilization, therapeutic overlap, generic availability, FDA-approved indications, and quality of the evidence, ramipril, lisinopril, captopril, fosinopril, benazepril and enalapril had higher clinical utility (clinical usefulness) relative to quinapril, perindopril, trandolapril, and moexipril.

If an attempt is made to rank the ACEs from #1 to #10, based on clinical attributes including FDA-approved indications, dosing schedule, and elimination routes, the following order occurs from highest rank to lowest rank: ramipril, trandolapril, enalapril, perindopril, captopril, lisinopril, fosinopril, quinapril, benazepril and moexipril.

Conclusion: The DoD P&T Committee concluded that ramipril, captopril, lisinopril, benazepril, enalapril, trandolapril, and fosinopril have increased clinical effectiveness relative to moexipril, quinapril, and perindopril.

Committee Discussion: There was lengthy discussion among the DoD P&T Committee members regarding the potential for non-formulary designation of ramipril, especially given its higher effectiveness in reducing death in patients at high risk for cardiovascular events compared to other ACE inhibitors. The results of a survey of providers at the MTFs were evenly split in terms of willingness to pay more for ramipril given the results of the HOPE trial. Several providers said the extra benefit was not worth the higher cost, especially since lower-cost, efficacious, generic ACE inhibitors are now available.

33% of the patients in the MHS receiving ramipril are receiving the drug for hypertension alone, and are not considered high risk patients. For hypertension, the clinical evidence shows that all of the ACEs inhibitors reduce blood pressure effectively. Likewise, for patients with heart

failure, those who have recently experienced a heart attack, or for those patients with diabetic or non-diabetic renal disease, several other ACE inhibitors with good evidence of mortality reduction or benefits on other clinical outcomes are available.

When the HOPE trial was first started approximately 10 years ago, the usage of background medications (statins for cholesterol, aspiring for heart attacks) which are now considered standard and life-extending was low. Therefore, it is unknown that if the trial were repeated today where the use of background medications would be high, whether the same benefits on mortality would occur. As was already pointed out, the patients enrolled in the HOPE trial had severe coronary artery disease and were considered unstable; in contrast in the trials with perindopril and trandolapril, the patients did not have as severe disease. A medication would be more likely to show a benefit in the most severely diseased patients.

The Committee did acknowledge the high numbers of patients currently receiving ramipril (over 115,000), but did feel that in the majority of these patients, another ACE inhibitor could be used without detrimental results. The DoD Committee did state that use of the medical necessity process would ensure that those patients who truly need ramipril (e.g. those meeting the criteria for the HOPE trial or very labile patients where a change in cardiovascular drug therapy could result in untoward outcomes) would be able to receive it at the lower co-pay.

Relative Cost Effectiveness:

The P&T Committee evaluated the relative cost-effectiveness of the ACEIs in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2).

To determine the relative cost effectiveness of the ACEIs, two separate economic analyses were performed, a pharmacoeconomic analysis and budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that ACE inhibitors: have similar relative clinical effectiveness in the treatment of hypertension, have similar safety and tolerability, but differ in clinical outcome evidence supporting their effectiveness in high cardiovascular risk, post myocardial infarction, heart failure, type 1 diabetes mellitus, type 2 diabetes mellitus, and non-diabetic nephropathy patients. In other words, the agents were shown to differ in relative clinical effectiveness.

A cost-minimization analysis (CMA) was first performed to stratify the agents solely on cost. The cost-minimization analysis revealed three distinct clusters along the cost-continuum: captopril, lisinopril, benazepril, and enalapril comprise a cluster of low cost agents, trandolapril and fosinopril comprise a cluster of moderate cost agents, and quinapril, moexipril, ramipril, and perindopril comprise a cluster of high cost agents.

Given the conclusion of the relative clinical effectiveness evaluation, the relative cost effectiveness of the agents was determined through a cost-effectiveness analysis (CEA). In this type of analysis, agents within a therapeutic class are competed on two dimensions, cost and effect or outcomes. The cost used in the analysis was the total weighted average cost per day of treatment for all three points of service. The effectiveness measure used for each agent was the composite score derived from the clinical effectiveness analysis, which ranked the agents based

on clinical outcome evidence. In this analysis, captopril was determined to be the most cost-effective agent, while tradolapril and ramipril were determined to be more costly and more effective. The other agents were shown to be more costly and less effective.

The results of the CMA and CEA were subsequently incorporated into a budget impact analysis (BIA). The reported budget impact analysis results represented the best relative estimate of the budget impact for the various analysis scenarios. The primary purpose of the budget impact analysis was to inform the DoD P&T Committee about the relative cost-effectiveness of agents within a ACE inhibitor therapeutic class using a model that accounts for other factors and costs associated with a decision to designate one or more agents as Non-Formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. These estimates were obtained from models dependent upon numerous assumptions. The assumptions used in the models were extensively reviewed by the DoD P&T Committee and deemed appropriate, until further data and information is available. Moreover, sensitivity analyses were performed on the most influential assumptions, particularly the percentage of patients willing to switch from a non-formulary to formulary agents. The goal of the BIA was to identify a group of ACEIs to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The results reported in the budget impact analysis represent the best approximation of the budget impact of a decision to designate one or more ACEs as non-formulary. Actual results may vary.

A primary decision for the DoD P&T Committee was whether or not to include ramipril on the Uniform Formulary. In general, after the relative clinical effectiveness presentation, the DoD P&T Committee acknowledged the evidence from the HOPE trial supporting ramipril's use in high-risk cardiovascular patients, but questioned the generalizability of the study's results to the DoD population. The related question, addressed in the relative cost-effectiveness presentation, was whether the additional clinical benefit was worth the significantly higher cost. To address this question, two separate budget impact analyses were performed, one with ramipril included on the Uniform Formulary and one without ramipril on the Uniform Formulary. Comparison of the results obtained from the two analyses showed that inclusion of ramipril on the Uniform Formulary would significantly increase drug class expenditures for the MHS. Once again, a lengthy discussion ensued regarding formulary status of ramipril, given the relative cost-effectiveness analysis results. All arguments considered post the relative clinical effectiveness presentation regarding ramipril's Uniform Formulary status were reconsidered this time along with the relative cost-effectiveness information.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstention, 0 absent) to accept the ACEI relative cost-effectiveness analysis presented by the PEC. The P&T Committee concluded that moexipril, perindopril, and quinapril, agents located in the high-cost cluster, were not cost-effective relative to the other ACE Inhibitors, since the agents were significantly more costly and less effective. Although ramipril was shown to be more costly and more effective in the CEA, the P&T committee questioned the generalizability of ramipril's clinical outcome evidence in high-risk cardiovascular patients to the DoD population and ultimately did not value the evidence enough to overcome its significantly higher cost. Taking into consideration the conclusions from the relative clinical

effectiveness and relative cost effectiveness determinations of the ACEIs, and other relevant factors, the P&T Committee recommended Uniform Formulary status for the ACE inhibitors.

