Uniform Formulary Beneficiary Advisory Panel

Meeting Summary
March 30, 2006
Washington, D.C.

Panel Members Present:

- Sydney Hickey, Military Coalition, Chairperson
- John Class, Military Coalition
- John Crum, TRICARE Network Provider
- Deborah Fryar, Military Coalition
- Marshall Hanson, National Military and Veterans Alliance
- Rance Hutchings, Uniformed Services Family Health Plan
- Lisa Le Gette, TRICARE Retail and Mail-Order Pharmacy Contract
- Jeffrey Lenow, Medical Professional
- Martha Miller, TRICARE Network Provider
- Charles Partridge, National Military and Veterans Alliance
- Marissa Schlaifer, Medical Professional

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.

MAJ Watson indicated this meeting of the Panel has been convened to discuss and review the recommendations of the Department of Defense (DOD) Pharmacy and Therapeutics (P&T) Committee meeting held on February 14-16 in San Antonio, TX.

Agenda

The agenda for the March meeting of the Panel is:

- Opening remarks and public comments
- Election of a new Chairperson
- Consideration of overactive bladder drug class recommendations
- Consideration of miscellaneous antihypertensive drug class recommendations
- Presentation on the outcomes of previous Uniform Formulary (UF) decisions
- Consideration of GABA analogs drug class recommendations
- Wrap-up comments

Opening Remarks

MAJ Watson stated that under 10 United States Code (U.S.C.) section 1074g the Secretary of Defense is required to establish a DOD Uniform Formulary of pharmaceutical agents, review the formulary on a periodic basis and make additional recommendations regarding the formulary as the Committee deems necessary and appropriate.

10 U.S.C. section 1074g also requires the Secretary to establish a Uniform Formulary Beneficiary Advisory Panel (BAP) to review and comment on the development of the Uniform Formulary. The Panel shall include members that represent non-governmental organizations and associations that represent the views and interests of a large number of eligible covered beneficiaries. Comments of the Panel must be considered before implementing changes to the Uniform Formulary. The Panel's meetings are conducted in accordance with the Federal Advisory Committee Act (FACA).

The duties of the Uniform Formulary Beneficiary Advisory Panel are:

- To review and comment on the recommendations of the P&T Committee concerning the establishment of the Uniform Formulary and subsequent recommended changes. Comments to the Director, TMA, regarding recommended formulary status, pre-authorizations, and suggested dates for changing from "formulary" to "non-formulary" status must be reviewed by the Director before making a final decision.
- To hold meetings in an open forum quarterly. The Panel may not hold meetings except at the call of or with the advance approval of the Chairman of the Panel.
- To prepare minutes of the proceedings and preparing comments for the Secretary or his designee regarding the Uniform Formulary or changes to the Formulary. The minutes will be available on the website and comments will be prepared for Dr. Winkenwerder, Director, TRICARE Management Activity (TMA).

As guidance regarding this meeting, MAJ Watson said the role of the Beneficiary Advisory Panel is to comment on the Uniform Formulary recommendations made by the P&T Committee at their last meeting. While the Department appreciates that the BAP may be interested in the drug classes selected for review, drugs recommended for the basic core formulary (BCF) or specific pricing data, these topics do not fall under the purview of the BAP.

The P&T Committee met for approximately 20 hours to consider the class review recommendations presented today. Since this meeting is considerably shorter, the Panel will not receive the same extensive information that is presented to the P&T Committee members. However, the BAP will receive an abbreviated version of each presentation and its discussion.

Detailed minutes of this meeting are being prepared. The BAP minutes, the DOD P&T Committee meeting minutes and Dr. Winkenwerder's decisions will be available on the TRICARE website in approximately four weeks.

MAJ Watson next reviewed the ground rules for conducting the meeting:

- All discussion takes place in the open public forum. There is to be no committee discussion outside the room, during breaks or at lunch.
- Audience participation is limited to private citizens who signed up to address the Panel.
- Members of the Pharmacoeconomic Center (PEC) and the P&T Committee are available to answer questions related to the BAP's deliberations. Should a misstatement be made, these individuals may interrupt to ensure that the minutes accurately reflect relevant facts, regulations or policy.

MAJ Watson introduced the members of the Beneficiary Advisory Panel present as well as individuals in the audience who might be participating in the session.

MAJ Watson then briefly reviewed housekeeping considerations.

Election of a New Chair

MAJ Watson announced that the Panel would elect a new Chairperson of the Panel at this meeting. As the Chair switches annually, the new Chair's duties will begin with the next quarterly meeting in June. Panel Chairs are elected from the membership for a term of one year. Members were asked to vote for one individual on the prepared ballot. The winner will be the individual with the most votes. In the event of a tie, a runoff vote will he held among the tied individuals. If there is still a tie, MAJ Watson will select a new Chair.

The Panel elected John Class to serve as the Chairperson for the next year beginning with the June 2006 meeting.

MAJ Watson thanked Ms. Hickey for her leadership during the Panel's inaugural year.

Private Citizen Comments

MAJ Watson opened the meeting for private citizen comments. There was no response.

He noted that 15 emails had been submitted from providers and private citizens, the majority relating to Lyrica – a drug in one of the classes to be discussed at this meeting. MAJ Watson said he would not go into the details of these communications in open meeting because the communications will be published on the BAP website (with email addresses, phone numbers and personal health information redacted).

MAJ Watson announced that, lacking oral public comments, items on the published agenda will occur earlier than planned and turned the meeting over to the Panel Chair, Ms. Sydney Hickey.

Chairperson's Opening Remarks

Ms. Hickey began by thanking the individuals who have participated on and supported the Panel during its first year. She also announced that work has been completed on a standard press release to expedite communications to beneficiaries and providers about Dr. Winkenwerder's decisions soon after they are made – within a couple of days.

She then turned the podium over to Major (Maj) Wade Tiller, Chief Pharmacoeconomic Analyst at the DOD Pharmacoeconomic Center to begin the presentation of drug class reviews.

Overactive Bladder (OAB) Drug Class Review

[Insert script, pages 1 through 9]

Physician Perspective on OAB Drug Class Recommendations

Maj Tiller introduced Captain (CPT) Jill Dacus, an Army Internal Medicine Physician, to provide the physician perspective on this drug class review. CPT Dacus began by noting that the drugs in this class are prescribed mostly for older patients. She was surprised to find that patients are not taking these medications every single day because the side effects are bothersome. She prefers to prescribe medications that have less severe side effects than the immediate release doses. Detrol IR, which is recommended for non-formulary, has to be dosed three times a day. Since physicians don't usually prescribe drugs that have to be dosed three times a day, the impact of moving this agent to non-formulary should be minimal. Similarly, Sanctura, which is one of the newer medicines, has to be dosed twice a day. The problem with Oxytrol is that the medication stays in the blood a long time so a patient using the patch doesn't have the option of not taking the drug on a particular day. The patch also tends to cause rashes. CPT Dacus also observed that patients who really need one of the three drugs recommended for non-formulary will be able to justify that through medical necessity. They are probably the three least-used drugs in her practice.

Panel Questions on OAB Drug Class Recommendations

Ms. Hickey noted a sharp increase in the number of Vesicare and Enablex prescriptions shown on the Figure 2 graph on page 4 of the handout and asked if they were included on the Basic Core Formulary. The answer provided was that they were not included on the BCF. The increase is all from private providers. Ms. Hickey also noted that Sanctura prescriptions increased rapidly for a time and then leveled off. She was also surprised about the "persistence" problem – only 43 percent of patients using this class of drugs get their refills on time. She asked whether some providers might consider the patients who take one of these medications only occasionally for social situations as "persistent" even though the system would not. Maj Tiller said when the PEC made its survey, providers were allowed to define "persistent" however they wanted to. Even so, only 43 percent said their patients were using the medications persistently.

Ms. Hickey said she is also somewhat concerned about the 3,000 beneficiaries who use the TRICARE Mail-Order Pharmacy (TMOP). The 60-day implementation means that these people will only find out that their drugs are non-formulary and will cost more when they have to come for a refill. Dr. Dave Meade of the PEC said that with the persistence rates as they are for this class, even 180 days might not be sufficient to catch all of the people because they do not get their refills in a timely manner. Many people just stop using these medications altogether after 90 days.

Dr. Crum stated he thought the analysis is well-reasoned, although he would favor a little longer implementation period, perhaps 90 days. He is concerned about how the decision will be communicated to beneficiaries.

Mr. Class asked about provider input to the recommendations for this drug class, specifically from physicians outside the Military Health System (MHS). Maj Tiller replied that the PEC currently has no mechanism for obtaining input from network providers, so all of the input now is from MTF providers. Mr. Class asked if the PEC plans to look at that situation. His concern is that MTF providers may or may not have access to the newer drugs. CPT Dacus said that MTF providers do have access to all of the newer drugs and asked for further comment on how the Panel thinks MTF providers are different from civilian providers. Mr. Class explained that

his concern is that the opinions of only a small part of the total provider population are represented and those individuals are all of the same circumstance.

Ms. Hickey added that the Panel has the responsibility of representing all of the beneficiary groups in the TRICARE population. She observed that the number of beneficiaries being treated in the MTF system is quite small compared to the total population. This is the source of the Panel's concern with the representation of outside providers in the body of opinion on a given drug class.

Dr. Hutchings observed that in a lot of cases outside providers are just responding to whatever insurance providers are concerned about. He thinks that going outside might start tainting things. Other people's formularies don't necessarily apply to the MHS pricing schedule.

Mr. Class commented that it was very helpful to have the cost range comparisons that were provided for this class ("over 15-fold more costly"). But he noted that some agents were simply labeled as "more expensive" with no quantification. Maj Tiller said that since the other drugs were not recommended for non-formulary status, the PEC didn't feel it was necessary to provide that information. He said that all of the "sustained release" products were greater than 15-fold more expensive than the generic or ditropan products.

Ms. Fryar asked, in relation to implementation, what constitutes a "significant number" of beneficiaries and what constitutes a "low number" of beneficiaries. Specifically, she asked whether it is greater or less than 50,000. Maj Tiller answered that one of the things the PEC considers is whether the usage is chronic or acute. In this case, although the drugs are chronic meds, people don't really use them chronically. He said the PEC looks at past decisions that the P&T Committee has made and makes a decision relative to those. In the case of this class, they would be compared to the calcium channel blockers and also the alpha blockers. This case represents one of the lowest numbers of beneficiaries affected by a P&T Committee decision. The objective is to implement the decision in a fashion that is not inconvenient for a large number of beneficiaries.

Mr. Hanson said he, too, supports a longer implementation period. The Department of Defense is currently trying to get people to switch over to the TRICARE Mail-Order Program. So a greater period of time would help to support the DOD objectives here and will encourage people to switch.

Dr. Hutchings said that it is pretty hard for his organization to notify people in less than 90 days just because of the process that is involved after the decision comes out.

MAJ Watson said the implementation process has been a learning process for all concerned. Direct member mailings have been tried and TMA is also evaluating the effectiveness of the call center approach. More passive types of information – such as press releases – are also being used and an effort is being made to get those out on a timelier basis. In the future, TMA plans to include member mailings as part of its follow-on contracting efforts. However, that won't affect the current situation.

Dr. Hutchings said his organization has found that people feel better about making a switch if you give them a large enough window to work with.

Mr. Class said he is glad to hear that TMA realizes there is an issue with the time frame. He still thinks the better answer now would be to set a longer time frame for implementation while TMA is getting the process fixed.

MAJ Watson suggested that the Panel might want to incorporate that thought into its comments.

Dr. Hutchings asked if dementia was looked at as one of the possible side effects in this drug class. The answer provided was that it was not.

Panel Discussion of OAB Drug Class Formulary Recommendations

Dr. Hutchings said he thinks the recommendations are sound but he is concerned about having Detrol LA on the Uniform Formulary while Detrol is non-formulary. He isn't sure that it's a good idea to have one formulation on formulary and another off. This will result in one formulation having a $9 cost and the other a $22 cost to beneficiaries.

Ms. Hickey agreed, saying she thinks it would be less confusing to have a drug either on or off formulary in all of its different formulations. But she doesn't feel strongly enough about it to vote against the recommendation.

Panel Discussion of OAB Drug Class Implementation Period

Ms. Fryar said she has the same concern about this recommendation that the Panel has had at previous meetings with the implementation time. She is not in favor of 60 days.

Ms. Le Gette asked the Military Coalition members of the BAP to comment on what kinds of communications their organizations use. Ms. Hickey answered that it depends on the organization. All have some sort of publication. In her case, there is a two month lead time for getting information out through that publication. Many organizations also have websites. Some, but not all, publish this kind of information on them.

Ms. Le Gette said that as a result of not sending beneficiary notification letters for the last set of non-formulary changes, her organization's call volume in reference to these changes has gone from 10 percent to 25 percent of weekly calls, just in retail. She stated that her organization is able to implement the changes whenever the government desires; however, she would be willing to agree to a longer implementation period if it allows more time for the military coalition to get the word out through their own communications.

Ms. Fryar said it would also be useful to try to help beneficiaries understand the process better. She noted that things that are not a problem for the MTFs might be a problem for beneficiaries.

Ms. Schlaifer said the traditional reason for a longer implementation time is to do the notification. But it sounds to her like the way everyone finds out is by going to get their prescription refilled. If that's true, it doesn't matter whether the time is 60 days or 90 days – the beneficiary still won't find out until they go to get their prescription filled. She asked whether there would be a real difference.

Mr. Class replied that the problem is with the notification process. For those who rely on the notification process, the time does make a difference. The information his organization puts out reaches some beneficiaries. For that, the extra time does make a difference.

Mr. Partridge said that beneficiaries read his organization's magazine. It's a valuable way to communicate. He thinks 120 days is better than 90 days, although 90 days is sometimes adequate.

Ms. Hickey noted that a 60 day notification period would be adequate only for a website. For other forms of communication, notification just wouldn't happen. She also suggested that someone – either the P&T Committee or TMA – might want to look at the difference in migration when letters did not go out because of the short time frame and when they did – 120 days or longer.

Dr. Hutchings said when his organization gets the letters out a month in advance, the call center gets almost no calls. Communicating with the patient does make a big difference in the number of calls. Without the communication, the first assumption a patient makes is that "somebody has made a horrible mistake." Most patients haven't been affected by a change in co-pay so it's off their radar.

Panel Vote on OAB Recommendations

Chairperson Hickey called for the Panel vote on the overactive bladder drug class formulary recommendations:

"Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the OAB agents, and other relevant factors, the P&T Committee recommended that tolterodine IR (Detrol), oxybutynin patch (Oxytrol) and trospium (Sanctura) be classified as non-formulary and that darifenacin (Enablex), oxybutynin IR (Ditropan), oxybutynin SR (Ditropan XL), solifenacin (Vesicare), and tolterodine ER (Detrol LA) remaining on the UF."

The Panel voted 11-0 to concur with the recommendation.

Ms. Hickey next called for the Panel vote on the implementation period:

"The Committee voted to recommend an implementation period of 60 days."