Committee Action: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstention, 0 absent) to recommend that moexipril, perindopril, quinapril, and ramipril (and their respective combinations with HCTZ, if any) be classified as non-formulary under the Uniform Formulary, with benazepril, captopril, enalapril, fosinopril, lisinopril, and trandolapril (and their respective combinations with HCTZ, if any) remaining on the Uniform Formulary.

Implementation Plan: Because there are a large number of patients who are receiving ramipril (Altace) at any MHS pharmacy point of service (17% of all patients receiving an ACE inhibitor (MHS =115,000 unique utilizers/670,470 Unique Utilizers = 17%) the Committee proposed an effective date no later than the 1st Wednesday following a 120-day transition period for implementation of a decision by the Director, TMA, to classify ramipril as non-formulary on the Uniform Formulary. There are lower numbers of patients receiving quinapril, perindopril and moexipril.

Patients wishing to fill prescriptions for Non-Formulary drugs at the Retail network pharmacies or the TMOP would then have to pay the non-formulary cost share unless medical necessity for these agents are established by the beneficiary or their provider. MTFs are not allowed to have non-formulary pharmaceutical agents on their local formularies. MTFs will be able to fill non-formulary requests for non-formulary agents only if both of the following conditions are met: 1) the prescription is written by a MTF provider and 2) the beneficiary and his or her provider has established medical necessity for the agent. MTFs may (but are not required to) fill a non-formulary prescription written by a non-MTF provider to whom the patient was referred as long as medical necessity has been established.

Committee Action: The P&T Committee voted to recommend an effective date no later than the first Wednesday following a 120 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Calcium Channel Blocker (CCB) Drug Class Review

Relative Clinical Effectiveness:

Background

The relative clinical effectiveness of the CCBs takes into consideration their relative safety (likelihood to do no harm), tolerability (likelihood to be taken), and efficacy (likelihood to work).

There are nine CCBs marketed in the US; eight of these are used for cardiovascular conditions. The CCBs are further classified by their structure and mechanism of action, into three sub-classes. (see table 5 on page 6 of your handout). The DHP CCBs are nifedipine, amlodipine (Norvasc), felodipine (Plendil), isradipine (DynaCirc), nicardipine (Cardene) and nisoldipine (Sular). Verapamil is a non-dihydropyridine which is in a class by itself, and diltiazem is another non-dihydropyridine which is also in a class by itself.

There are several different formulations and strengths of verapamil, diltiazem, nifedipine, isradipine and nicardipine. These formulations differ based on how frequently they are administered. The immediate release products must be given 3 to 4 times a day. The sustained release products can be dosed twice a day, and the extended release products only need to be taken once a day by the patients. For all of the longer acting products, there is some manipulation of the tablet or capsule to allow once daily dosing, which releases drug over a full 24 hours into the blood stream. A patient is likely to be more compliant with a medication that is dosed only once a day, vs one that requires dosing 3 to 4 times a day. Amlodipine inherently can be dosed once a day without further pharmaceutical manipulation. There are generics available for several of the long acting products. Because the long acting formulations all have different ways that they release the drug, the FDA doesn't necessarily consider them all to be equivalent to each other. However, the P&T committee decided that it was the active ingredient that was important to look at, not how it was made to last 24 hours. Don't be too concerned with all of these different products, just look at the active ingredient when we are talking about the clinical effectiveness. If you need to be aware in the differences in the release mechanism, I'll point that out. Also, when we discuss the cost effectiveness, then we will discuss various products, rather than just the active ingredient.

In Table 5, the drugs that are bolded and italicized are not available in generics. There are three verapamil products which are not available generically – Verelan is an extended release product dosed once a day. Covera HS and Verelan PM are also dosed once a day, but they are specifically labeled to be given at bedtime. For the diltiazem products, the only product not available in a generic is Cardizem LA, which is an extended release product dosed once a day at bedtime. I will talk about this bedtime dosing later in the "other factors" section. For the DHPs, amlodipine, isradipine, nicardipine sustained release and nisoldipine are not available generically. Generic competition for amlodipine (Norvasc) is not expected until Sept 2007.

The CCBs are sometimes used for conditions other than cardiovascular uses (migraine headaches, premature labor, movement disorders, Raynoud's phenomenon), however for the purposes of this review, only the cardiovascular uses will be evaluated. Nimodipine (Nimotop) is also a DHP CCB, but it is not used for treating hypertension; it is used for treating bleeding

into the brain (subarachnoid hemorrhage) so it will not be mentioned further here. Because of the special use of nimodipine, it will be added to the Uniform Formulary. Nifedipine immediate release is no longer used for cardiovascular conditions (it is sometimes used in premature labor) due to an increased risk of death and heart attack. There are only 2,100 unique utilizers of immediate release nifedipine in the MHS, thus it will not be discussed further. The CCBs that are available in combination with an ACE inhibitor are not included in this review.

Generic Name	Brand Name	Available generically
Non-dihdyropyridines (non-DHP)		
Verapamil	Calan, Calan SR, Verelan PM, Covera HS	Various, except for Verelan PM, and Covera HS
Diltiazem	Cardizem, Cardizem CD, Cardizem LA	Various, except for Cardizem LA
Dihydropyridines (DHP)		
Nifedipine	Procardia XL; Adalat CC; Procardia, (nifedipine immediate release)	Yes
Amlodipine	Norvasc	No
Felodipine	Plendil	Yes
Isradipine	Dynacirc, Dynacirc CR	No
Nicardipine	Cardene, Cardene SR	Yes for Cardene, but not Cardene SR
Nisoldipine	Sular	No
Nimodipine*	Nimotop	Yes

* Nimodipine is not used for hypertension

Relevance to MHS and Utilization: The CCBs currently rank #9 in terms of Military Health System (MHS) drug class expenditures. Over $121 million dollars was spent in FY 2004 in all three points of service (retail, mail order, and military treatment facility – MTF) on this drug class. (Refer to Figure #2 on page 7 of your handout – however your handout lists numbers of prescriptions, which is similar to numbers of unique utilizers). There are 365,000 unique utilizers of CCBs in the MHS, of whom 210,000 are receiving amlodipine. Diltiazem and nifedipine are numbers 2 and 3, in terms of CCB utilization in the MHS.

FDA Indications: The eight CCBs used for treating cardiovascular conditions are all approved for treating hypertension.