The Panel voted 11-0 to non-concur with the recommendation.

Ms. Hickey asked whether there might be a consensus among the Panel as to what the implementation period should be.

Mr. Partridge said 120 days would be better than 90 in this case.

Dr. Hutchings commented that longer lead times sometimes cause communications to be forgotten. He said 90 days would be just right for his organization, but he is willing to vote for 120 days.

Mr. Class said that 90 days is fine if don't notify people but not adequate if you do. 90 days is a comfortable notification time, but not if publications are used. If TMA is relying on the associations to notify beneficiaries, the implementation period should be 120 days.

Mr. Partridge agreed, saying his organization knows they will reach everybody if the time allowed is 120 days.

Mr. Hanson also supported Mr. Class' phrasing that if TMA is relying on the associations to get the word to the beneficiaries, the implementation period should be 120 days.

Ms. Schlaifer said that she thinks it depends on the drug class. In this case, it's not a critical problem if a patient misses a dose. She thinks 90 days would be acceptable for this class.

The Chair called for a vote of the Panel on a 120-day implementation period. The Panel was unanimous (11-0) in indicating it would be comfortable recommending a 120-day implementation period.

Panel Comments on OAB Drug Class Implementation Plan

The Panel's comment on this drug class is:

The Panel does not concur with the recommended 60-day implementation period and recommends a 120-day implementation period. Notification within the beneficiary community, with the exception of the Uniformed Services Health Plan, relies on the associations and that time frame is needed to get the information into their publications.

Miscellaneous Antihypertensive Drug Class Review

The Chairperson announced the next agenda item for consideration: the antihypertensive drug class review and recommendations of the P&T Committee. Dr. Dave Meade of the PEC began the presentation.

[Insert script, pages 10 through 18]

Physician Perspective on Antihypertensive Drug Class Recommendations

CPT Dacus again provided the physician perspective for this drug class. She said she agrees that it is a good idea to have one combination calcium channel blocker-ace inhibitor on the Uniform Formulary. The choice – Lotrel with amlodipine and benazepril – is a good one. Combo products are good because they really help patient compliance. But there are some difficulties with the combination products. To clarify, she said when the Joint National Commission, in talking about hypertension, says that two products are better than one, what they mean is that two medium doses of different products are better than one high dose in controlling blood pressure. But two individual products in one pill are not better than individual pills taken at separate times. She also pointed out that the individual products of Lexxel – felodipine and enalapril – are both available on the Uniform Formulary as are the individual ingredients in Tarka – verapamil and

trandolapril. She thought this decision was relatively clean and those patients who should be on a combination drug can be treated with Lotrel.

Panel Questions on Antihypertensive Drug Class Recommendations

Dr. Lenow asked about the final status of Prazosin. The answer given was that it is included.

Dr. Lenow said that when he was in med school, students were working with minoxidil and noticed that hair growth was a side effect. This was formulated as a cream and named "regain" which was commercialized as "Rogaine." He noted that the drug has pretty much been shunned as being a dangerous drug. He said he'd be interested to see how many of the older drugs – like Aldomet, Prazosin and Reserpine – are recent, newly-started scripts versus continuations of scripts for older people. If people are being started on these as new drugs, he would like to hear an explanation of why.

The Chair said this drug class raises an issue for her. She realizes the Panel's mandate is to review and comment on the recommendations of the P&T Committee. However, several Panel members are aware that the new pharmacy contract will give contractors an incentive to move beneficiaries to a "class generic" rather than to the specific generic that is identical to the brand name drug. There is already a DOD policy that says that if there is an identical generic, patients cannot get the brand name drug without a medical necessity waiver. Ms. Hickey said she is uncomfortable with having the Panel vote on a drug like Prazosin, which is not considered a good drug for anti-hypertension. Although it does have other uses, she is uncomfortable with voting for it or not voting for it based on this classification. Ms. Hickey noted that the Panel has had this issue before – with the calcium channel blockers – and needs to find some other way of dealing with it. She would like to know how many of the prescriptions for these drugs are for anti-hypertension and how many are for the off-label uses. If the drugs are being kept on the formulary for off-label purposes, the decision should state that. But she is greatly concerned about keeping them in the drug class where the contractor would benefit economically by inducing people to move to them, especially when they have been proven over the years to be less effective or even harmful. Ms. Hickey asked for comments.

MAJ Watson began his answer by saying he would not comment on the new contract. He then stated that clinical considerations always trump any kind of economic decisions involved in the process. The clinical aspects of the products have to be such that clinical quality would not be degraded by any program to encourage use within a particular therapeutic class. The clinical aspects would not be compromised.

Ms. Hickey said her concern is that the financial incentive in the new contract lies in the other direction. She understands MAJ Watson's statement that the clinical concerns would override that. But she said she is not so sure what might happen when money is involved. Her concern is with drugs that are on the formulary for off-label uses. She believes there needs to be some mechanism for dealing with drugs that are looked at for off-label uses. She understands the need to consider drugs in groups. She knows about DOD studies involving off-label uses and doesn't want to take the drugs off the formulary, but they are not there as an anti-hypertensive agent.

Dr. Hutchings noted that all of the agents are used for hypertension. Even if patients were to be steered to these agents, they would just be steered to a $3 ACE or a $3 calcium channel blocker.

Ms. Schlaifer commented that if the decision was made to switch a patient, it would be within a class and the class would not be "anti-hypertension." It would be within the same type of medication, for example an ACE inhibitor for an ACE inhibitor or a calcium channel blocker for a calcium channel blocker.

Dr. Lenow said it depends on how low you cut. At one time, SSNRIs (Selective Serotonin Norepinephrine Reuptake Inhibitors) and SSRIs (Selective Serotonin Reuptake Inhibitors) were lumped together in one class. They have since backed away from that. He would argue that these are really different kinds of medications and shouldn't be interchanged, even though they have the same purpose. Prazosin is an anti-hypertensive. He said the concern is legitimate because some agents are used for other things.

MAJ Watson noted that a substitution of one product for another requires the involvement of a physician. A generic substitution can be made at the point of service, but these types of substitutions would require the consent of a physician.

Ms. Hickey said her concern is still that ethics can go out the window when money gets involved and she doesn't want beneficiaries exposed to that.

MAJ Watson said he understood the comment and that it could be incorporated into the recommendations.

Mr. Class asked CPT Dacus about her background. She answered "internal medicine."

Mr. Class also asked for a further explanation of what goes into the cost-effectiveness ratio that the PEC uses. Maj Tiller explained that the procedure compares two or more products. One is a standard intervention or current-care product and the second is a new intervention that is being evaluated. The ratio involves calculating the cost of the standard and new interventions and dividing that figure by the effect of the standard and new interventions. The result is the cost-effectiveness ratio. The lower the ratio the better. Typically, the newer agents are more costly, so if it is much more effective you will get a lower ratio. When plotted on a graph, you will get a low flat slope if the ratio is favorable and a steep slope if it is not. The idea is that there has to be a significantly increased effect with a new drug because you have to pay a lot more for it.

Mr. Class asked if there is reason why the Panel couldn't get the ratio numbers for the medications to be reviewed. He said that when statements are made about there being "significant differences" he is curious about what the differences are and what makes them significant.

Commander (CDR) Richerson asked if Mr. Class was looking for a table that has the cost-effectiveness ratios for each of the drugs evaluated in a particular class. He said the first thing the PEC does is to scrub the class clinically. Factors other than cost and effectiveness are looked at before getting into an in-depth evaluation of a drug like amlodipine – utilization, whether there is a potentially significant economic benefit, whether clinical outcomes would be improved. If making a drug non-formulary wouldn't result in a significant clinical or economic advantage, the PEC won't evaluate it. In short, the PEC is not calculating cost-effectiveness ratios for all the agents. Instead, they are looking for those that clinically fall into a particular niche and have relatively low cost compared to the other agents. Future drug classes are likely to have a high

percentage of agents where there is little advantage economically or clinically. It wouldn't make sense to spend a lot of resources trying to evaluate those.

Mr. Class noted that the ratios are cited as being part of the decision process. He's not concerned about the agents the PEC didn't do, but he would like to have some kind of quantification to go with statements like "these two are lower than this one." When the analysis has been done and is part of the decision process, he would like to see the information shared.

CDR Richerson said he understands the frustration involved and he acknowledged that the P&T Committee has the advantage of seeing the numbers and the math. The PEC is trying to provide as much information as it possibly can without even the remote possibility that the Panel could back into any specifics.

Mr. Class explained that the analysis starts to get hazy when it says there are no published studies of some agents yet the cost-effectiveness ratio was applied to them. This makes it seem like the decision is being based on money rather than on potential clinical effect.

Maj Tiller explained that the cost-effectiveness ratios for calcium channel blockers and ACE inhibitors were based on three observational studies. The clinical effectiveness evaluation did say that there were no evidence-based indications of relative effectiveness. But the literature does have observational studies. He said his cost-effectiveness analysis was based on the effect that potential increased compliance would have. The analysis wasn't looking at the clinical merit of the agents, but at compliance.

Dr. Hutchings asked for clarification of the studies that the effectiveness numbers were based on. Maj Tiller said they were, in general, large organizational database studies that looked at compliance. Dr. Hutchings explained that his concern is with the statement that using agents separately, Norvasc in particular, is more cost-effective than using a combination drug. Maj Tiller replied that he took a weighted average of dihydropyridine calcium channel blockers and a weighted average of ACE inhibitor products available on the Uniform Formulary based on market share.

Dr. Hutchings said his concerns relate to persistence on combination products where, a lot of times, patients are on separate drugs and one is dropped, there may be a need to titrate it. He asked what methods were used in the studies. Did they show that Lotrel is better at compliance because we weren't taking into account all of the other factors that occur naturally when we're trying to titrate? He also commented that the studies may have been designed poorly. On page 6 of the handout, on the chart in Figure 3 there is a sharp spike in the last quarter for Lotrel which coincides with the change in co-pay. This implies people are moving to Lotrel to get around the higher co-pay. We may be inadvertently forcing people on to Lotrel so they can have their amlodipine at a $9 co-pay. Dr. Hutchings said he is very uncomfortable with keeping Lotrel on formulary. He thinks it's inconsistent to tell patients they can have their amlodipine but they'll have to take benazepril to get it.

CPT Dacus said she doesn't believe physicians would prescribe amlodipine with benazepril if they didn't think both of those drugs were necessary. Dr. Lenow agreed, saying the only time he would use a combination drug like that is if the patient is already on both drugs or if he wanted to add one and it would be easier to do it in combination.

Dr. Hutchings said he isn't clear on what the problem would be in taking patients off of the combination tablet and having them take two tablets at the same time in the morning. He asked whether it is cost effective, tablet-to-tablet, if going to benazepril plus Norvasc instead of Lotrel. One of the reasons he voted for Norvasc when it came up was that there is a small group of people who benefit from Norvasc that can't benefit from other agents.

Ms. Schlaifer said she isn't clear how a switch from non-formulary amlodipine to formulary felodipine with an ACE inhibitor would be handled with patients. She asked whether the idea is to keep patients on two separate drugs that are on formulary rather than switch them. CPT Dacus agreed that it is more difficult to titrate with a combination drug and there are compliance issues. Ms. Schlaifer's view was that people might jump to a combination drug if they can't use the two drugs separately. CPT Dacus agreed that choices will have to be made. The agents would have to be titrated separately until a stable level is reached. But after that there should be fewer compliance issues.

Ms. Hickey noted MTF patients would have to show medical necessity to get on the single amlodipine in order to titrate that separately before they could be put on a combination drug. CPT Dacus said another way to change a patient over would be to titrate up on felodipine.

Dr. Hutchings observed that titrating on a combination product might results in a physician getting seven days in on a ninety-day supply and finding that blood pressure is too low. He is afraid there will be a lot of waste.

Ms. Schlaifer asked how BiDil fits into this formulary review. The answer given by the PEC staff is that it is on the Uniform Formulary because it hasn't been reviewed. It will be looked at in a future drug class.

Ms. Hickey asked for clarification of her understanding that everything that has not been reviewed is automatically on the Uniform Formulary; only after agents have been reviewed and Dr. Winkenwerder has made a decision do some agents become non-formulary. MAJ Watson confirmed that understanding.

Panel Discussion of Miscellaneous Antihypertensive Drug Class Recommendations

Dr. Crum said he, too, is concerned about having one of the ingredients of Lotrel not available on formulary except with titration. He said good practice is to avoid combination drugs unless you know that the combination represents the correct ingredients. You can't ever really know that if you start out with a combination drug. He thinks it would be better practice to have chosen Lexxel to be the formulary product.

Ms. Schlaifer said that was also her first thought. But the utilization figures show less than 1,000 people on Lexxel and 25,000 people on Lotrel.

Dr. Lenow noted the same issue came up with Viagra several sessions ago where 77 percent of the users were using that drug because it was the first one out. But the decision was made that it would be non-formulary, even though there would have to be a huge shift.

Dr. Lenow said this case seems based on flawed logic. By separating out the components, you are really reducing the use of combination drugs down the road because there is no way to titrate

to it. He agreed with Dr. Hutchings that physicians wouldn't titrate to combination drugs because it's incredibly wasteful. He doesn't know if that was factored into the cost-effectiveness equation, but it would certainly jack up the cost. Logic demands that if you are going to allow a combo as one component and disallow the individual components, people will get confused and you will get complaints.

Dr. Hutchings agreed with Dr. Lenow from a cost standpoint. For a patient to be on two generic, co-pays would cost $6.00 (2 times $3.00) instead of a $9.00 co-pay for one and $25.00 for a combo plus a generic. His question is why Lotrel is not being recommended for third tier. He would prefer that none of them be on formulary, just to be consistent.

Mr. Class said that would amount to a statement that MHS will not be using combination drugs. All three would then be non-formulary, which would discourage their use. He asked if that is acceptable to physicians as a matter of clinical practice.

Dr. Crum said his view is that if you are going to have a combination drug its ingredients should be available on formulary.

Dr. Hutchings said the number of combination drug users is very small. His organization has steered its physicians away from dual drugs.

Mr. Hanson said he can understand why the recommendation is to leave Lotrel on formulary as an option. He suggested it might be possible to support the recommendation but with a comment to the effect that the Beneficiary Advisory Panel is bothered by the fact that a combination drug is on the formulary but one of the ingredients is not.

Dr. Lenow said the proposed decision offends common sense. It is recommending practice behavior that is not normal. JNC-6 and JNC-7 recognize that there are situations in which it makes sense to use combination drugs. The reason to use a combo drug is that the patient is on the two drugs already and the combination would save on the co-pay and you might promote a more compliant pattern. Beyond that, to use a combo med that you can't titrate up to is anathema to normal medical practice. His view is why bother even having it if you can't get to it because one of the components isn't there to begin with. He can't embrace the recommendation because it works against his common sense as a clinician and doesn't represent normal medical practice.

Mr. Class said that taking this action would amount to discouraging all use of the combination.

Dr. Hutchings asked if there would be a way to obtain "medical necessity" so the co-pay would be $9.00, at least after the patient is stable on both components.

Ms. Hickey noted that amlodipine is perfectly available to someone who is not a Military Treatment Facility beneficiary. They just have to pay $22. If the physician really wanted to get a patient to the combination drug, they could do the titration with the beneficiary paying the extra amount of money. Her concern is with MTF patients who don't have that option because the prescribing physician would have to establish medical necessity in order to use non-formulary drugs. She thinks that might be hard if the patient is already taking felodipine or something else that is already on the formulary.

Mr. Hanson said the Panel appears to have three choices: one to support the recommendation, one to comment that Lotrel should be moved to non-formulary and the third to comment that Lexxel should be moved into the formulary because its ingredients are already there. He said he's having a hard time trying to figure out what the Panel is trying to say and if there is consensus on that.

Ms. Schlaifer asked if this issue was explored during the P&T discussion. CDR Richerson's reply was that the decision is a matter of public record. In some cases they have a unanimous vote and in some cases they don't. There was lots of discussion in this case but the vote was unanimous.

Ms. Hickey asked if the Committee looked at the spike in Lotrel usage and wondered if it was caused by people trying to get amlodipine. Dr. Bretzke of the PEC answered that the data for January was not yet available at the time of the P&T Committee meeting. However, feedback from MTFs indicated that this was one option that was being used to try to address the amlodipine issue. There is a significant amount of people who were using amlodipine or other ACE inhibitors for whom moving to a combination product is a logical move.

Dr. Crum asked if the decision to select Lotrel as a primary product instead of Lexxel was based solely on the fact that Lotrel had so many more users and that would avoid disruption or if there were other factors that caused the Committee to think that Lotrel was the preferable product. The question is whether Lotrel has any advantage over Lexxel as the formulary choice other than the fact that so many people are already on it.

Maj Tiller replied that the evaluations showed that the two agents have similar relative clinical effectiveness. One was not determined to be superior to the other.

Dr. Hutchings said that statement would indicate that Lexxel was more cost-effective than Lotrel.

Maj Tiller stated that the decision was based on several factors: the relative clinical effectiveness presentation, the relative cost-effectiveness presentation, utilization and other factors considered by the P&T Committee.

Ms. Schlaifer said it sounds like what Maj Tiller is saying is that safety is pretty much equal, cost is pretty much equal and effectiveness is pretty much equal. The significant difference is that there are 25,000 people on Lotrel and only 1,000 people on Lexxel.

Maj Tiller said that was part of it. The other consideration was that both ingredients in Lexxel are available generically so there was no reason to keep a product that a patient could get for two generic co-pays ($6.00) versus a branded co-pay ($9.00). If the MHS was going to keep a combination product, Lexxel didn't make a whole lot of sense from that perspective. He said he understands the Panel's concerns. However, even with Lexxel being widely available, almost no one is using it. In contrast, Lotrel is being used. Another consideration was the 250,000 Norvasc users who might potentially benefit from a combination product if they are already taking an ACE inhibitor.

The Chairperson asked how many Panel members would be comfortable concurring with the recommendation with a comment that it is concerned with having one of the calcium channel blockers that is in the combination drug not available on formulary.

Ms. Schlaifer said the comment would have to be phrased so that it doesn't sound like the Panel is encouraging putting amlodipine back on the formulary. She wouldn't favor that. She would prefer that both be off.

Dr. Hutchings suggested the Panel might want to non-concur with the P&T Committee and recommend that Lexxel be kept on formulary status rather than Lotrel or move both to non-formulary status. He said he is more inclined to nix both.

Dr. Miller said she would recommend that both be taken off the formulary.

Dr. Crum said his first preference would be to keep Lexxel rather than Lotrel on formulary and his second choice would be to take them both off. The current arrangement is inconsistent with how people practice medicine.

Dr. Lenow said there seems to be a domino effect at work because everybody who is on Lotrel is faced with a big tick up in their co-pay where they are going to have to be switched again. He would like to be cautious about doing too much juggling. He said he could support concurrence with a carefully worded concern, but he could also support non-concurrence as recommended by Dr. Hutchings.

Ms. Schlaifer said there is no reason to keep Lexxel on formulary.

Dr. Hutchings said if Lexxel were kept on formulary, the patient co-pay would then be $9.00, but there would still be a cost advantage in using the separate components. Ms. Schlaifer pointed out that $9.00 is only the patient cost, not the actual cost.

The Chairperson summarized the options on the table: one, to concur with the recommendation of the P&T Committee; two, concur with the recommendation and make a comment about the Panel's concern about having the separate agents of the combination drug be non-formulary; three, non-concur with the recommendation with the added stipulation that the Panel recommends that Lexxel be on formulary; and four, non-concur, with the comment that none of the combination drugs should be on formulary.

She noted that option four would preclude MTF patients from being able to get amlodipine in any way.

After a brief discussion, Ms. Hickey said the first thing needed was to get concurrence or non-concurrence. She wants everybody to know what they are voting for.

Mr. Hanson asked how the vote would work – whether the Panel would be asked to vote for the four options or just vote to concur or non-concur and see what happens after that.

MAJ Watson reminded the Panel that Dr. Winkenwerder cannot make a drug non-formulary unless that is recommended by the P&T Committee. In this case, Lotrel was recommended to be on the formulary and he cannot move that to non-formulary without the recommendation of the

P&T Committee. In response to a question from the Chair, MAJ Watson said that Dr. Winkenwerder can send a matter back to the P&T Committee for reconsideration.

Dr. Hutchings then asked if the way to communicate his view that both combination drugs should be non-formulary is to concur and comment that the Panel recommends that Lotrel should be sent back to the P&T Committee. Ms. Hickey said that after the Panel votes to concur or non-concur, she will ask for comments. Everybody can make their own comments then.

Ms. Schlaifer asked whether the Panel has to concur or non-concur with the whole thing or can it be selective. Ms. Hickey said the Panel has to concur or non-concur with the whole recommendation.

Panel Vote on Formulary Recommendations for Miscellaneous Antihypertensive Drugs

The Chairperson read the recommendations of the P&T Committee concerning the miscellaneous antihypertensive drug class:

"Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the miscellaneous antihypertensive agents, and other relevant factors, the P&T Committee recommended that Lexxel (felodipine/enalapril) and Tarka (verapamil/trandolapril) be classified as non-formulary. The P&T Committee also recommended that clonidine tablets, clonidine patches, Lotrel (amlodipine/benazepril) hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF."

The vote of the Panel was 9 concur, 2 non-concur.

Panel Comments on Formulary Recommendations for Miscellaneous Anti-hypertensive Drugs

The Chair called for comments from the Panel members who voted to concur. A brief discussion ensued as to what types of comments might be offered in this instance. Ms. Hickey noted that individual Panel members can make comments as well as the Panel as a whole.

Ms. Schlaifer said her comment would be that she questions the wisdom of keeping a medication on formulary when the ingredients of that medication are not also on formulary.

Dr. Hutchings said his comment would be that Lotrel should be returned to the P&T Committee for further review and designation to non-formulary.

Dr. Lenow commented that he concurs with the recommendations because he wants to avoid disruption and doesn't want to see removal of all combinations nor any of the other meds that are approved. But he is concerned that there is a logical inconsistency in having a combination product on board for which you cannot individually titrate up because one of the agents has already been removed from formulary.

Mr. Hanson commented that he is also concerned with having a combination drug on the formulary when its ingredients are not also on formulary.

Mr. Partridge, Ms. Le Gette and Dr. Hutchings agreed with Dr. Lenow and Mr. Hanson's comments.

The Chairperson then solicited comments from the Panel members who non-concurred.

Mr. Class commented that doing this has the effect of limiting the use of combination drugs altogether.

Dr. Crum commented that a combination ACE/CCB inhibitor should be available on formulary, provided that its individual ingredients are also available on formulary.

Panel Vote on Implementation Plan for Miscellaneous Anti-hypertensive Drugs

The Chair read the P&T Committee's implementation recommendations:

"The P&T Committee voted to recommend an implementation plan of 60 days."

Mr. Hanson commented that if the associations will be used to get the information out the implementation period should be 120 days.

The Panel vote was:

0 Concur; 11 non-concur.

By vote, the Panel also unanimously agreed that the implementation period should be 120 days.

Afternoon Session

At the beginning of the afternoon session the Chairperson announced that the order of the agenda would be changed to accommodate the schedules of Panel members who are traveling out of town. The "GABA Analog" drug class review will now be taken up first followed by the presentation on the outcomes of previous Uniform Formulary decisions.

GABA Analog Drug Class Review

The Chair turned the podium over to Dr. Bretzke for the presentation of the GABA Analog drug class review.

[Insert script, pages 20 through 28]

Physician Perspective on GABA Analog Drug Class Recommendations

CPT Dacus also spoke to the recommendations for this class of drugs. She indicated that this is the class of patients she deals with in her practice. She has a large number of diabetic patients, many with diabetic neuropathy. She said her patients do complain to her about neuropathic pain. She has prescribed gabapentin for this condition for years and is most comfortable with it. She said that Pfizer has been heavily marketing their new drug Lyrica. She was approached and

provided materials so that she could have an informed opinion about whether gabapentin or Lyrica would be preferable. Nowhere in those materials is there any mention of differences in efficacy, safety or tolerability. The company is using other issues to promote the product, one of which is linear kinetics. She said while the company can show studies about improved absorption, it doesn't speak to the efficacy, safety and tolerability of the drug for diabetic nerve pain. They also talk about the length of titration. The problem is the faster you titrate it the more side effects there are, so maybe a short titration period isn't an advantage. She also noted that the drug has not been shown to work for alleviating diabetic nerve pain in the majority of patients and the company's literature does not mention that it failed. She said it's important to keep an open mind and ask questions when dealing with the company's literature about Lyrica. She said it is different, but not necessarily better.

Dr. Lenow said he practices in an academic family practice setting with a very large population. There are a huge number of diabetics. He said he has not yet used Lyrica or had occasion to. Everything he has heard about it has been positive – no one has complained about it. But the experiences have been anecdotal, much like the letters that the Panel received. This is what he wants to comment on. One of the things he does is teach about pharmaceutical compliance issues. The world physicians all live in right now is tightly regulated. Every week he reads about a request from the Senate Finance Committee for information on marketing practices by the industry. He personally met and talked with the Chief Counsel for the OIG (Office of the Inspector General) about these issues and was told that their number one target right now has to do with issues of off-label marketing. He said it is ironic that the subject matter today is gabapentin, which is the poster child for corporate integrity agreement law. While not Pfizer's fault, it is probably the most famous and most methodical case that involved a half billion dollar settlement that led to a very major corporate integrity agreement. Pfizer is probably one of the most compliant of all entities among all the pharmaceutical manufacturers he has dealt with and he knows their Chief Compliance Officer personally. He knows they are trying to run the straight and narrow. The total is now probably over $3.5 billion paid for this whole subject matter.

With that as background, Dr. Lenow said he did an analysis of the letters received from the public on this drug class. By his count, seven mentioned true, appropriate FDA on-label uses and about seven requested that the drug be maintained on formulary for reasons that were non-FDA uses – things there are no studies for and no label indications. One letter was neutral. Some letters mentioned both appropriate and non-appropriate uses, so the total numbers may not match the number of letters received. The thing that concerns him is that two of the letters make mention of the fact that they were contacted by a rep from the company – one for a labeled use, one for a non-labeled use. One was from a pharmacist at the Naval Medical Center in Portsmouth talking about anti-coagulation therapy and stating that the Pfizer representative had asked to have the information relayed. The other is from a neurologist who was notified by Pfizer that there may be an option to have Lyrica placed on DOD formulary. Dr. Lenow noted that this plea was based on experience with a handful of patients. He hopes that these letters are anecdotal examples and not an organized marketing strategy. But if, in fact, the public comment process is in any way being perverted by attempts by the industry to influence decisions made at this Committee by impacting on military providers, the Office of the OIG is not going to be happy about that nor will the Senior Compliance Officer of the company. He cautioned that that would be a stupid thing to do.

For now he will chalk it up to exuberance about what appears to be a very good product. He does not discard the other 13 impassioned comments, nor does he discard the anecdotal references from his own colleagues who say there is something here. But it is too new. He believes the P&T Committee did a very thoughtful and very comprehensive analysis and is "spot on."

Mr. Hanson added that he came up with more than just two references to Pfizer, so he shares the concern that there may have been a campaign here. But he also has a feeling that the recommendations may be premature. It's a new product for which we are seeing new applications. From a beneficiary perspective, he does not want to see a drug taken away from people who may badly need it. If its efficiency is equal, its safety is equal and its tolerability is equal, it again comes down to the decision being made on a cost basis. He said the presentation today reflects a number of similar TRICARE issues that some associations have been fighting over for the past few weeks. What he is reading from the emails is that the generic drug is slower to combat pain, and that Lyrica is easier to titrate. Mr. Hanson said what concerns him is that they are using this drug with combat veterans who come back from Iraq and Afghanistan and are suffering neurological pain. He doesn't want to take anything out of the MTF that can help our young men and women who have been maimed in war. It's important to give them every available drug that can be utilized as a tool, even if just for its placebo effect. If patients perceive that their pain is relieved faster with this drug, he thinks that is something that needs to be taken into consideration. Furthermore, the system is dealing with a generation of Vietnam War veterans who have been exposed to Agent Orange and are suffering a higher and higher rate of diabetes. There, too, we shouldn't be taking the tools out of the tool box just because it is cost convenient. He thinks we have to offer the best to our combat veterans who have suffered and have sacrificed. To take something away just because of the cost issue is not correct. The up-tick shown on the graph on page 8 (of the handout) indicates that there is something out there. Maybe it is excellent marketing. But it could also be that the actual providers are seeing a need for this drug that has caused it to go from a very low state at introduction to an up-tick. He doesn't know if this trend will continue, but it is why he thinks it might be premature to make this decision at this time.

CPT Dacus addressed the issue of amputees. She said that gabapentin is the only one of the three medications that actually does have controlled trials. In that respect it does have an advantage over Lyrica, which does not have any.

Ms. Schlaifer noted that the graph (page 8, Figure 7) shows that Lyrica was being used at a low level until August 2005. She asked if that is correct. CPT Dacus replied that Lyrica was introduced to the market in August 2005. The line on the graph denotes zero usage, but is should not be there. The upward trend started when the drug was released.

Dr. Hutchings asked whether there was discussion about other uses of Lyrica. Dr. Bretzke replied that there was but the uses are very minor because there are other drugs that have better efficacy. There is a tremendous amount of data from efficacy trials for gabapentin for the treatment of pain so it would be tried first.

Ms. Hickey said that the PEC makes a strong effort to get provider input within the MTFs, so she is a little surprised that the Panel is getting emails from those same providers. She questioned whether or not those providers responded to the PEC when it went out. The answer provided was that some emails have the same names as those of the replies that the PEC received.