Now look at Table 6 on page 8 of the handout. In addition to hypertension, some of the CCBs have other indications such as angina (diltiazem, nifedipine, amlodipine and nicardipine), or cardiac arrhythmias (diltiazem and verapamil). None of the CCBs are approved for use in treating patients with heart failure, however amlodipine and felodipine have been found to not adversely affect heart failure symptoms when used in these patients. I'll talk about heart failure later.

Based on the relative clinical effectiveness review the DoD P&T committee concluded that:

1) All eight CCBs have similar relative (relative meaning in comparison to the CCBs with indications for hypertension) clinical effectiveness for treating hypertension.
2) There is no evidence that verapamil, diltiazem, nifedipine, amlodipine, isradipine, nicardipine or nisoldipine differ with respect to their efficacy for reduction in death in patients who have hypertension.

3) There is no evidence to suggest that amlodipine, diltiazem, nifedipine, nicardipine, or nisoldipine differ with respect to their efficacy for reducing symptoms of angina when used for at least 8 weeks.
4) In patients who have heart failure (left ventricular systolic dysfunction), evidence shows that amlodipine and felodipine do not adversely affect cardiovascular outcomes, such as mortality or hospitalizations for heart failure. The other non-dihydropyridine CCBs have not been studied in patients with heart failure.
5) There is insufficient evidence to clearly differentiate the individual CCBs on the basis of adverse events. The most common adverse events are dizziness, peripheral edema (swelling in the legs), headache and flushing.
6) The Committee agreed that there are differences in the CCBs in terms of other factors, including pediatric use, dosing intervals, sustained release formulations, and efficacy for bedtime dosing which will be discussed further).

The DoD P&T Committee's conclusion was determined after answering the following key questions based upon the Relative Clinical Effectiveness Review:

Key Questions:

1) Are there any differences in the efficacy of the CCBs used for treating hypertension?
2) Are there any differences in the efficacy of the CCBs at reducing mortality when used for treating hypertension?
3) Are there any differences in the efficacy of the CCBs in reducing symptoms of angina?
4) Are there differences in the CCBs when used for treating chronic heart failure and whether they increase the risk of death or need for hospitalization?
5) Are there differences in the safety and tolerability profiles of the CCBs?
6) Are there differences in the CCBs in terms of other factors such as use in pediatrics, numbers of doses required daily, sustained release mechanisms, compliance, or efficacy when used at bedtime?
7) Do MHS providers prefer one CCB over another in their patients?

(Data Source): To answer these key questions the CCB relative clinical effectiveness analysis evaluated information from randomized, clinical trials (which were used to produce the CCB class review). Additional published clinical trials were found using a Medline Search, searching major medical journals table of contents, and manufacturer press releases. Proceedings from the major Cardiology group meetings (American Heart Association, American College of Clinical Cardiology, and the European Society of Cardiology) were also reviewed to find published clinical trials. The FDA website was monitored for new indications.

(Efficacy for Hypertension):

Key question #1: Differences in efficacy of the CCBs when used for treating hypertension were reviewed by the DoD P&T Committee. No clinically relevant differences in blood pressure reduction are seen when the CCB doses are adjusted to reach target blood pressure goals. Head to head trials comparing one CCB with another have not shown that one CCB is better than another at reducing blood pressure.

Place in therapy for hypertension: A government group of hypertension experts that published guidelines in 2003 for treating high blood pressure recommended that CCBs should not be used first line in patient with hypertension; diuretics are recommended as first line. CCBs are considered as appropriate therapy when added on to other blood pressure drugs as 2nd or 3rd line therapy. CCBs are appropriate when used in patients with hypertension and heart disease or diabetes, but other blood pressure drug are favored here (beta blockers for patients with heart disease, or ACE inhibitors for patients with diabetes).

Conclusion: The DoD P&T Committee agreed that there is no evidence that any one CCB is more efficacious than the others for lowering elevated blood pressure.

To answer key questions #2; the DoD P&T Committee then reviewed the Efficacy of the CCBs for reducing mortality when used in patients who have hypertension: What we are looking at here is whether the CCBs not only lower a patient's blood pressure, but whether they also reduce a patient's risk of dying. The DOD P&T Committee concluded that studies with CCBs that have shown a benefit in reducing the risk of death would be the most important factor in determining efficacy.

There are no head to head trials of an individual CCB vs another CCB that

have looked at reductions in the risk of death. However, there are 18 studies of CCBs vs other blood pressure drugs (ACEs, diuretics, beta blockers) that have evaluated mortality. The CCBs were similar to the other blood pressure drugs in reducing mortality; they were no better and no worse than the comparators. No differences were seen between the CCBs, but since they were not compared directly, it is difficult to make definitive conclusions here. All of the CCBs except felodipine were studied in these 18 trials. Felodipine has been studied in two trials, but it is difficult to determine whether felodipine when used by itself reduces mortality in patients with hypertension as one of the trials did not have a rigorous study design, and the other studied felodipine in combination with an ACE inhibitor. Two new trials with amlodipine, the ASCOT trial and the CAMELOT trial do not prove superiority of amlodipine over the other CCBs, as the ASCOT trial used amlodipine in combination with the ACE inhibitor perindopril, and in CAMELOT there was no difference in mortality between amlodipine and the ACE inhibitor enalapril.

Conclusion: The DOD P&T Committee concluded that there is no evidence to suggest that verapamil, diltiazem, nifedipine, amlodipine, nisoldipine, nicardipine, or isradipine are any different relative to each other in reducing the risk of death in patients with hypertension. There is no evidence for felodipine when used alone.

Efficacy for patients with angina (key question #3): The DOD P&T Committee has determined that outcomes of interest in patients with angina are whether the CCBs reduce symptoms, such as the number of angina symptoms experienced weekly, how long the patients can exercise on a treadmill, and the number of doses of sublingual (under the tongue) nitroglycerin used weekly.

Place in therapy: The American College of Cardiology and the American Heart Association have developed guidelines for treating angina. For angina, improved mortality has been seen with aspirin, lipid management, and use of beta blockers. The CCBs do not reduce mortality;

they are used only to reduce symptoms of angina. The beta blockers are recommended as initial therapy for angina. CCBs or long acting nitrates are recommended as first line therapy in only three circumstances: if a beta blocker is contraindicated (or should not be used, like in patients with asthma or emphysema, or in patients who have heart conduction problems); if a beta blocker is not successful when used by itself (a CCB is added on to the beta blocker), or if a beta blocker has caused intolerable side effects.