Mr. Partridge asked if there are any studies going on with Lyrica that just haven't been completed yet. Dr. Bretzke said there are, as there always are with new drugs entering the market. But it could be years before the results become available. Like anything else, when these results are brought to the table they might change the decisions. CPT Dacus said there are trials of Lyrica in children for partial seizures. Gabapentin and Gabitril are both approved for use in children. She thinks Lyrica will probably be approved for use in children in a couple of years.

Referring to table 5 (Handout page 8), Mr. Class asked about the relative importance of FDA approval relative to other evidence. Dr. Bretzke replied that the FDA indication has as much to do with money and politics as anything. If the sponsor of the drug performs a study and wants the resulting information included in the labeling, it seeks an extension or an inclusion of the trial information to receive an indication for its use or an approval to be used in that category. Beyond that, if drugs are being tried and the company does not want to sponsor its change in labeling, that information is out there on the market but no indication is approved. In the case of a product that is generic or is going to go generic, there would be no sponsor to seek a change in its indication status. That's true of all drugs, not just this class.

Panel Discussion of GABA Analog Drug Class Recommendations

Ms. Fryar commented that she feels the Lyrica decision may be a little premature. Since the drug is so new, it might be good to give it more time to see how effective it really is. Some of the beneficiary letters sound like the drug really helped them.

Dr. Hutchings said some of the letters indicated that Lyrica has been prescribed as initial therapy instead of the tried-and-true gabapentin, which he found interesting. He takes the opposite view of the question about whether the decision is premature. A lot of drugs come on the market for which the profession doesn't know all the dangers. With drugs that have been on the market for years and years, we know what the side effects are. With Lyrica, we don't yet know whether it will have very serious side effects because it is so new. His feeling is that this might be the appropriate time to make the non-formulary decision. He feels it is better to impact a small number of patients now than having to switch 100,000 patients off it down the road.

Mr. Class said that sounds like a recommendation to toss all new medications onto the third tier until enough time has passed. The reason he asked the FDA question is that they have a process to approve new drugs for certain indications. His question would be what criteria should be used to determine if a drug is safe if not FDA approval.

Dr. Hutchings said this is a special case. Gabapentin has been the workhorse in this area for many years with no real competition. All of a sudden the same manufacturer comes out with a brand new drug. His concern is that we have something that we know is safe and all the clinical trials show that there is no difference in efficacy with Lyrica. If both are equal and gabapentin is safer, he would prefer to go with it.

Mr. Class said he is still uncertain about what level of assurance is required. It sounds to him like a slippery slope.

Dr. Lenow pointed out that while the 13 supporting letters for Lyrica may be compelling, the Panel doesn't get letters from the thousands of satisfied people on gabapentin because there is no reason to write those letters. He said he doesn't slam all new drugs, but he is much tougher on them when their use is off-label. He pointed out that there is no evidence-based rationale for these uses. The people who are asking for this drug are not necessarily dealing with the two indications for pain: hepatic neuralgia and diabetic neuropathy. They are asking for the drug for other indications, including trigeminal neuralgia, otalgia and generalized neuropathic pain – for which there is no published evidence to support the use of Lyrica. If something bad should happen down the road, the physician wouldn't have a leg to stand on. His concern is that some of the requests are coming from people who are using it first-line, trying out the new drug, and somebody is making them most anxious to keep it alive for off-label usages. Therein lies the rub. There have been too many incidents of this type already.

Mr. Hanson said he doesn't see where there is a safety issue. Dr. Lenow replied there is a real safety issue when it comes to off-label indications. Mr. Hanson repeated that the Panel is dealing with a process where it is easier to put a drug in the non-formulary tier. He thinks the assumption is being made that a lot of people are using Lyrica for non-appropriate uses and there will be all sorts of complications. He said that assumption could be used to put a lot of other drugs off formulary very easily. Dr. Lenow said he was not making that assumption. There are only so many dollars available for health care. If we fall prey to the ease of allowance on the hopes that it might work without evidence to support it, that's not the right thing. Wenburg wrote about this in the early 1980s in the New England Journal of Medicine and Science and it turned the medical community upside down. There is an unexplained variability in random use that is not evidence-based. This is a classic example. Physicians have the prerogative of using meds off-label, but the industry can't promote them like that. In the absence of hard evidence to the contrary, without a compelling reason to use the medicine off-label, logic dictates that the community should be concerned about safety, which is paramount, but also the cost of care, which is out of sight.

Ms. Fryar asked whether Lyrica, if it were put in the non-formulary category, would be eligible to be put back on the formulary after clinical trials were done. Ms. Hickey said that the P&T Committee can call up drugs any time it chooses to do so if there is compelling evidence.

Ms. Hickey also commented that some of the letters do indicate that the patient has not had a good outcome when they used a generic drug. It seems to her that such cases are exactly what medical necessity was designed to deal with so that patients can get non-formulary drugs. She said she is leaning toward concurrence.

CDR Richerson addressed the question of how new drugs are dealt with. As the formulary is being implemented one class at a time, the P&T Committee hasn't really had the opportunity yet to address new drugs. However, the regulation states that it is the Committee's duty, and the Panel's, to evaluate new drugs as they enter the market. The issue of new drugs versus old therapy will be a standard part of this discussion from now on.

Mr. Hanson said his concern is that the P&T Committee's workload and the need to review a lot of new categories will make it harder to go back to old categories after they have been completed. He recalled a discussion earlier in the day to the effect that taking something out of the MTF system and forcing people to generic might deprive military medical doctors of an

option just because it is easier for them to go with the available drug than with one that is non-formulary.

Ms. Hickey replied that her comment concerned the combination drug, where the decision would have made it impossible for the provider to use medical necessity.

Mr. Hanson said his concern is not that of an advocate for a particular drug. His concern is that this is a premature move with a drug that might help veterans coming back. He wants to make everything available if it helps bring a quicker alleviation of pain. He doesn't want our young men and women to be in pain because they've been given a generic drug because that's what they've been directed to be given.

Ms. Le Gette said if you look at the implementation table, almost all the use of Lyrica is among retail beneficiaries – 27,000 out of 30,000 users. She will probably concur with the recommendation because her company recommends the use of step therapy programs to manage the trend in this class of drugs, which requires that members use gabapentin before Lyrica unless they have a medically necessary reason to bypass the use of gabapentin.

Dr. Lenow also recalled the discussion of Viagra at an earlier Panel meeting. His question then was whether it was worth it because of the delicate emotional issues of erectile dysfunction in people who fought for all of us. He thinks you could probably make that argument for any drug class on the formulary, which would lead him to the final conclusion, "What are we doing here?" We might as well not have these discussions because the argument can always be made that we might be depriving a veteran of having the odd chance of getting something that might be a little better even if it's ten times the cost. If that's the case, we shouldn't limit any drug. There should be a wide open formulary and we shouldn't waste the PEC's time. The question is where you draw the line on the slippery slope.

Mr. Hanson replied that when it comes to the combat veteran he doesn't like to "nickel and dime" our young men and women. We could also buy them a cheaper set of protection vests, too, and save some money. He acknowledged that he is responding emotionally.

Dr. Crum said he has not heard any evidence that Lyrica offers any advantage and he will vote to concur with the recommendation.

Dr. Miller said her view is that we already have a safe drug that is generally effective in gabapentin and we should prefer its use.

Mr. Burleson of the TRICARE Office of General Counsel spoke to the matter of P&T procedures. He told the Panel that he sits in on the meetings of the P&T Committee. Their decisions are never cost driven. Moreover, every single drug, even those in the non-formulary tier, is still available for any beneficiary at the branded co-pay if medical necessity is shown. The procedures for establishing medical necessity are such that there is very little if any second-guessing of the providers' decision that medical necessity exists. He suggested that Ms. Le Gette might also want to speak to that as her folks handle medical necessity determinations. It is not a steep or slippery slope to try to establish medical necessity.

Mr. Hanson said he doesn't want his remarks to be interpreted as casting doubt on the process. He has often suggested the alternative of medical necessity when others have questioned a

particular recommendation. One advantage of the Panel is that it represents many different interests, different perspectives and different beneficiaries. This allows for a debate as different classes of drugs are looked at where different people can offer different views.

Mr. Burleson agreed, saying he thinks it is a great process. He was only offering a reminder of the context in which these recommendations come to the Panel for consideration and comment.

Mr. Class asked again about the email information suggesting that Lyrica was being used inappropriately. He asked if the generic drug wasn't also being used for off-label purposes. Dr. Hutchings replied that gabapentin is being used for other purposes. But with gabapentin there are clinical trials supporting its use. So there is some evidence. But with Lyrica, there is no evidence. One of the things he likes about the P&T Committee is that they not only discuss approved and non-approved uses, but what evidence is behind it.

Ms. Hickey asked about the cost to a drug company when they ask for another use of a drug. Discussion with the PEC staff indicated that the cost of obtaining approval for a second use would be prohibitive for a drug that is generic or going generic, but it might be acceptable for a new drug.

Dr. Lenow noted that using drugs off-label is a common practice. There are strict laws that don't allow the industry to promote a medication for off-label indications. There is nothing that prevents a practitioner from using drugs off-label. It is a common and accepted pattern. When he was an obstetrician back in the 1970s they stopped premature labor with an off-label drug because an approved drug didn't exist yet. The reason Pfizer got hammered, originally through Parke-Davis, was for promoting off-label use of Neurontin. His point is that when this kind of expense is involved, when the indications are off-label and when there is no evidence, it's really hard to justify spending the extra money. The burden of proof is on the manufacturer. He thinks the Committee acted responsibly in looking at those factors.

Dr. Bretzke said it is common knowledge that it costs millions of dollars to conduct a trial and also millions of dollars to change the labeling. A company might want to do that for business reasons, such as promoting that product. But if the drug is at the end of its cycle or the company doesn't feel it will be lucrative, they might not ever go through the process to make changes even though the evidence might be there. There are perfectly legitimate economic and business reasons for official indications. But physicians generally feel comfortable when there is evidence to support other uses.

Panel Vote on GABA Analog Drug Class Formulary Recommendations

The Chairperson read the P&T Committee's recommendation:

"The P&T Committee, based upon its collective professional judgment, recommended that pregabalin be classified as non-formulary, with gabapentin and tiagabine remaining on the UF."

The Panel vote was 8 concur and 3 non-concur.

Panel Consideration of GABA Analog Drug Class Implementation Period Recommendation

Ms. Hickey opened the floor for discussion of the Committee's implementation recommendation, which is for a 60-day implementation period.

Ms. Schlaifer said she understood the reason for preferring 120 days to 60 days in the earlier discussions. However, in this case, she takes a different view. Looking at the graph on page 8 (of the Handout), it is clear that the use of Lyrica has grown rapidly in the last 120 days. By postponing the implementation here you might be making the situation worse rather than better. She thinks that 120 days from now the use of Lyrica may be double what it is today.

In response to a question from Ms. Hickey, it was stated that 30,000 beneficiaries will be affected by this decision. Ms. Hickey said it would be reasonable to assume that in 60 days there might be 60,000 and in 120 days there might be 120,000.

Dr. Hutchings said he thinks it is an excellent point and agrees with it. By waiting, the decision will affect more people.

Dr. Miller and Dr. Crum also agreed with Ms. Schlaifer.

Ms. Fryar said she also agrees with the point and will concur with the 60 day period.

Dr. Bretzke said this was the overriding factor in the Committee's decision to choose a 60-day implementation period.

Mr. Hanson said he can't support 60 days here and 120 days on other classes. He thinks the Panel should be using the same approach with everything. Otherwise the Panel will be contradicting its own decisions.

Dr. Hutchings said in the case of the other drugs, the trend was fairly flat. Here that isn't the case. He is afraid the delay will cause more problems.

Mr. Partridge said he thinks it would be possible to get a message out to people who need to have it to allow time to make the change without the abruptness that you will have with a 60-day period. He would still favor a longer period to get the word out and make the transition. There is nothing wrong with making the transition early if the doctor sees it coming.

Panel Vote on GABA Analog Drug Class Implementation Period Recommendation

Ms. Hickey called for a Panel vote on the P&T Committee's recommendation:

"The P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA."

The Panel vote was 8 concur and 3 non-concur.

A vote of those non-concurring indicated that all would concur with a recommendation for a 120-day implementation period.

Presentation of Previous Uniform Formulary Decisions

MAJ Watson next turned the podium over the Dr. Bretzke for a presentation to the Panel on the results of previous Uniform Formulary decisions, asking that questions be held until the end of the presentation.

[Insert PowerPoint presentation]

Dr. Bretzke began the presentation with a chart (Slides 1 through 4) summarizing the drug class decisions that were made at each meeting of the P&T Committee during its first year, beginning in February 2005 and ending with the November, 2005 meeting – 4 meetings in all. The chart shows, for each class, the drugs recommended for formulary status, those recommended for non-formulary status, the implementation dates for the third tier co-pay, the drugs included in the BCF (Basic Core Formulary) as MTF-preferred items, and those in the ECF (Extended Core Formulary). The chart also shows the FY 2005 rank of each drug class in the MHS (Military Health System) and what the total expenditures for that drug class were. Dr. Bretzke pointed out that two of the three drug classes reviewed in August just began their implementation in February, so the data is very limited (only through February). All the data on these classes pertain only to MTFs. He also said nobody changes until after the co-pay kicks in. The drug classes reviewed by the Committee in November will not be addressed at all because their implementation dates are still in the future.

The next chart (Slide 5) shows a schematic representation of the timeline for Uniform Formulary decision making and implementation, with the P&T Committee meeting occurring first, followed by the BAP meeting about 30-45 days later. Both the P&T Committee recommendations and the Panel comments are presented to Dr. Winkenwerder for approval; about 2-3 weeks after the BAP meeting. MTFs begin making their conversions immediately, prior to the final implementation date. Mail-order and retail pharmacies usually don't convert until the scheduled implementation date, although the PEC would prefer that they begin earlier.

Dr. Bretzke next discussed a line graph (Slide 6) showing total prescriptions between October 2004 and February 2006 for all points of service combined by drug class. The graph shows that no one is lacking therapy because their drug got put into the third tier. People are doing what they need to do – making the co-pay, switching to a different drug or seeking medical necessity determinations. The graph shows a pretty consistent steady upward trend, largely due to new TRICARE For Life patients. But the upward trends of previous years are now beginning to level off.

Next, Dr. Bretzke discussed a graph (Slides 7 and 8) which shows the percentage of prescriptions by UF status over time for those classes handled in February and May – for which there is more than one month of third tier retail data available. The line showing usage for non-formulary, third tier drugs, has been steadily declining since the first decisions were announced in July 2005 – about 33 percent in all. Similarly, the line for MTF-preferred drugs shows increasing use, indicating that the migration effects are occurring. Dr. Bretzke said most of the migration happens within the MTF point of service.

Raw prescription counts aggregated for all reviewed classes of drugs shows a dramatic decrease in people using third tier non-formulary drugs within the MTFs – about an 80 percent drop.

There is almost no change in the use of these drugs within the mail-order system and a drop, although less significant, in the retail pharmacies. The chart also indicates that people are not shifting out of MTFs to retail or mail-order pharmacies but are staying where they are.

The next chart (Slide 9) shows the percentage of prescriptions by UF status over time but adds data for the three drug classes reviewed in August. Again the graph shows a significant drop in the use of non-formulary third tier drugs and an increase in the use of MTF-preferred drugs. The early projections were for a migration of 80 percent in the first year. To date, 20 percent has been achieved. Progress is being made.

The next several charts went into detail on a class by class basis.

Proton Pump Inhibitor (PPI) Class

For the Proton Pump Inhibitor (PPI) class (Slides 10 through 14), the co-pay implementation date was July 17, 2005, so there are 8 months' worth of data. In this class, only esomeprazole (Nexium) was moved to non-formulary. Dr. Bretzke noted that the individual agents in this class are highly interchangeable. Esomeprazole was little used at MTFs and always had a higher cost, so the MTFs weren't significantly affected by this decision. The graph shows a substantial drop in the use of esomeprazole (25-30 percent), mostly in the retail network. Most of the drop appears to have been absorbed by the generic omeprazole. The graphs also show that Julys are always up and Februarys are always down. The PEC believes this is because people stock up before they go away for vacation and again after the holidays in January. And February is also the month with the least number of days.

The cost per day of therapy for the PPI class shows that there really hasn't been a dramatic change in the cost per day. Dr. Bretzke pointed out that there is no mechanism to offer a discount in the retail network for switching from one high dollar brand name to another high dollar brand name. As all of the agents are similarly priced on the commercial side, there has been no real change. The increase in the cost per day in the mail-order stems from a price increase in one of the agents.

Slide 13 shows retail prescriptions for PPIs, where a significant drop in esomeprazole has been accompanied by increases in the use of formulary drugs.

By point of service, the market share for Nexium has dropped to about 15 percent (Slide 14), with an increase in the use of MTF preferred items. The overall decrease to date has amounted to about 24 percent compared to a projected decrease of 80 percent for the first year. By point of service, the MTF decrease has been 31 percent and the retail decrease has been 28 percent. Mail-order use has actually increased by 7 percent. The conversion rate is lower than usual for MTF because the use rate for Nexium is low in MTFs to begin with.

The next two slides show the medical necessity numbers (requested and approved) for Nexium by month (about 40,000 users per month). The table shows that not a lot of beneficiaries either qualify for or are seeking medical necessity determinations.

Angiotensin Receptor Blocker (ARB) Class (Slides 17 through 23)

The ARB class implementation date was July 17, 2005 after resolution of a protest, so there is also 8 months' worth of data for this class. Again only one drug, eprosartan (Teveten), was placed into the third tier and it was little used at any point of service. Telmisartan (Micardis) is the MTF-preferred drug in this class.

The use chart for this class (Slide 18) shows that the usage of the preferred class is increasing. There is very little change in the use of the third tier drug because its use was very low to begin with.

The cost per day of therapy in this class (Slide 19) is also decreasing, especially in the MTF but also in the mail-order pharmacy and overall. The costs are now about half what they were in October 2004 (to $.60 from $1.40 per day for MTFs). Retail costs per day have increased somewhat, to about $1.70 per day.

The chart showing MTF prescriptions in this class (Slide 20) shows a significant and steady growth in the use of the MTF-preferred drug Telmisartan since the decision was announced in July 2005 (from 2000 users to almost 6,000 users).

The migration graph (Slide 21) indicates that 51 percent of users of the third tier drug (eprosartan) have migrated to other drugs since the co-pay was changed. The goal for the first year was 80 percent. Nearly all of the conversions have come from retail users (50 percent) and mail-order users (54 percent). There was almost no use of the drug at MTFs.

Medical necessity applications for eprosartan (Slide 22) have been low – single digits at first and none recently – only 8 in total since August 2005. Retail use of eprosartan is only 500 users per month.

PDE-5 (Phosphodiesterase Type 5) Inhibitors Class (Slides 24 through 30)

The PDE-5 Inhibitors drug class recommendations were implemented in October 2005 with only 5 months of data available. In this class, two drugs – Sildenafil (Viagra) and Tadalafil (Cialis) -- were designated as non-formulary. Vardenafil (Levitra) was selected as the MTF-preferred drug and is the only agent remaining on formulary.

The data (Slide 25) shows that the number of prescriptions for sildenafil has dropped dramatically from about 33,000 in August to 15,000 in February, while use of the preferred drug, vardenafil, has increased correspondingly (from about 5,000 to about 23,000 in the same time period). As expected, the data on the next chart (Slide 26) shows that the overall cost per tablet has dropped from $7.00 to $6.00 with drops in all points of service. The cost per tablet figure is used in this class because the drug is not used every day. This is a class where the change in co-pay greatly affects the cost per prescription. DOD has a quantity limit here of 6 tablets per month. MTF prescriptions for Viagra dropped from 17,000 to 2,000 (Slide 27) while Levitra increased from 2,000 to about 13,000. Dr. Bretzke said this is a tremendous amount of movement in a short amount of time.

The projected migration for this drug class (Slide 28) was also 80 percent for the first year. In the first five months, a 44 percent reduction has been achieved overall. However, the MTF migration, which is much more of a managed environment, has been 78 percent. Mail-order migration has been 29 percent and retail has been 20 percent.

Medical necessity requests in this class (Slide 29) have ranged from about 100 to a little over 200, with a high percentage of approvals. Dr. Bretzke said he isn't sure why. There are about 15,000 users per month of the non-formulary drugs in this drug.

Topical Antifungal Drug Class (Slides 31 through 34)

The topical antifungal drug class recommendations were implemented in August 2005, so 7 months of data are available. For this class, there was a 30-day implementation period. Dr. Bretzke said they learned a lot from the short implementation period and probably won't try to do that again. However, the agents are acute medications, which made it a little more palatable.

Five agents in this class were designated non-formulary: Ciclopirox, Econazole, Oxiconazole, Sertaconazole, and Sulconazole. Most of these are branded drugs with a big difference in cost but not in effectiveness. A wide variety of drugs remain on the Uniform Formulary, with Clotrimazole and Nystatin being the MTF preferred agents.

Overall there has been about a 30 percent reduction (Slide 32) in the use of non-formulary scripts (32 percent compared with the 80 percent projection for the first year) for all points of service combined. MTF migration has been 78 percent; mail, 23 percent; and retail 18 percent.

With about 4,000 non-formulary users per month, the number of medical necessity applications (Slide 33) has been very low (less than 10 every month) with only three drugs ever requested (Ciclopirox, Econazole and Sertaconazole).

Multiple Sclerosis (MS-DMDs) Medications (Slides 35 through 37)

No drugs in this class were recommended for third tier, so there is nothing to report. Avonex was designated as the preferred agent. The changes have been slight if any. The relatively new drug, Rebif, has shown a growth pattern similar to other new drugs. No migrations projections were appropriate because there were no third tier drugs in this class.

Angiotensin-converting Enzyme (ACE) Inhibitors (Slides 38 through 41)

The changes to this class took effect in February, so there are only two weeks of data. However, the MTFs had the information in October, so there is more data from this point of service. Four drugs (Moexipril, Perindopril, Quinipril and Ramipril) were designated as non-formulary. Several drugs are still available, and two – Captopril and Lisinopril – are MTF-preferred.

The usage graph (Slide 39) indicates that Lisinopril is by far the most heavily used agent in this category, even before the BCF designation, and its use has increased since October. Overall, there have been no changes in this market.

Even with incomplete implementation, there has been a 52 percent reduction (Slide 40) in the use of third tier agents against a projection of 80 percent for the first year – all in MTFs.

There have only been a handful of medical necessity applications so far (Slide 41), but there was a larger number (80) in February, most of which were approved. There are 30,000 retail users of

non-formulary drugs each month. The process used allowed medical necessity applications to be filled earlier for this class. The requirements for medical necessity are fairly open.

BPH (Benign Prostatic Hyperplasia) Alpha Blockers (Slides 42 through 45)

The changes to this class also took effect in February after a 90-day implementation period. Three of the four drugs remain Uniform Formulary, with Tamsulosin (Flomax) designated as non-formulary. Terazosin and Alfuzosin are the MTF-preferred drugs in this class.

The limited data available (Slide 43) shows Alfuzosin (Uroxatrol) use is increasing and Tamsulosin is beginning to drop as the MTF prescriptions take effect. To date, there has been almost a 60 percent reduction in the use of third tier drugs at MTF points of service (again compared to an 80 percent migration projection for the year). There has been a reciprocal increase in the use of MTF-preferred agents.

Although it is too early to tell, the number of medical necessity applications (Slide 45) has been relatively small to date. There are about 20,000 retail users of non-formulary agents (Flomax) each month.

Calcium Channel Blockers (CCBs) (Slides 46 through 49)

The calcium channel blocker class has a March 15 implementation date, so no data is available yet. A wide variety of drugs remain on the Uniform Formulary, with Nifedipine ER, Diltiazem ER and Verapamil ER being the MTF-preferred agents. Among the non-formulary agents, Amlodipine (Norvasc) was the most extensively used. Others designated non-formulary included Diltiazem and Verapamil. So far there seems to be a little more pronounced drop (Slide 47) in Amlodipine with somewhat of a reciprocal increase in Nifedipine and Felodipine.

In MTFs alone (Slide 48), there has been a dramatic drop in the use of Amlodipine since October – a 43 percent migration against a projected 80 percent for the full year. There have also been increases in Verapamil and Felodipine.

With 50,000 monthly users of Norvasc and the other non-formulary agents, there have been only a small number of medical necessity applications (Slide 49), although it is still way too early to be able to tell anything.

Summary (Slide 50)

Dr. Bretzke said it is clear that the move from second to third tier and the accompanying $13 spread in the co-pay changes the selection significantly for a significant fraction of DOD beneficiaries. People are willing to change based on that spread. One of the biggest lessons learned is that the change is different by point of service.

The differences in the migration rate for non-formulary agents between different points of service indicate that the migration projections need to be tempered by point of service. Figures to date suggest that MTF migrations are about 81 percent, TMOP migrations are about 12 percent and retail migrations are about 26 percent. The PEC needs to adjust its models to account for the differences.

Dr. Bretzke also said the Uniform Formulary structuring has validated the centralized pricing model. In the old days, MTFs were allowed to make their own deals.

Panel Questions on the Presentation

Dr. Lenow noticed that there has been an upward tick in some of the ARBs anyway, even though only one agent (eprosartan) was designated non-formulary. Since the ACE class is so new, he wondered if there had been some independent activity or a relative effect where the change in one would impact the other or if it is just too early to tell. Dr. Bretzke said he thinks it is really too early to tell. The ARB class is really designed to be a replacement for the ACE inhibitors, at a higher cost, so he would expect an up-tick. But there are clinical benefits. The general trend in the commercial world is that there is essentially a replacement of ARBs for ACEs. That hasn't yet happened in the MTFs to a large degree. But they are fighting against the normal trend in this case of replacing non-marketed generic products. The other thing noticeable in the graph is that the only line increasing is telmisartan, which is the MTF-preferred product. All the other ones are just generally increasing just like every other drug class. It just comes from having more users. The only thing a little bit disheartening is that there was no reciprocal decrease for the increase in telmisartan.

Dr. Lenow said he gets the sense that nobody is really marketing ACEs anymore, whereas ARBs are the darling of the marketing world. So he would expect to see a steady rise in the use of ARBs.

Ms. Hickey said she would be interested to know if, when ESI sent out letters to beneficiaries, that created faster movement in retail and TMOP than when they didn't. That might be an important piece of information to have before the new contract goes into effect in '08 – whether there could be a cost saving if notification increased the movement more rapidly. Dr. Bretzke said it is hard for him to comment since the PEC wasn't involved in the mailing. However, there is no data to suggest that the class they sent letters on changed either earlier or to a greater extent. But he agrees there are a lot of other issues. Literature sources suggest that a letter to the beneficiary is not a very effective means of communicating formulary changes. But some would argue that you should require one regardless of the effectiveness.

Ms. Hickey also asked if the PEC looked at the decrease in amlodipine and the increase in Lotrel to determine if there was a tit for tat. Dr. Bretzke said they haven't looked at that yet. They have been waiting for that change and as today's data shows there was a significant increase in Lotrel. The PEC will monitor that situation even though the agents are in different classes. Ms. Hickey noted that the concern is that somebody would be moving to Lotrel just to get the amlodipine and DOD will be paying more for it.

Ms. Hickey asked about the cost analysis, which includes calculations for migration, the cost of medical necessity, the extra cost of going to the doctor to get a prescription changed and all kinds of things like that. One of the things she would like to see is picking a month or a class and comparing the PEC's original dollar projections to the actual numbers. The idea would be to compare what the PEC thought they were going to get in the way of cost savings and what actually happened.

Dr. Bretzke said he is aware of the Panel's interest in this and there are people elsewhere in his organization who also want to know the answer. The projected goal of managing is to have these

desired outcomes. He said that just because the outcomes don't happen at the rate at which the PEC feels they should doesn't necessarily mean that the decision made was the wrong one. Some people would say "You didn't meet your cost goals so you should reverse that decision." It really has nothing to do with the relative clinical effectiveness or cost effectiveness of drug therapy if the system fails to take advantage of the opportunities that are out there. It is the PEC's desire for both the MTFs and the prescribers outside the MTFs to take full advantage of the cost difference opportunities where clinically appropriate and in most cases the PEC feels they are absolutely clinically appropriate. Dr. Bretzke said that is something that the PEC tracks internally and reports up the chain. But he isn't sure that the information is available to be presented outside the organization.

Ms. Hickey said she is making a formal request that the Panel be able to look at that information. The reason she is doing this is not to second-guess whether the decisions are right or wrong but to look at the process. The PEC has already changed its process for looking at cost effectiveness based on migration. The Panel would like to know if changes might be appropriate for areas other than migration. The reply given was that most of the other variables, such as the cost of a medical necessity determination or an appointment to re-do a med, are fixed and don't change. The major assumption that affects the decision based on dollars is the adoption number. All the other factors are insignificant to the total. He isn't sure whether it is even possible to track the basis for some of the other things, like how many people have to go to the doctor to get a prescription fixed. Because the migration numbers have the most effect, the PEC is making the greatest effort to get accurate data there.

Mr. Class said he understands the answer, and he hates to base decisions on dollars. However, a lot of the decision is based on cost. The Panel has questions about what is involved in the computations. For example, the fixed cost of a medical waiver could include or not include a lot of things, such as trying numerous other drugs first, secondary costs related to a reaction, etc.

Mr. Class also asked about the across-the-board projection of 80 percent migration for every drug class and whether those projections vary according to time or point of service. Dr. Bretzke said it is still early for most of the data. The projections are based on literature and "best guesses." The 80 percent projections are for a full year.

Mr. Class asked if there is a breakdown of the migration that the PEC expected to achieve for each venue. It seems to him as though most people are just willing to pay the extra co-pay. The answer was that the PEC now thinks that the 80 percent overall projection is too low and maybe it should be 90 percent. However, people just don't want to change. The idea was to see if changing the co-pay would influence people to make the change.