There are five small (less than 300 patients) head to head trials conducted with six of the CCBs that have looked at efficacy for reducing symptoms of angina; these CCBs were amlodipine, diltiazem, nisoldipine, nicardipine, nifedipine and verapamil. There was no difference between these CCBs in their efficacy at relieving symptoms. There were no studies that compared felodipine or isradipine for angina. One study with amlodipine evaluated whether this CCB would reduce the progression of heart disease (size of the blockage in the heart arteries). Amlodipine did not reduce the size of the blockage and did not reduce the development of stroke or heart attack, but it did reduce the need for patients to go to the cath lab. Some experts have concluded that the benefits of amlodipine here were due to its ability to lower blood pressure.

Conclusion: In patients with angina, the DoD P&T Committee agreed there is no evidence to suggest that amlodipine, diltiazem, nisoldipine, nicardipine, nifedipine or verapamil are superior to another when used to relieve symptoms of angina.

Efficacy for use in heart failure (key question #4) The American College of Clinical Cardiology and the American Heart Association have published guidelines for treating patients with heart failure. CCBs are not recommended for use in patients with heart failure, because some of the CCBs can reduce the force of the heart beat, which can worsen the symptoms of heart failure, such as congestion in the lungs, shortness of breath, and swelling of the legs. However, sometimes a CCB may need to be used if a patient with heart failure still has uncontrolled hypertension or continuing symptoms of angina, despite maximal therapy for the heart failure. The goal of therapy here is to treat the high blood pressure or chest pain without causing the heart failure symptoms of shortness of breath or leg swelling to worsen. The guidelines recognize that amlodipine and felodipine can be used in patients with heart failure and will not worsen the course of heart failure.

Amlodipine has been studied in one large trial in 1,153 patients with severe heart failure (this is called the PRAISE trial). Amlodipine had no significant effect (neither negative nor positive) on mortality or morbidity. Felodipine has been studied in one trial in 450 patients with mild to moderate heart failure and found no significant effect (neither negative nor positive) on mortality. There are no large studies with the other DHPs in heart failure. Also, verapamil and diltiazem are not recommended for use in heart failure, because they have a negative inotropic effects, which means they make the heart contraction less forceful, which will worsen the course of heart failure.

Conclusion: The DoD P&T Committee agreed that amlodipine and felodipine have not been shown to adversely affect the course of heart failure when used to treat concomitant high blood pressure or chest pain (angina).

Differences in safety and tolerability: (key question #5) The side effect profiles of the CCBs reflects their sub-classes. Remember that the three sub-classes of the CCBs were the DHPs, verapamil and then diltiazem, which are based on structure and mechanism of action. The DHPs are likely to cause swelling of the legs, headache, flushing, and an increase in heart rate. Verapamil reduces the force of the heart beat and reduces the heart rate. Diltiazem has side effects mid-way between verapamil and the DHPs.

There are no head to head trials of the CCBs looking at differences in side effects. An individual patient may be able to tolerate one CCB vs another, but it is difficult to know in advance whether one CCB will be better tolerated than another CCB. Head to head trials in patients with angina showed no difference in the percentage of patients who stopped therapy with their CCB due to adverse effects. For leg swelling, the percentage of patients experiencing this side effect ranges between 8-10%, in patients taking the CCBs; however, there are no differences in the percentage of patients discontinuing therapy due to this side effect

Conclusion: The DoD P&T Committee agreed that there is insufficient evidence to suggest that one CCB will have a lower risk of side effects than another. The most common side effects are dizziness, leg swelling, headache, and flushing.

Differences in other factors: (key question #6)
The DOD P&T Committee evaluated the CCBs in terms of other factors.
Pediatrics: Amlodipine is the only DHP CCB approved for use in children aged 6-16 years with hypertension. Diltiazem and verapamil are also used in pediatrics
Dosing intervals: In terms of dosing intervals, amlodipine requires more than 1 daily dose in 7% of patients in the MHS, while nifedipine extended release requires more than 1 dose in 10% of patients. This is not a major difference.
Sustained release or extended release properties: In terms of sustained or extended release characteristics, the DoD P&T Committee recognizes that there may be differences in the mechanism that causes a CCB to be released over a 24 hour dosing interval, and that the FDA may or may not consider one product to be equivalent to another, however, those products that contain the same active ingredient can be evaluated based on that active ingredient when we are looking at the clinical effectiveness.
Compliance: In terms of compliance, there is no evidence to suggest that compliance will be better with one CCB vs another.
Bedtime dosing: Two verapamil products, Verelan PM and Covera HS, and one diltiazem product, Cardizem LA are specifically labeled for use once daily at bedtime. The rationale for bedtime dosing is that studies have shown that strokes and heart attacks are more likely to occur in the early morning, which may be associated with an early morning surge in blood pressure. Thus, theoretically, if a blood pressure medication is given at bedtime, it will still have therapeutic levels in the blood to prevent this early morning surge in blood pressure. Although this concept is interesting, it has never been proven in a clinical trial. One study with Covera HS compared bedtime with morning dosing and did not find any difference in the number of morning heart attacks.

Use of CCBs in the VA: A representative from the Veteran's Affairs department presented information regarding the formulary status of CCBs in the VA. In 1999, the VA designated felodipine as their preferred CCB, since then felodipine has steadily increased in utilization, and has been the highest utilized CCB since the switch. The VA does have a mechanism for allowing use of amlodipine in those patients who have severe heart failure.
Use of CCBs in other Government agencies: The Bureau of Prisons has designated nisoldipine as their preferred DHP. The Indian Health Service has designated nifedipine extended release as their preferred DHP, but has noted increasing use of amlodipine for hypertension and recognizes that amlodipine's true utility is for a relatively limited subset of patients with heart failure.
Commercial Health Plans: Several health plans, including Aetna, Pacificare, and Group Health have designated amlodipine as non-formulary in their systems.

Conclusion: The Committee agreed that there are minor differences among the CCBs when evaluating other factors.

Differences in provider opinion in the MHS: (key question #7) Providers in the MHS from the army, navy and air force where surveyed regarding their opinions on the efficacy and safety of the CCBs. Over 50 responses were received from internists, family practitioners, cardiologists, nephrologists, and pharmacists throughout the US and those stationed overseas. The nephrologists were universal in recommending nifedipine extended release as their preferred product for treating hypertension in patients with impaired kidney function. The cardiologists felt that amlodipine did play a role in the small number of patients who have heart failure or angina, but that amlodipine should not be used 1st line in patients with hypertension. Some cardiologists commented that in angina, amlodipine is the preferred CCB because it is less likely to cause a reflux increase in heart rate, but other cardiologists disputed this fact. Several providers admitted that they had lots of experience using amlodipine, and less experience with using some of the other CCBs, and would be willing to switch when notified of the cost differences among these agents. Several of the providers had used felodipine and felt that it did not adequately control blood pressure. There was a wide perception that amlodipine was better tolerated than the other CCBs. Several providers commented that given the generic availability of other long-acting DHPs that there was nothing to justify the increased cost of amlodipine. Several also commented that brand familiarity was linked to the high utilization of CCBs. The other CCBs are available generically, or are marketed by small companies who are less likely to call on military providers, compared to larger companies that have a larger marketing force. Several physicians and pharmacists commented that making amlodipine non-formulary would result in an intense increase in work load. Several providers also acknowledged that even though CCBs should be used 2^{nd,} 3rd or 4th line for hypertension, they were over-used for this indication.