Ms. Hickey asked if there has been any significant migration from the retail to the TMOP. The answer was only for Nexium. Logically you would think that would happen but except for Nexium it hasn't. A PEC analysis for the first six months shows that there has been some migration, but is has been very small – less than had been hoped. Part of the problem is the PEC's lack of knowledge about how to deal with outside providers. Currently they don't have the resources or the tools to get the information they would like to have.

Ms. Hickey said that there may be more of a migration in the future as the MTFs are now advertising the mail-order for the first time. A lot of people don't use the mail-order because they don't know about it.

Closing Remarks

Ms. Hickey announced that the next meeting will be June 29 at the Naval Heritage Center at 8:00 a.m. The drugs to be looked at will include antiemetics, contraceptives and thiazolidinediones (TZDs).

Ms. Hickey thanked the Panel members and presenters for their support over the past year.

The meeting was adjourned at 3:00 p.m.

Appendix 1

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 inhibitors — Angiotensin-converting Enzyme inhibitors (a drug class)
- ARBs — Angiotensin Receptor Blockers (a drug class)
- BAP — Uniform Formulary Beneficiary Advisory Panel (the "Panel" referred to above)
- BCF — Basic Core Formulary
- BIA — Budget Impact Analysis
- BPH — Benign Prostatic Hyperplasia Alpha Blockers (a drug class)
- CCB — Calcium Channel Blocker (a drug class)
- CEA — Cost-effectiveness analysis
- C.F.R — Code of Federal Regulations
- CMA — Cost-Minimization Analysis
- CR — Controlled release (a drug formulation)
- DFO — Designated Federal Officer
- DOD — Department of Defense
- DPNP — Diabetic Peripheral Neuropathic Pain
- ECF – Extended Core Formulary
- ER — Extended Release (a drug formulation)
- ESI — Express-Scripts, Inc.
- FACA — Federal Advisory Committee Act
- FDA — U.S. Food and Drug Administration
- GABA — Gamma-aminobutyric acid
- HMO — Health Maintenance Organization
- IR — Immediate release (a drug formulation)
- MAH — Miscellaneous Antihypertensives (a drug class)
- MAUT — Multi-Attribute Utility Table (an analytical tool for quantifying effectiveness differences)
- MHS — Military Health System
- MS— Multiple Sclerosis
- MTF — Military Treatment Facility
- NMDA — Acetylcholinesterase inhibitor and N-Methyl D-Aspartate (a drug class)
- NNH — Number Needed to Harm
- NNT — Number Needed to Treat
- OABs – Overactive Bladder drug (a drug class)
- OHSU-DERP — Oregon Health & Science University Drug Effectiveness Review Project
- OTC — Over the counter

- PA — Prior Authorization
- P&T Committee — DOD Pharmacy and Therapeutics Committee
- PDE-5 — Phosphodiesterase Type 5 Inhibitors (a drug class)
- PEC — DOD Pharmacoeconomic Center
- PPI — Proton Pump Inhibitor (a drug class)
- SSNRIs — Selective Serotonin Norepinephrine Reuptake Inhibitors (a sub-class of the antidepressant I drug class)
- SR — Sustained release (a drug formulation)
- SSRIs — Selective Serotonin Reuptake Inhibitors (a sub-class of the antidepressant I drug class)
- SUI — Stress Urinary Incontinence
- TCA — Tricyclic antidepressant
- TMA — TRICARE Management Activity
- TMOP — TRICARE Mail-Order Pharmacy
- TRRx — TRICARE Retail Pharmacy Program
- TZDs — Thiazolidinediones
- UF — DOD Uniform Formulary
- U.S.C. — United States Code
- VA — U.S. Department of Veterans Affairs

30 March 2006 BAP Meeting Script

Good Morning,

I'm Major Wade Tiller, Chief Pharmacoeconomic Analyst at the PEC. Joining me today from the clinical PEC clinical operations staff are CPT Jill Dacus, Army Internal Medicine physician; Dr. Dave Meade, Staff Clinical Pharmacist; and Dr. Dave Bretzke, Staff Clinical Pharmacist and Contracting Specialist.

Also joining us are CDR Richerson, PEC Director and CAPT Patricia Buss, Chairman of the DoD Pharmacy and Therapeutics Committee. While we don't have any physician members of the Pharmacy and Therapeutics Committee present today, we do have CPT Jill Dacus to provide the physician perspective. In addition to her responsibilities at the PEC, CPT Dacus is a practicing physician and has a clinic at BAMC.

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).

Dave Meade, Dave Bretzke 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 Overactive Bladder Drugs, Miscellaneous Antihypertensive drugs and, GABA Analog drugs.
4) The DoD P&T Committee's 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.

We've given you a handout which includes the Uniform Formulary recommendations for all the drugs discussed today; this is found on page two. There are tables and utilization figures

for all the drug classes. We'll be using trade names, so you can refer to your handout throughout the presentation.

.Dave Meade will now present the first class review for Overactive Bladder Drugs.

We'll discuss the Relative Clinical Effectiveness first:

Members in the class: The drugs for the treatment of overactive bladder were reviewed for placement on the Department of Defense (DoD) Uniform Formulary. Refer to Table two on page three of your handout. There are five different drugs used in the treatment of overactive bladder. Some of these drugs are available in various dosage forms such as capsules, tablets, patches and syrup. There are 8 branded products on the market; oxybutynin immediate release (Ditropan), oxybutynin sustained release (Ditropan XL), oxybutynin patch (Oxytrol Patch), tolterodine immediate release (Detrol). Tolterodine sustained release (Detrol LA), trospium (Sanctura), solifenacin (Vesicare), and darifenacin (Enablex). Pay attention to when the drugs were approved by the FDA as I'll refer to the newer agents and older agents several times. With the newer agents, their claim to fame is that they cause less adverse effects than the older agents, because they act more specifically in the body – we'll discuss this later.

Generic Availability: Currently there is only one generic for this class, oxybutynin immediate release (Ditropan). The sustained release form of oxybutynin (Ditropan XL) is the next overactive bladder drug expected to be generic, but not until December 2006.

Table 1: Drugs for the treatment of overactive bladder available in the U.S *(package inserts)

Generic Name	Brand Name (Manufacturer)	Generics available	Strengths & formulations	FDA approval date
Oxybutynin IR	Ditropan, generics	Yes	5 mg tabs; 5 mg/mL syrup	1975
Oxybutynin SR	Ditropan XL (Alza, Ortho McNeil)	No	5 mg, 10 mg, 15 mg ER tabs	1999
Oxybutynin trans-dermal	Oxytrol (Watson)	No	3.9 mg/day patch	2003
Tolterodine IR	Detrol (Pfizer)	No	1mg, 2 mg tabs	1998
Tolterodine SR	Detrol LA (Pfizer)	No	2 mg, 4 mg caps	2000
Trospium	Sanctura (Odyssey / Indevus)	No	20 mg tabs	2004 (May)
Solifenacin	Vesicare (GlaxoSmithKline)	No	5 mg, 10 mg tabs	2004 (Nov)
Darifenacin	Enablex (Novartis)	No	7.5, 15 mg ER tabs	2004 (Dec)

Relevance to MHS and Utilization:

Please refer to figure one on page three in your handout. I'm going to refer to this class as OAB drugs. The drugs used for the treatment of overactive bladder currently rank #28 overall in terms of Military Health System (MHS) drug class expenditures. In FY 2004, $55 million dollars was spent on OAB drugs in all three points of service (retail [TRXX], mail order [TMOP], and military treatment facilities [MTFs]). Detrol LA (tolterodine sustained release) is the most

popular OAB drug in the MHS; it is ranked #1 in utilization in terms of number of prescriptions at all three points of service. This isn't shown in your graphs, but Ditropan XL (oxybutynin sustained release) is #2 in utilization in the mail and retail venues, while generic Ditropan immediate release is #2 in utilization in the MTFs. In the entire MHS, there are 147,508 unique utilizers of OAB drugs; 48% of patients are receiving Detrol LA (tolterodine sustained release), while 19% are receiving Ditropan XL (oxybutynin sustained release). Since it's hard to see the newer agents in Figure 1, we've broken out the utilization of these new OAB drugs into Figure two on page four of your handout. Even though the lines suggest a huge uptake of these newer OAB drugs, keep in mind that the overall number of prescriptions is low, at 5,000 Rxs per month, compared to the older agents at 10,000 to 25,000 per month.

We're going to give the conclusion first, then go back and discuss the differences between the drugs used for the treatment of overactive bladder. Based on the relative clinical effectiveness review the DoD P&T committee concluded the following six points:

1) In terms of efficacy, in comparable doses, the OAB drugs are equally effective at relieving symptoms of urge incontinence (wetting episodes), urge episodes (close calls) and total number of micturitions (bathroom visits).
2) In terms of side effects, all the OAB drugs have a similar side effect profile. Most profound are the drying effects: dry mouth and dry eyes. Constipation, somnolence and nausea are also part of the side effect profile. Immediate release products have a greater effect on causing dry mouth when compared to sustained release products. The newer drugs in the class, Vesicare (solifenacin) and Enablex (darifenacin), cause more constipation. The Oxytrol patch has less of a dry mouth effect, but can cause skin rash and redness at the application site.
3) In terms of number of doses required daily, Vesicare and Enablex are taken once daily due to their drug properties. The sustained release formulations of Detrol LA and Ditropan XL are also given once daily. Drugs that are dosed once a day are usually preferred over drugs requiring dosing twice or three times daily. Detrol and Sanctura are taken twice daily. Ditropan immediate release is taken up to three times daily. The Oxytrol patch is applied every 3 to 4 days.
4) For pediatric patients, Ditropan immediate release and Ditropan XL can be used in children older than 6 years of age. The manufacturer of Detrol is pursuing a pediatric indication.
5) In pregnant patients, Ditropan immediate release and Ditropan XL have an FDA pregnancy category B rating. As a reminder category B indicates that animal studies have not shown fetal risk but there are no human studies to back up those results. The other OAB drugs have a FDA pregnancy category C rating. A category C rating indicates either animal studies have revealed adverse effects on the fetus and there are no controlled human studies to back up these results or there are no studies at all in animals or humans.
6) Patients tend not to refill prescriptions for this class of drugs possible because the OAB drugs did not relieve their symptoms or because of the nagging side effects. In an MHS study, after 90 days, less than ½ the patients refilled their OAB prescriptions in a timely manner that would indicate that they are taking the medication as prescribed by the

provider. After one year only one in seven patients were refilling the prescription "on-time" to indicate that they're taking the medication as prescribed by the provider.

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) What are the differences in efficacy among the OAB drugs?
2) What are the differences in safety and tolerability among these drugs?
3) Are there differences between OAB drugs in other factors, such as frequency of dosing, approval in pediatric patients, and use in pregnancy that are likely to affect compliance or adherence to therapy.

(Data Source): To answer the key questions, the relative clinical effectiveness analysis evaluated information from meta-analyses, systematic reviews, published head-to-head randomized clinical trials, and placebo controlled trials. Several sections of the review were also adapted from the Veterans Administration Pharmacy Benefits Management Strategic Healthcare Group OAB Drug Class Review which was completed in January 2006. The published clinical trials were found using a Medline Search, searching major medical journals table of contents, and manufacturer press releases. The FDA website was monitored for updates.

Key question #1 What are the differences in efficacy among the OAB drugs?: Most of the clinical trials used endpoints of wetting episodes, urgency episode (barely making it to the toilet), number of times needed to go to the bathroom in the middle of the night, number of bathroom visits, and changes in urine amount (or volume). All levels of evidence, including head to head trials, placebo controlled trials, and systematic reviews concluded that all the OAB drugs, when taken in appropriate doses, were equally effective at relieving wetting and urgency episodes. Though better than placebo, none of the drugs had an overwhelming reduction in the endpoints mentioned above.

Conclusion: The DoD P&T Committee agreed there is no evidence to suggest that any one OAB drug is more efficacious than another in reducing the endpoints of wetting episodes etc.

Key question #2 What are the differences in side effects between the drugs used for the treatment of overactive bladder? Is there a difference in the safety and tolerability between agents?

Most side effects related to the drugs used to treat overactive bladder are anti-cholinergic in nature. The mnemonic, "dry as a bone, blind as a bat, red as a beet" summarizes the classic combination of anti-cholinergic effects.

Dry as a Bone: The most frequent patient complaint with OAB drugs is dry mouth. There are significantly more complaints with the immediate acting agents compared to the long acting agents. Though the newer agents, Vesicare (solifenacin) and Enablex (darifenacin), claim to have selective binding in the bladder, this increase in selectivity does not relate to

less complaints of dry mouth compared to the other agents. With all the drugs in the class, as the dose is increased, dry mouth worsens. Constipation and somnolence are the second most reported adverse events by providers. Higher rates of constipation are noted with the newer agents Enablex (darifenacin) and Vesicare (solifenacin), especially in higher doses, compared to older agents.

Blind as a Bat: Visual changes can be caused by either dryness of the eyes and/or changes in visual accommodation. Again, there appears to be a dose effect in this side effect for all the OAB drugs.

Red as a Beet: This side effect is usually seen when oral doses are excessive. However the Oxytrol patch can cause a local skin redness and irritation which can cause patients to discontinue treatment.

I want to mention the safety of the OAB drugs in older patients. Somnolence can occur with the OAB drugs and is the second most common side effect. The immediate release form of oxybutynin, (Ditropan immediate release) is included in the Beer's Criteria, which is an accepted list of potentially harmful medications in older adults. Sedation and muscle weakness are the reasons why Ditropan immediate release has been included on the list. The risk of using Ditropan immediate release in older patients occurs because there is an increased risk of falls. None of the other OAB drugs are listed in the Beer's criteria. This is not a comprehensive list, and hasn't been updated since 2002.

Next I want to mention tolerability. By in large, tolerability is not good with this class of drugs. One way to figure out if patients are tolerating the drugs is to see if they still continue to get their refills on time. We call this persistence. Two studies indicate that after 1 year, 10% or less of patients started on Detrol LA (tolterodine), Ditropan XL (oxybutynin SR), and Ditropan immediate release were still getting their refills. When Major Tiller conducted a similar study of DoD beneficiaries on the same medications, only slightly better persistence occurred. After one year only 16% of patients on Detrol LA were still getting in their refills on time. This compares to 13% of patients on Ditropan XL and 5% on Ditropan immediate release. This shows that patients were more likely to get their prescriptions filled if there were on a sustained release product, rather than an immediate release product. The newer agents, Enablex (darifenacin) and Vesicare (Solifenacin) did not have enough prescriptions to accurately predict persistence rates in DoD.

Beneficiaries using the mail order had almost double the MHS persistence rates. Beneficiaries using the retail sector had slightly lower rates than all the MHS. In the DoD there were a number of patients refilling the medication 30-90 days after the expected refill date. We asked providers about this, and they indicated that a number of patients use these drugs on an as needed basis depending on social requirements. If the patient was going out and was not sure where a toilet was located, they would take the drug. If they were going to be at home or close to a toilet, they would not. The doctors though that this "as needed" usage was used to avoid the anti-cholinergic side effects noted above.

Conclusion: The side effect profiles of these drugs are similar and can be a nuisance. The drying effect of the drugs is the major side effect noted by patients and providers. Side

effects are more prominent with the immediate release formulations than sustained release products. The "selectivity" of the newer products does not seem to lessen these side effects and may increase the incidence of constipation. An exception may be Ditropan (oxybutynin) immediate release which is included in the Beer's criteria of drugs potentially harmful to the elderly. These drugs are not well tolerated and are being used in some cases on an as needed basis to avoid the side effect profile.

Key question #3 Are there differences between the OAB drugs in other factors, such as frequency of dosing, approval in pediatric patients, and use in pregnancy that are likely to affect compliance or adherence to therapy.

Dosing frequency: Most of the products are marketed for once daily administration. Theoretically once daily dosing may result in improved patient compliance vs. products requiring multiple daily dosing. Ditropan XL, Detrol LA, Vesicare and Enablex are dosed once a day, while Detrol and Sanctura require at least twice daily dosing. Ditropan immediate release may be used up to three times per day. The Oxytrol patch is changed every 3-4 days.

Pediatric Populations: Ditropan immediate release and Ditropan XL are indicated for use in children down to the age of 6 years. Detrol is in the process of getting FDA approval for use in the pediatric population.

Pregnancy: All of the drugs used to treat overactive bladder are rated FDA pregnancy category C (risk cannot be ruled out) except Ditropan immediate release and Ditropan XL, which have a FDA Category B rating (low risk in humans).

Conclusion: The DoD P&T Committee agreed there are some small differences between the drugs for the treatment of overactive bladder in terms of dosing frequency, use in pregnancy, or use in pediatric patients.

Provider Opinion: MTF providers were surveyed regarding their opinions on the OAB drugs. Overall, physicians preferred a product that was dosed once daily over immediate release products.

Detrol LA is the most popular OAB drug at the MHS (used in 55% of patients). However, some providers did indicate that their preference for Detrol LA was due to familiarity with the drug rather than better efficacy. About 25% of the responding providers had not heard of the new agents, Vesicare (solifenacin), Enablex (darifenacin), and Sanctura (Trospium). About 50% had heard of the new agents, but had not prescribed the drugs.

Overall Conclusion to Relative Clinical Effectiveness: The DoD P&T Committee concluded that the OAB drugs show similar efficacy and safety profiles, when dosed appropriately. As mentioned early, minor differences are apparent in the side effect profiles. Minor differences were also noted between the products in terms of other factors, such as dosing, use in pregnancy, or used in pediatrics. Overall persistence is low with these drugs, particularly with the immediate release formulations.

Maj Wade Tiller will now present the cost effectiveness analysis for the OAB drugs.

Overactive Bladder (OAB) Uniform Formulary Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the OABs 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).

The conclusion of the evidenced based relative clinical effectiveness evaluation was that there was insufficient evidence to suggest that the agents within the OAB class differ in regards to efficacy. However, safety and tolerability differences were noted in the literature and from our own persistence study between the IR and SR agents, with the SR agents having a more favorable side effect profile and improved tolerability. To account for the differences in relative clinical effectiveness between the IR and SR agents and potentially between agents in the IR and SR sub-classes, a cost-effectiveness analyses (CEA) was performed. This CEA was based on the results of a DoD prescription database analysis. Remember, in a CEA, the agents within a therapeutic class are competed on two dimensions, cost and effect (outcomes).

The DoD prescription database analysis was a one-year sample based retrospective cohort database analysis. Cohort studies are observational studies which identify subsets of a defined population and follow them over time, looking for differences in outcome. In a retrospective cohort study, all relevant events (both exposures and outcomes of interest) have already occurred when the study is initiated. In this study, patient subsets were defined by exposure to treatment intervention and six intervention groups were selected for observation: DoD patients filling prescriptions for oxybutynin IR (Ditropan), oxybutynin SR (Ditropan XL), oxybutynin patch (Oxytrol patch), tolterodine IR (Detrol), tolterodine SR (Detrol LA), and trospium (Sanctura) between 01 July 2004 and 30 September 2005. Patients taking any OAB agent, in the 6 month period prior of their observed period of enrollment, were excluded to capture new users only. Note, darifenacin (Enablex) and solifenacin (Vesicare) were not included in the study since these agents are new and lacked a year's worth of utilization data. The drug cost used in the analysis was the point of service adjusted total weighted average cost per day of treatment (for all three points of service) and the outcome of interest was adherence to treatment, where adherence to treatment was measured by total days of treatment. Theoretically, adherence to treatment is a surrogate indicator of efficacy, safety, and tolerability. Basically an assumption was made that a patient is more inclined to adhere to treatment if the agent works (efficacy) and is tolerated to the extent that the benefits of treatment outweighs the risk of side effects (tolerability and/or safety).

The results from the sample based retrospective cohort database analysis were then incorporated into a cost-effectiveness analysis. The cost used in the analysis for each agent was the mean cost of treatment for one-year and the effect/outcome was the mean days of treatment for one-year. Overall, the results of the CEA were as follows:

- Overall, Ditropan immediate release (oxybutynin IR) was determined to be the most cost-effective agent and Detrol LA (tolterodine SR) was determined to be significantly more costly and effective along the efficiency frontier

- Among the multiple daily-dosed immediate release agents, Ditropan immediate release (oxybutynin IR) was determined to be the most cost-effective agent; Detrol (tolterodine IR) was determined to be slightly more effective but significantly more costly (> 15-fold) compared to

Ditropan immediate release (oxybutynin IR); and Sanctura (trospium IR) was determined to be slightly less effective and significantly more costly (> 15-fold) compared to Ditropan immediate release (oxybutynin IR).

- Among the once dosed agents, Detrol LA (tolterodine SR) was determined to be the most cost-effective agent; Oxytrol patch (oxybutynin patch) and Ditropan XL tablet were dominated (less costly and less effective) compared to Detrol LA (tolterodine SR).

Since Enablex (darifenacin) and Vesicare (solifenacin) lacked sufficient utilization data to be included in the CEA analysis, the agents were evaluated on their point of service adjusted total weighted average cost per day of treatment only. The manufacturers of Enablex (darifenacin) and Vesicare (solifenacin) submitted highly competitive prices for their respective agents, which made them significantly less costly compared to the most cost-effective extended release agent, Detrol LA (tolterodine SR). For purposes of the cost-effectiveness evaluation, the DoD P&T Committee assumed that Enablex (darifenacin) and Vesicare (solifenacin) would have similar relative clinical effectiveness compared to Detrol LA (tolterodine SR), based upon the conclusion of the overall relative clinical effectiveness presentation.

The results of the CEAs were incorporated into a budget impact analysis (BIA). The BIA accounted for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, provider switch costs, and medical necessity processing fees. Five different UF scenarios were considered.

After the BIA presentation, the DoD P&T Committee engaged in considerable discussion regarding the OAB UF decision. One of the issues encountered by the DoD P&T Committee was whether or not the two new competitively price agents, Enablex (darifenacin) and Vesicare (solifenacin) had sufficient relative clinical effectiveness data to safely supplant the considerably more costly and highly utilized (53% market share) Detrol LA (tolterodine SR) from formulary status. From a cost perspective, the difference in cost between the more expensive Detrol LA (tolterodine SR) and the less costly two new agents, Enablex (darifenacin) and Vesicare (solifenacin) was more than sufficient for a recommendation of non-formulary status. However, given that there was less than a year's worth of post-marketing efficacy, safety, and tolerability data, the Committee was reluctant to remove Detrol LA (tolterodine SR) from formulary status. Another point of discussion was the uncertainty surrounding the generic availability and future generic pricing for Ditropan XL (oxybutynin SR), which is projected to go generic sometime in 2006. Ultimately, the Committee elected to maintain Ditropan XL (oxybutynin SR) on the formulary for two reasons: 1) cost reductions resulting from generic competition may eventually make this drug the most cost-effective extended release formulary alternative, 2) Once generically available, this drug would provide the first and only sustained release OAB drug for the generic copay. In regards to Detrol (tolterodine IR), Sanctura (trospium), and Oxytrol patch (oxybutynin patch), the Committee agreed that these agents offered no additional benefit at a substantially increased cost to the MHS and should be designated as non-formulary.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 2 abstention, 1 absent) to accept the OAB cost-analysis presented by the PEC. The P&T Committee concluded that: Detrol (tolterodine IR), Oxytrol patch (oxybutynin patch), and Sanctura (trospium) were not cost-effective relative to the other OAB agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost

effectiveness determinations of the OABs, and other relevant factors, the P&T Committee recommended Uniform Formulary status for the OAB class.

Committee Action: The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstention, 3 absent) to recommend that Detrol (tolterodine IR), Oxytrol patch (oxybutynin patch), and Sanctura (trospium) be classified as non-formulary under the UF, with Enablex (darifenacin), Ditropan immediate release (oxybutynin IR), Ditropan XL (oxybutynin ER), Vesicare (solifenacin), and Detrol LA (tolterodine ER) remaining on the UF.

Implementation Plan: Due to the low number of beneficiaries who would be affected by this formulary action (19,118 patients known to be taking Detrol (tolterodine IR), Sanctura (trospium) or Oxytrol patch (oxybutynin patch) across the MHS), the P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval of the Director, TMA.

Committee Action: The P&T Committee voted (13 for, 2 opposed, 1 abstention, 2 absent to recommend an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Dave Meade will now present the miscellaneous anti-hypertensive drug class review

Background: Our next class review is the miscellaneous anti-hypertensive drugs. The reason for this rather vague name is that we are going to discuss several drugs with different mechanisms of action that belong to many different sub-classes. Previously, we've talked about the angiotensin receptor blockers, the ACE inhibitors, and the calcium channel blockers. This miscellaneous classification is a way for us to make sure we are evaluating all the different types of anti-hypertensive or cardiac drugs. In other words, we want to pick up any "stragglers" that we didn't talk about previously, and not leave any drugs out.

FDA Indications: All these drugs we're going to talk about are all approved for treating hypertension, which means that they lower high blood pressure. Some of them are also used for other purposes besides high blood pressure, and I'll discuss those when appropriate.

Table 3: Miscellaneous anti-hypertensive drugs

Generic	Brand (Manufacturer)	Generics available	FDA approval date
ACE inhibitor / Calcium Channel Blocker Combinations			
Amlodipine + benazepril	**Lotrel**	No	1995
Felodipine + enalapril	**Lexxel**	No	1996
Verapamil sustained release + trandolapril	**Tarka**	No	1996
Vasodilators (direct acting)			
Hydralazine	Apresoline	Yes	1951
Minoxidil	Loniten	Yes	1979
Centrally acting α-2 agonists			
Clonidine tablets **Clonidine transdermal patch**	**Catapress** **Catapres TTS**	Yes No	1960s 1984
Methyldopa	Aldomet	Yes	1962
Guanabenz	Wytensin	Yes	1982
Guanfacine	Tenex	Yes	1986
Peripheral α-1 antagonists			
Prazosin	Minipress	Yes	1976
Adrenergic antagonists			
Reserpine	N/A	Yes	1949
Guanadrel	Hylorel	Yes	1982
Guanethidine	N/A	Yes	1959
Ganglionic Blockers			
Mecamylamine	Inversine	No	1950s, 2002

Definition of the class: If you turn to table 3 on page 5 of your handout, you'll see the drugs we'll be talking about. There are 15 drugs in this class, however, the main discussion will concern 5 drugs; those are bolded for you to follow along. We'll explain in detail later why we

are only focusing on 5 drugs. We've broken the class down into sub-classes. The main sub-class that we are going to focus on is the ACE inhibitor and calcium channel blocker combination drugs; there are three of these, Lotrel, Lexxel, and Tarka. The other sub-classes are the vasodilator drugs, the centrally acting alpha 2 agonist drugs, the peripheral alpha 1 antagonists, the adrenergic antagonists, and the ganglionic blockers. The other two drugs we're going to discuss in detail, in addition to the 3 ACE inhibitor/ calcium channel blocker combination drugs, fall under the centrally acting alpha 2 agonists category - Catapres (or clonidine) tablets and Catapres patches. You'll see that in the last column, under the FDA approval data that some of these drugs have been on the market since the 1950's and 1960s.

Relevance to MHS and utilization: Let's move on to how much these drugs cost the MHS, and their utilization. If you turn to page 6, you'll see figures 3 and 4. In fiscal year 2005, the ACE inhibitor / calcium channel blocker combination drugs were ranked #53 in overall MHS cost, at $27 million dollars. The other drugs in the miscellaneous anti-hypertensive drug class have been on the market for several years, and some for several decades, so most of them are available in generic formulations, with the exception of the Catapress (clonidine) patch. Figure 3 shows the utilization of the ACE inhibitor / calcium channel blocker combinations by themselves. You can see that Lotrel has the majority of the market share, at about 23,000 Rxs/ month, from a time frame of Feb 2005 – Jan 2006. Tarka and Lexxel are way behind Lotrel in utilization, at < 1,000 Rxs per month. Figure 4 shows the top 8 drugs in the whole miscellaneous anti-hypertensive drug class from the time period of Nov 2004 to October 2005 in the entire MHS (MTF, Retail Network, Mail order). For the entire class, Lotrel has the majority of the market share, followed by clonidine tablets at about 20,000 Rxs/ month. The remaining drugs have less than 5,000 Rxs dispensed per month, which fall out in order of the Catapress patch (at about 5,000 Rx/ months), followed by the others. We don't have a cost ranking of the other miscellaneous anti-hypertensives, because they have low utilization, and since most of them are generic, they are low cost.

Next I want to talk a little more about why we defined the class this way, and the impact of previous Uniform Formulary Decisions. The three ACE inhibitor / calcium channel blocker combinations are obviously comprised of two ingredients into one tablet or capsule. The individual components were discussed back Sept when we presented the class reviews for the ACE inhibitors and the calcium channel blockers. However, we did not address the combination products back then, so we are taking care of it now. Lotrel is made up of the ACE inhibitor benazepril and the calcium channel blocker amlodipine, which is the active ingredient in the product Norvasc. Back at the September 2005 BAP meeting, the recommendation was to place Norvasc as non-formulary on the Uniform Formulary, with an implementation deadline of March 15, 2006. The other two drugs in the class, Tarka (verapamil and trandolapril) and Lexxel (felodipine and enalapril) are made up of individual ACE inhibitor and calcium channel blockers that are on the Uniform Formulary.

Let's move on to the details of the clinical effectiveness review.

Data source: For the clinical effectiveness evaluation, we looked at the usual sources of information. We analyzed published clinical trials, we obtained unpublished information from the manufactures, and also looked at the drugs' package inserts. Since several of these drugs

have been on the market for several decades, sometimes we were not able to find good clinical trials that discussed efficacy, because the clinical trials conducted today have a much more rigorous study design than early trials from 50 years ago. As a way to get around the lack of good clinical trials, we looked at national guidelines from the Joint National Commission that publish recommendations on the place in therapy for blood pressure drugs. We also surveyed our MTF providers to determine how they use these drugs, not only for high blood pressure, but also for other indications.