Overall Conclusion to Relative Clinical Effectiveness:

Conclusion: The P&T Committee concluded (1) that for hypertension, there is no evidence that one CCB is more efficacious than another, (2) that there is no evidence of superiority of verapamil, diltiazem, nifedipine, amlodipine, nicardipine, nisoldipine, or isradipine in terms of reducing mortality in patients with hypertension; that (3) there is no evidence of superiority of verapamil, nifedipine, amlodipine, diltiazem, nicardipine, or nisoldipine at reducing symptoms of

angina; that (4) amlodipine and felodipine do not adversely affect heat failure symptoms; and that (5) there is insufficient evidence to conclude that one CCB is more or less likely to cause side effects than another CCB, and that (6) there are minor differences in the CCBs in terms of other factors.

Discussion: There was lengthy discussion regarding the clinical effectiveness analysis of the DHP CCBs. It was acknowledged that in the MHS, most patients who are receiving a calcium channel blocker are receiving it first line for hypertension, which is not in agreement with national guidelines. Other anti-hypertensive agents such as diuretics or ACE inhibitors can often be used 1st line instead of the CCBs. It was also acknowledged that even though the numbers of patients with heart failure who need a CCB are not large, there is a benefit of amlodipine and felodipine in this patient population vs the other DHP CCBs. Also, the Committee recognized that in the pediatric population, amlodipine has been studied and is approved by the FDA for use in children aged 6-16 yrs. However, there is also a role for verapamil and diltiazem in selected pediatric patients. The Committee also acknowledged that it would be important to have at least one extended release product available from the verapamil, diltiazem, and DHP CCB sub-classes that is dosed once daily.

Calcium Channel Blocker Relative Cost-Effectiveness

The P&T Committee evaluated the relative cost effectiveness of the agents within the calcium channel blocker class in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. A separate relative cost-effectiveness analysis was performed for each calcium channel blocker therapeutic sub-class: dihydropyridine, verapamil, and diltiazem. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2).

To determine the relative cost-effectiveness of the agents within each of the calcium channel blocker therapeutic sub-classes, two separate economic analyses were performed: a cost-minimization analysis (CMA) and a budget impact analysis (BIA). A cost-minimization analysis was deemed as the appropriate type of pharmacoeconomic analysis, since overall, the DoD P&T Committee concluded that the agents within each of the therapeutic sub-classes were similar in regards to effectiveness, safety, tolerability, and clinical outcomes. Therefore, the agents within each therapeutic sub-class were competed solely on cost. The agents within each therapeutic sub-class were further stratified by duration of action. Each therapeutic sub-class had agents that were considered short-acting or long-acting. The cost used in each cost-minimization analysis was the total weighted average cost per day of treatment for all three points of service: MTF, retail, and mail. The cost-minimization analysis and budget impact analysis results will first be presented for the dihydropyridine sub-class, followed by the verapamil and diltiazem therapeutic sub-classes, respectively.

Dihydropyridine (DHP) CCBs

For the cost minimization analysis, the different DHP formulations (not just the active ingredients) were evaluated. Nifedipine extended release products include a core coat formulation (CC), and two osmotic pump formulations, (CR/XL); there are generics available for these three products (CC/CR/XL). For the immediate release, sustained release and extended release dihydropyridine calcium channel blockers, the results of the cost-minimization analysis revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. For the sustained release and extended release dihydropyridines, the low cost cluster included nifedipine CC/CR/XL and felodipine. The moderate cost cluster included amlodipine, and nisoldipine. Within the moderate cost cluster, amlodipine was at the high end of the cluster, and nisoldipine was at the low end. Isradipine controlled release (CR) (a product that is dosed once daily), and nicardipine sustained release (SR) (a product that is dosed twice daily) were included in the high cost cluster. Similar results were seen in the CMA for the immediate release dihydropyridine calcium channel blockers, which are not used as frequently as the long-acting agents (nifedipine immediate release, nicardipine immediate release, and isradipine immediate release). Based on this use of cost-minimization to determine the relative cost-effectiveness of the agents within dihydropyridine calcium channel blocker therapeutic sub-class class, nifedipine immediate release, nifedipine extended release, and felodipine were the most cost-effective agents.

The results of the CMA were subsequently incorporated into a budget impact analysis (BIA). The goal of the BIA was to identify a group of dihydropyridine calcium channel blockers to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS when compared to other combination groups of DHP calcium channel blockers. The BIA results revealed that a group of dihydropyridine calcium channel blockers that included nifedipine, felodipine, and nisoldipine best achieved this goal, and thus were determined to be more cost-effective relative to other combination groups.

Discussion: There was lengthy discussion regarding the clinical and cost effectiveness analysis of the DHP CCBs, which centered on the feasibility of placing amlodipine in the non-formulary tier, due to its high cost and lack of superiority for treating hypertension compared to the other CCBs. A retrospective analysis of health care claims data indicated that in DoD, of the 210,000 patients receiving therapy with amlodipine, 38% are receiving it for hypertension, vs 9% for angina, and 5% for heart failure. It is widely accepted that CCBs are not first line for hypertension, however, this usage accounts for a large number of patients receiving amlodipine. The DoD P&T Committee also acknowledged that even though the evidence does not show superiority of amlodipine for treating hypertension or angina, it is widely perceived as being superior to the others, which may reflect familiarity due to wide market penetration by this CCB. The DOD also considered the fact that the VA was quite successful in switching their patients to felodipine, without an apparent increase in adverse events or worsening of efficacy. The DoD P&T Committee acknowledged that a successful implementation of this formulary recommendation would require increased efforts of MTF physicians and pharmacists, however, passive means to improve CCB prescribing have not been successful, thus a more binding measure is needed. The DOD P&T Committee did acknowledge that for pediatric patients or patients with heart failure or angina who are stabilized on amlodipine, the medical necessity

process would adequately allow those patients to continue therapy at the reduced co-pay of $9 instead of $22. Amlodipine is not anticipated to have generic competition until Sept 2007, thus increasing expenditures is expected. Given these facts, and the likelihood that amlodipine utilization will only increase, the P&T Committee recommended non-formulary status for amlodipine.

Conclusion: The P&T Committee concluded that isradipine IR and CR, and nicardipine IR and SR, and amlodipine were not cost-effective relative to the other DHP calcium channel blockers. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the DHP calcium channel blockers, and other relevant factors, the P&T Committee recommended UF Formulary status for the dihydropyridine calcium channel blockers.

Committee action: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstention, 0 absent) to recommend formulary status for nifedipine IR, nifedipine CC/CR/XL, felodipine, and nisoldipine; and non-formulary status for isradipine IR and CR, nicardipine IR and SR, and amlodipine under the UF.

Verapamil Calcium Channel Blockers

From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that verapamil calcium channel blockers: have similar relative clinical effectiveness in the treatment of hypertension and angina, have similar safety and tolerability, but differ in their indications for night-time dosing. However, the Committee agreed that the night-time dosing indication was of minimal clinical importance as there was no literature evidence that night-time dosing has a positive benefit on clinical outcomes.

The results of the cost-minimization analysis revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included verapamil immediate release (IR) and verapamil sustained release (SR), whereas the moderate cost cluster included the Verelan brand of verapamil extended release capsules. Verelan PM and Covera HS, two extended release, night-time dosed verapamil brands, represented the high cost cluster. Based on this use of cost-minimization to determine the relative cost effectiveness of the agents within the verapamil calcium channel blocker therapeutic subclass, verapamil IR and verapamil SR were determined to be the most cost-effective agents.

The results of the CMA were subsequently incorporated into a budget impact analysis (BIA). The BIA results revealed that a group of verapamil calcium channel blockers that included verapamil IR and verapamil SR were more cost effective relative to other combination groups.

Conclusion: The P&T Committee concluded that Verelan, Verelan PM, and Covera HS were not cost-effective relative to the other verapamil CCBs, they were more costly and provided no additional clinically meaningful benefit over the most cost-effective agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the verapamil CCBs, and other relevant factors, the P&T Committee recommended UF Formulary status for verapamil calcium channel blockers.

Committee Action: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstention, 0 absent) to recommend formulary status for verapamil IR and verapamil SR; and non-formulary status for Verelan, Verelan PM, and Covera HS under the UF.

Diltiazem Calcium Channel Blockers

From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that diltiazem CCBs: have similar relative clinical effectiveness in the treatment of hypertension and angina, have similar safety and tolerability, but differ in their indications for night-time dosing. However, the Committee agreed that the night-time dosing indication was of minimal clinical importance as there was no literature evidence that night-time dosing has a positive benefit on clinical outcomes.

For the cost minimization analysis, the different extended release diltiazem formulations (not just the active ingredients) were evaluated together, and the lowest cost agent was used in the cost calculations. There are several diltiazem extended release preparations available (Cardizem CD, Dilacor XR, Cartia XT, Taztia XT, Diltia XT, and Tiazac [these are designated as CD/XR/XT hereafter]). The results of the cost-minimization analysis revealed three distinct clusters along the cost-continuum: low, moderate, and high cost agents. The low cost cluster included diltiazem immediate release (IR) whereas the moderate cost cluster included diltiazem CD/XR/XT and diltiazem sustained release (SR). Diltiazem extended release for bedtime dosing (Cardizem LA) represented the high cost cluster. Based on this use of cost-minimization to determine the relative cost effectiveness of the agents within the diltiazem CCB therapeutic sub-class, diltiazem IR, diltiazem CD/XR/XT, and diltiazem SR were the most cost-effective agents.

The results of the CMA were subsequently incorporated into a budget impact analysis (BIA). The BIA results revealed that a group of diltiazem CCBs that included diltiazem IR, diltiazem CD/XR/XT, and diltiazem SR were more cost-effective relative to other combination groups.

Conclusion: The P&T Committee concluded that diltiazem extended release for bedtime dosing (Cardizem LA) was not cost-effective relative to the other diltiazem CCBs, since it was more costly and provided no additional clinically meaningful benefit over the most cost-effective agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the diltiazem CCBs, and other relevant factors, the P&T Committee recommended UF Formulary status for the diltiazem calcium channel blocker therapeutic sub-class.

Committee Action: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 0 abstention, 0 absent) to recommend formulary status for diltiazem IR and diltiazem CD/XR/XT; and non-formulary status for Cardizem LA under the UF.

Implementation Plan:

Because there are a large number or patients who are receiving amlodipine (Norvasc) at any MHS pharmacy point of service (58% of all patients receiving CCBs (MHS =210,000 unique utilizers/365,000 Unique Utilizers = 58%) the Committee proposed an effective date no later than the 1st Wednesday following a 150-day transition period for implementation of a decision by the Director, TMA, to classify amlodipine as non-formulary on the Uniform Formulary. Non-formulary status was also recommended for isradipine (controlled release and immediate release), nicardipine (controlled release and immediate release, Covera HS, Verelan, Verelan PM and Cardizem LA.

Patients wishing to fill prescriptions for Non-Formulary drugs at the Retail network pharmacies or the TMOP would then have to pay the non-formulary cost share unless medical necessity for these agents are established by the beneficiary or their provider. MTFs are not allowed to have non-formulary pharmaceutical agents on their local formularies. MTFs will be able to fill non-formulary requests for non-formulary agents only if both of the following conditions are met: 1) the prescription is written by a MTF provider and 2) the beneficiary and his or her provider has established medical necessity for the agent. MTFs may (but are not required to) fill a non-formulary prescription written by a non-MTF provider to whom the patient was referred as long as medical necessity has been established.

Committee Action: The P&T Committee voted to recommend an effective date no later than the first Wednesday following a 150 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

$ALPHA_1$ ADRENERGIC BLOCKERS (Alpha Blockers)

Background:
The clinical review of the alpha blockers took into consideration their relative safety (likelihood to do no harm), tolerability (likelihood to be taken), and efficacy (likelihood to work.

Symptoms associated with benign prostatic hyperplasia (BPH) can be obstructive (voiding problems) or irritative (storage problems). The obstructive symptoms include urinary hesitancy, a weak urine stream, dribbling, incomplete evacuation or incontinence. Irritative symptoms are generally considered to be increased urinary frequency or urgency, nighttime urination, and painful urination. Standard treatments include watchful waiting in patients with mild symptomatic BPH, treatment with alpha-blockers and 5-alpha reductase inhibitors in patients with moderate-to-severe symptomatic BPH, and surgery in patients with severe symptomatic BPH.

This class review concentrated on the alpha-blockers and not the 5-alpha reductase inhibitors dutasteride (Avodart) and finasteride (Proscar). The therapeutic class was defined to include four alpha-blockers: terazosin (Hytrin), doxazosin (Cardura), tamsulosin (Flomax), and alfuzosin (Uroxatral).

Alpha-blockers are effective treatment in resolving both the obstructive and irritative symptoms of BPH. Alpha-blockers are classified as first, second, and third generation agents based on their specificity for certain receptors (prostate and bladder neck).

First generation alpha-blockers (i.e., phenoxybenzamine) are considered to be the least uroselective of the alpha-blockers and therefore have a higher incidence of adverse events. Because of the cardiac side effects of phenoxybenzamine (i.e., reflex tachycardia, syncope, and cardiac arrhythmias), the first-generation alpha-blockers have been replaced by second generation (terazosin, doxazosin) and third-generation (tamsulosin, alfuzosin) alpha-blockers.

Second generation alpha-blockers (terazosin, doxazosin) are considered non-uroselective because they have affinity for more than one receptor subtypes. Third generation agents (tamsulosin, alfuzosin) are uroselective, exhibiting a high degree of specificity for one receptor (which is found in the prostate).

TABLE 1: Alpha$_1$ adrenergic blockers used in BPH available in the United States

GENERIC	BRAND (Manufacturer)	FDA approval date
Terazosin	Hytrin (Abbott, generic)	08/07/1987 tablets 12/14/1995 capsules
Doxazosin	Cardura (Pfizer, generic)	11/02/1990 tablet 02/22/2005 XL tab
Tamsulosin	Flomax (Boehringer Ingelheim)	04/15/1997
Alfuzosin	Uroxatral (Sanofi- Synthelabo)	06/12/2003

Relevance to MHS and Utilization: The P&T Committee agreed that in the Military Health System (MHS) alpha-blockers are considered a gold standard for treating symptoms of BPH. During a twelve month period ending 30 April 2005, approximately 196,388 patients were prescribed an alpha blocker. This class is now ranked 25th in MHS drug class expenditures.

FDA Indications: All four alpha-adrenergic blockers are approved by the Food and Drug Administration for the treatment of BPH.

The DoD P&T committee's conclusion was determined after answering the following key questions based upon the Relative Clinical Effectiveness Review:

Key Questions:

1) Are there differences in the efficacy of the alpha-blockers for treating symptoms of BPH?
2) Are there differences in the safety and tolerability profiles of the alpha-blockers?

Data Source: To answer these key questions the alpha-blocker relative clinical effectiveness analysis evaluated information from randomized, clinical trials. Additional published clinical trials were found using a Medline search; searching major medical journals table of contents, evidence based systematic reviews and manufacturer press releases. Proceedings from major Urology group meetings and clinical guidelines were also reviewed to find published clinical trials. Manufacturers were invited to present new data, and the FDA website was monitored for new indications.

Efficacy for alpha-blockers:

Key question #1: Are there differences in the efficacy of the alpha-blockers for treating symptoms of BPH? All four alpha-blockers are FDA approved for the treatment of BPH. There are limited head-to-head trials comparing the four alpha-blockers. The available placebo controlled trials and meta-analyses were reviewed. Although all alpha-blockers were found to be clinically effective when compared to placebo, variability in study design, demographics, and outcome measures precluded the ability to designate one alpha-blocker as clinically superior. Universal agreement between the Cochrane Database, Clinical Evidence, and the American Urological Association (evidence based healthcare systematic reviews) concurred that all four alpha-blockers are clinically interchangeable in regards to efficacy. In the tools used to measure effectiveness, all four drugs relieve BPH symptoms, improve standardized testing symptom

scores (a validated survey on patient's degree of symptoms) and improve urinary flow rates to the same extent. There is no evidence to suggest clinical superiority based on these differences.

Conclusion: The DoD P&T Committee concluded that all four alpha blockers have similar relative clinical effectiveness for treating the symptoms of BPH.

Key question #2: Are there differences in the safety and tolerability profiles of the alpha-blockers? The P&T Committee found that the alpha-blockers had similar safety data within their generation with respect to drug interactions, and adverse drug reactions. Adverse effects are primarily related to the agent's receptor specificity (terazosin and doxazosin are nonselective; tamsulosin and alfuzosin are selective). As of August 2005 all agents have similar alpha-blocker postural hypotension warnings. Nonselective agents (terazosin and doxazosin) exhibit increased vasodilatory (dizziness, asthenia, postural hypotension) effects while selectives (tamsulosin and alfuzosin) show decreased vasodilatory effects. Tamsulosin and alfuzosin are better tolerated than terazosin and doxazosin as measured by withdrawals due to adverse events and discontinuation of therapy.

Conclusion: The DoD P&T Committee concluded that there may be a marginal benefit of selective alpha blockers (tamsulosin, alfuzosin) over non-selective alpha blockers (terazosin, doxazosin) with respect to safety and tolerability.

Relative Cost Effectiveness:

The P&T Committee evaluated the relative cost-effectiveness of the agents within the alpha-blocker class in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2).

To determine the relative cost-effectiveness of the agents within the alpha-blocker therapeutic class, two separate economic analyses were performed, a pharmacoeconomic analysis and budget impact analysis (BIA). From the preceding relative clinical effectiveness evaluation, the P&T Committee determined that alpha-blockers have similar efficacy in the treatment of lower urinary tract symptoms often associated with benign prostatic hyperplasia, but differ in safety and tolerability, especially in comparison of non-selective alpha-blockers with selective alpha-blockers. The agents within the alpha-blocker therapeutic class were thus shown to differ in relative clinical effectiveness.

A cost-minimization analysis (CMA) was initially performed to stratify the agents solely on cost. The results of the cost-minimization analysis show two distinct clusters along the cost continuum: doxazosin and terazosin form a cluster of low-cost agents and alfuzosin and tamsulosin form a cluster of high cost agents. These results were expected since doxazosin and terazosin are multi-source generic products and alfuzosin and tamsulosin are single-source brand name products. The results of the cost-minimization analysis revealed that non-selective alpha-blockers were more cost-effective compared to selective alpha-blockers, based on the total weighted average cost per day of treatment (for all three points of service). Within the non-selective alpha-blocker sub-class, doxazosin was found to be slightly more cost-effective compared to terazosin and within the selective alpha-blocker sub-class alfuzosin was found to be considerably more cost-effective compared to tamsulosin.

Next, a cost-effectiveness analysis (CEA) was employed, which accounted for differences in safety and tolerability between the non-selective alpha-blocker sub-class and the selective alpha-blocker sub-class. In this type of analysis, agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes). For this particular CEA, a Markov model was constructed based upon the outcomes reported in the Medical Therapy of Prostatic Symptoms Study (MTOPS) for the doxazosin arm. The direct medical costs included: the total weighted average drug cost per day of treatment (for all three points of service), medical treatment costs associated with disease clinical progression, and medical treatment costs associated with adverse drug events.

Two cost-effectiveness analyses were performed. In the first analysis, the effect (outcome) was defined as successfully treated patient. Overall, the results from the first CEA paralleled the results obtained in the CMA: non-selective alpha-blockers and selective alpha-blockers were equally effective, non-selective alpha-blockers were more cost-effective compared to selective alpha-blockers, doxazosin was slightly more cost-effective compared to terazosin, and alfuzosin was considerably more cost-effective compared to tamsulosin. However, when the cost of adverse events associated with non-selective alpha-blocker treatment was considered, the difference in cost per successfully treated patient between the non-selective and selective alpha-blockers was significantly closer than what was indicated by the CMA.

In the second CEA, the effect was defined as successfully treated patients without adverse drug events, more specifically, cardiovascular/ hypotensive adverse drug events associated with non-selective alpha-blockers. The results from the second CEA revealed selective alpha-blockers were more effective (more patients successfully treated without adverse drug events) but still more costly compared to non-selective alpha-blockers

In summary, the CEAs show that non-selective alpha-blockers are more cost-effective compared to selective alpha-blockers, but the marginal difference in cost of treatment between the sub-classes is not as great when the costs of clinical progression and treatment of adverse events are considered.

The results of the CMA and CEA were subsequently incorporated into a budget impact analysis (BIA). Three different budget impact scenarios were modeled. A budget impact scenario with just the non-selective alpha-blockers on the UF was not considered because of a previous DoD P&T Committee decision to include at least one selective alpha-blocker on the UF. Examination of the budget impact analysis revealed maintaining doxazosin, terazosin, and alfuzosin on the UF and designating tamsulosin as non-formulary best achieved the DoD P&T Committee's goal of identifying a group of alpha-blockers to be included on the UF which best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstention, 1 absent) to accept the BPH alpha-blocker cost-analysis presented by the PEC. The P&T Committee concluded that doxazosin and terazosin had similar relative cost-effectiveness in the non-selective alpha-blocker subclass, but determined that tamsulosin was not cost-effective relative to alfuzosin in the selective alpha-blocker sub-class. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee recommended that tamsulosin be classified as non-formulary under the UF and that alfuzosin, doxazosin, and terazosin be classified as formulary on the UF.

Committee Action: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstention, 1 absent) to recommend formulary status for alfuzosin, doxazosin, and terazosin and non-formulary status for tamsulosin under the UF.

Implementation Plan: Because a number of patients are currently receiving tamsulosin from one of the three MHS pharmacy points of service (89,926 patients, 46% of all patients receiving alpha-blockers) the P&T Committee proposed a 120-day transition period for implementation of the decision to designate tamsulosin as non-formulary on the UF. Patients wishing to fill prescriptions for tamsulosin at retail network pharmacies or the TMOP would then have to pay the non-formulary cost share unless medical necessity for these agents is established by the beneficiary or their provider.

MTFs (Military Treatment Facilities) will not be allowed to have tamsulosin on their local formularies. MTFs will be able to fill non-formulary requests for tamsulosin only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) the beneficiary provider must establish medical necessity for these agents. MTFs may (but are not required to) fill a prescription for tamsulosin written by a non-MTF provider to whom the patient was referred, as long as medical necessity has been established.

Committee Action: The P&T Committee voted to recommend an effective date of no later than the first Wednesday following a 120-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

PRIOR AUTHORIZATION REQUIREMENTS FOR PRAMLINTIDE (SYMLIN)

Background: Pramlintide (Symlin) is a synthetic analog of amylin, a naturally occurring hormone that works with insulin to reduce elevations in blood glucose that occur after meals.

Pramlintide has been approved by the FDA for use in type 1 diabetics (who need insulin) or type 2 diabetics who are also taking insulin at mealtimes (there are some type 2 diabetics who do take insuline). Pramlintide should be used in patients who are taking insulin, but still have poor blood glucose control, or who are taking oral medications and still have poor blood glucose control. Pramlintide is not indicated for use in pediatric patients.

Since pramlintide is given with insulin, this combination can increase the risk of blood glucose levels dropping dangerously low (severe hypoglycemia), which can sometimes result in coma or death. This usually occurs within 3 hours following a pramlintide injection, and is more likely to occur in type 1 diabetics. Doses of insulin must be adjusted when pramlintide therapy is started, changed, or stopped. Mealtime insulin doses should be reduced by half when a patient is first started on pramlintide. There is a black box warning in the package insert for pramlintide that discusses the risk of very low blood sugars, and also cautions that patients need to be careful when driving or operating heavy machinery.

Pramlintide is given by an injection immediately prior to each major meal. It is available only in vials and not in a pen or other dosing device (insulin is available in vials and automatic pen injection devices). A patient uses an insulin syringe to draw up and administer the pramlintide. In order to calculate the correct dose, a conversion table is in the package insert. Patients need to be educated that pramlintide should not be mixed in the same syringe with any type of insulin and should not be injected at the same site as their insulin injection. Since a patient taking pramlintide will already be receiving insulin, the number of injections the patients needs each day will increase when pramlintide therapy is started.

Patient Selection Requirements

Pramlintide is not intended for every patient with diabetes – there are specific requirements for the appropriate patients in the package insert. Pramlintide should only be used by patients with a HbA1c < 9% (a lab test that tells how well blood glucose levels are controlled over several months), who have not reached their blood glucose goals despite all efforts with their diet, taking their insulin correctly, monitoring their blood sugars, and routinely following up with their providers. Patients using pramlintide must understand how to adjust pramlintide and insulin doses, and must be able to have self-awareness of the signs of dangerously low blood glucose levels.

PA Criteria

Refer to pages 18 and 19 of your background document (not the handout) that lists the actual prior authorization criteria. The prior authorization criteria are based on the requirements for selecting patients who would be good candidates for pramlintide. The major concern of the DOD P&T Committee was to ensure that patients receiving pramlintide would be able to safely manage the dosing, administration, and monitoring requirements, and that they would benefit from its use.

Recommendations

Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended that a prior authorization be required for pramlintide. The Committee recommended that the PA should have an effective date no later than the first Wednesday following a 30-day implementation period. This implementation period represents the minimum feasible time for technical implementation requirements to be completed and the PA criteria and form made available on the TRICARE website.

In order to avoid interruptions in therapy, which would require adjustments in insulin dosage, and potentially cause disruptions in blood glucose control for patients stabilized on therapy, the DOD P&T Committee further recommended that patients who received pramlintide from a DoD pharmacy point of service prior to the PA effective date should be allowed to continue to receive pramlintide. The implementation period will begin immediately following the approval by the Director, TMA.

Committee Action: The DoD P&T Committee voted (17 for, 0 apposed, 0 abstentions, 0 absent) that a prior authorization be required for pramlintide, with an effective date no later than the first Wednesday following a 30-day implementation period.