Let's go over our conclusions from the review first, then go back and discuss the details.

1). The three ACE inhibitor / calcium channel blocker combination drugs (Lotrel, Tarka, Lexxel) show similar effects in lowering blood pressure.
2). For the three ACE inhibitor / calcium channel blocker combination drugs, there does not appear to be differences in their ability to lower blood pressure in different sub-populations of patients (for example those with diabetes, African Americans, or elderly patients), although there are no published trials with Lexxel.
3). For the three ACE inhibitor / calcium channel blocker combination drugs, there are no published studies looking at clinical outcomes such as death, stroke or heart attack, but there is some evidence to suggest a benefit with the individual components.
4). For the three ACE inhibitor / calcium channel blocker combination drugs, their safety profiles reflect the individual calcium channel blocker components.
5). Of the three ACE inhibitor / calcium channel blocker combination drugs, Tarka is not interchangeable with Lotrel and Lexxel, due to the differences in the individual calcium channel blocker components.
6). For the clonidine preparations, the clonidine tablets and Catapress patches, neither one is a candidate for non-formulary placement.
7). For the remaining members of the miscellaneous anti-hypertensive drug class, none of the products are candidates for non-formulary placement.

The DoD P&T Committee's conclusion was determined after answering the following key questions based on the relative clinical effectiveness review:

Key question #1: What are the differences in efficacy, safety and other factors for the ACE inhibitor and calcium channel blocker combinations?

Let's briefly talk about pharmacology differences first. Both Lotrel and Lexxel contain calcium channel blockers belonging to the dihydropyridine sub-class. Lotrel contain amlodipine and Lexxel contains felodipine. In contrast, the calcium blocker component of Tarka is verapamil, which is a non-dihydropyridine. While both types of these calcium channel blockers reduce blood pressure, they do have some differences in mechanism of action. The verapamil component of Tarka can slow the heart rate. Lexxel and Lotrel calcium channel blockers don't affect the heart rate, but they do cause the veins in the legs to dilate, which can cause leg swelling. However, in some cases, you would want the heart rate to be slowed with Tarka, for example in a patient with a rapid heart rate (atrial fibrillation).

Let's move on to discussing high blood pressure. The rationale for combining two different anti-hypertensive drugs into one tablet is that you get an additional effect of lowering blood pressure, compared to giving the two individual agents alone. Also it is convenient to the patient because they only have to take one tablet, rather than two, which may improve compliance.

So how do these three combination drugs compare with their ability to lower blood pressure? We looked at data from clinical trials and found that they all reduce blood pressure to the same extent. We next wanted to see if there were differences in efficacy for different types of people with high blood pressure, like African Americans, diabetics, and elderly patients. There were no published studies with Lexxel for these different populations, but we would still expect Lexxel to work here. For Lotrel and Tarka, there were several published trials showing that these two drugs reduce blood pressure in these types of patients.

Next we wanted to see if there was any data showing that not only do these combination drugs reduce blood pressure, but that they also reduce the risk of death, stroke, or heart attack. There are no published trials with Lexxel. There are also no published trials with Lotrel, but several studies are underway, so we will have more data in a couple of years. With Tarka, the manufacturer has one large trial showing that the individual components of Tarka reduced death, stroke, and heart attack, but this study wasn't with the actual Tarka tablet. There are trials (which we discussed back in Sept) showing that the other individual components have studies showing benefits on these outcomes. So we can't say that Tarka is better at reducing death than the Lotrel and Lexxel.

Let's move on the safety. Remember that we said the calcium channel blocker component of Tarka is different from the Lotrel and Lexxel? Because of this, there are differences in the side effect profiles of these drugs. Tarka should not be used in patients with certain types of heart problems, because it slows down the heart rate. Lotrel and Lexxel don't have this precaution. For all three products, the side effects of the individual ACE inhibitor components are similar, so the precautions would be the same here.

In terms of other side effects, Lexxel and Lotrel are associated with edema and headache, while Tarka is associated with constipation and heart rhythm disturbances. Drug interactions are more of an issue with Tarka, compared to the other two ACE inhibitor calcium channel blocker combinations. If we look at clinical trial data and see how many patients have to drop out due to some side effect, the percentages are similar; there is a 2.8% drop-out rate with Lexxel, compared to 4% with Lotrel, and 2.6% with Tarka.

For other factors, we wanted to see if there were differences in the products in the persistence rates (remember we talked about persistence earlier with the OAB drugs). Recall that one potential benefit of a combination drug is that you may have better patient compliance, so we wanted to see if this was true. There are no published studies with Lexxel or Tarka. For Lotrel, we found two studies that showed that persistence was improved by about 7-20% if they took Lotrel, instead of taking a Norvasc tablet and a benazepril tablet separately. However, these two trials did not have the most rigorous study design.

We are going to move away from the ACE inhibitor calcium channel blocker combinations and go on to **key question #2. Key Question #2 asks whether there is a clinical reason why either clonidine tablets or Catapress patches could be made non-formulary on the Uniform Formulary.**

Clonidine tablets and Catapress patches have the same active ingredient (clonidine), but different dosage forms (an oral tablet vs. a patch). The clonidine tablets are available generically, while the patches are not. Recall that the clonidine tablets and Catapress patches rank #2 and #3 overall in MHS prescription utilization, second only to Lotrel. The Joint Commission National guidelines state that clonidine is a 2nd or 3rd line drug for treating high blood pressure, however it is still widely used as an anti-hypertensive agent. Clonidine is frequently used for many other reasons, besides high blood pressure, including smoking cessation, menopausal hot flashes, behavior problems in children and alcohol or illicit drug withdrawal.

For hypertension, clonidine tablets must be dosed two to three times a day. If you suddenly stop therapy, there is a risk that a patient could develop something called "rebound hypertension", where there is a sudden dangerous rise in blood pressure. One benefit of the Catapress patches is that they are changed once a week. The patches have a long duration of action, and when you remove the patch, it takes about 5 days for the blood levels to return to normal. Because of this, the risk of rebound hypertension with the Catapress patches is much lower than with the clonidine tablets.

Other benefits of the Catapress patches are that they are very useful in patients with swallowing difficulties (for example in stroke patients) who need blood pressure medication. Another benefit is that the Catapress patches can potentially improve patient compliance and simplify the dosing for those with complicated regimens where 3-4 blood pressure medications are needed. Despite the fact that the Catapress patches cost more than the clonidine tablets, the Committee deemed that the patches are valuable in DoD, based on these unique clinical issues.

Let's now move on to the remaining drugs in the miscellaneous anti-hypertensive drug class. **The 3rd key question asks whether any of these remaining agents would be candidates for non-formulary placement on the Uniform Formulary based on their clinical attributes alone.**

The rest of the class includes hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, prazosin, reserpine, guanadrel, guanethedine, and mecamylamine. These drugs are all available in generic formulations, and some of them have very low utilization.

I just want to briefly mention some clinical issues with these products. The Joint National Guidelines support the use of methyldopa, hydralazine, minoxidil, reserpine and guanfacine as antihypertensive drugs, although their use is somewhat limited by tolerability issues. Hydralazine is the 4th most commonly utilized miscellaneous antihypertensive agent in the MHS. Although it is often used for treating hypertension, it also has a role in treating patients with heart failure. Minoxidil is also frequently prescribed for patients who need 4-5 drugs to control their blood pressure. Methyldopa has a unique place in therapy for treating pregnant women with high blood pressure, since it has been shown to be safe in pregnancy in long-term studies.

Guanfacine is also used for children with behavior problems. Prazosin and reserpine are still used for treating high blood pressure, although rarely There were 25,000 Rxs for prazosin, and 1,400 Rxs for reserpine in the entire MHS in Fiscal Year 2005. Guanabenz is rarely used today, and for fiscal year 2005 there were only 485 prescriptions in the entire MHS. Mecamylamine was one of the first anti-hypertensive drugs on the market back in the 1950s, but is rarely used today, due to side effects. There were only 59 prescriptions for mecamylamine in the MHS in Fiscal Year 2005. The reason that there is very low utilization for several of these drugs is that their side effect profile limits their use, and they have been replaced by newer drugs, such as ACE inhibitors, beta blockers, angiotensin receptor blockers, and calcium channel blockers. Since several of these drugs have unique places in therapy, some are still listed in JNC VII recommendations, and the rest have very low utilization, the Committee concluded that based on clinical issues alone, none would be candidates for non-formulary designation.

Overall conclusion: For the ACE inhibitor / calcium channel blocker combinations, the Committee concluded that there is insufficient evidence to suggest that the blood pressure lowering effects of Lotrel, Lexxel, and Tarka differ significantly. Lotrel and Tarka have evidence of benefit in different sub-populations of people with hypertension. There are no studies with the actual combination drugs showing a benefit on outcomes, but there is evidence with the individual components. The side effect profile of the ACE inhibitor / calcium channel blocker combinations are reflected by their calcium channel blocker component; because of this, we can't interchange Lexxel and Lotrel with Tarka, but we can use Lexxel and Lotrel interchangeably. The percentage of patients who have to discontinue therapy due to side effects is similar for the three ACE inhibitor / calcium channel blocker products. For clonidine tablets and Catapress patches, clinically, the Catapress patches fill a unique niche for patients with hypertension who cannot take oral medications. Clonidine tablets are still highly utilized in the MHS, not only for high blood pressure but for other uses. For the remaining drugs in the class, none of these are candidates for non-formulary placement.

Maj Wade Tiller will now present the cost effectiveness analysis for the miscellaneous anti-hypertensive drugs.

Miscellaneous Antihypertensives (MAH) Uniform Formulary Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the miscellaneous antihypertensive agents 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).

Given the heterogeneous nature of this therapeutic class, three separate pharmacoeconomic analyses were performed. The first analysis examined all the agents listed in the therapeutic class, except for the ACE inhibitor / calcium channel blocker combinations and Catapress patches. If you will once again refer to table 3 in your handout on page 5, you will see that I'm specifically referring to the vasodilators (hydralazine and minoxidil), the centrally acting α-2 agonists (methyldopa, guanabenz, and guanfacine), the peripheral α-1 antagonists (prazosin), the adrenergic antagonists (reserpine, guanadrel, guanethidine), and the ganglionic blocker (mecamylamine). For this analysis a simple cost-analysis was performed, but other factors considered included generic availability and utilization. Upon review of this analysis, the DoD P&T Committee concluded that these agents should be maintained on the UF given their established place in therapy, generic availability, low utilization, and low cost.

The second cost analysis was performed to compare Catapress patches and clonidine tablets. The comparison of cost was based on the point-of-service adjusted total weighted average cost per day of treatment. As expected, the results of the cost-analysis revealed that Catapress patches were significantly more costly compared to clonidine tablets.

The third analysis compared the ACE inhibitor / calcium channel blocker combinations. To account for the primary potential benefit of combination products, improved patient compliance with medication therapy, a cost-effectiveness analysis (CEA) was performed based on the results of three observational studies examining compliance with combination antihypertensives.

The observational studies included two studies that examined compliance with the combination product Lotrel (amlodipine/benazepril) and another study that examined compliance with combination ACE inhibitor/HCTZ products (enalapril/HCTZ and lisinopril/HCTZ). These studies revealed increased compliance ranging from 7% to 20% with the combination antihypertensives compared to the respective agents given separately. For purposes of the CEA, the increased compliance associated with combination antihypertensive products was assumed to be 10%. To determine the relative cost-effectiveness of the combination products, two simple cost-effectiveness decision models were constructed, one comparing the dihydropyridine/ACE combination products [Lotrel (amlodipine/benazepril) and Lexxel (felodipine/enalapril)] to their respective agents given separately and another comparing the verapamil/ACE combination product [Tarka (verapamil/trandolapril)] to its respective agents given separately. The cost used in the model was the total cost of drug treatment for one-year. The outcome/effect was 'days of treatment'. Theoretically, 'days of treatment' is a surrogate indicator of compliance. Likewise, compliance with drug therapy theoretically results in overall improved blood pressure control.

The results from the CEAs are as follows:

- Dihydropyridine/ACE combination

- The two individual ACE inhibitor and dihydropyridine calcium channel blocker components given separately were more cost-effective compared to Lexxel (felodipine/enalapril) and Lotrel (amlodipine/benazepril). However, the incremental cost-effectiveness ratio was relatively low, indicating that the combination products may be a cost-effective alternative therapy.

- Verapamil/ACE combination
  - The two individual components (verapamil and trandolapril) given separately were more cost-effective compared to Tarka (verapamil/trandolapril). For this comparison, the incremental cost-effectiveness ratio was relatively high, indicating that the combination product is not a cost-effective alternative therapy.

The results of the CEAs were subsequently incorporated into a budget impact analysis (BIA). A BIA accounts for other factors and costs associated with a potential decision to recommend that one or more agents be classified as non-formulary, such as: market share migration, cost reduction associated with non-formulary cost shares, and medical necessity processing fees. The goal of the BIA was to assist the Committee in determining which group of miscellaneous antihypertensive drugs best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. The DoD P&T Committee considered six different budget impact scenarios.

After the BIA scenarios were presented, the DoD P&T Committee entered into a lengthy discussion regarding the UF status of Lotrel (amlodipine/benazepril) and Catapress Patches (clonidine). In the discussion, the DoD P&T Committee re-examined the evidence supporting the relative clinical effectiveness of the agents, the relative cost-effectiveness of the agents, current utilization, and the number of beneficiaries affected by a potential decision to designate one or more agents as non-formulary, and MHS provider opinion.

In consideration of Lotrel, the Committee evaluated Lotrel as a potential cost-effective therapy alternative for patients currently taking a dihyropyridine calcium channel blocker and an ACE inhibitor as separate drugs. To put this consideration in proper perspective, I would like to refer you now to Figures 5 and 6 located on page 7 of your handout. The cost-effectiveness plane, which is shown in Figure 5, is used to categorize interventions in terms of their cost (on the y-axis) and their health effectiveness (on the x-axis). For interventions that can improve health and save money at the same time (SE quadrant), there is no need for analysis; they should be adopted. Similarly, there is no question that interventions that decrease health and cost money (SW quadrant) should be discontinued if currently used and not adopted if new. Interventions falling into the other two quadrants, however, require choices if health benefit is to be maximized subject to available resources. The decisions most often encountered by the DoD P&T Committee involve interventions falling into the NE quadrant, which are more costly and more effective. Figure 6 represents a cost-analysis comparing the dihydropyridine calcium channel / ACE inhibitor combination product Lotrel with Norvasc. In this graph, cost appears on the y-axis. As you can see here, even if you disregard the potential increased effectiveness due to increased compliance with the combination product, Lotrel compares favorably with the dihydropyridine and ACE inhibitors given as separate agents and is even considerably less costly compared to Norvasc alone. Ultimately, the DoD P&T Committee agreed that Lotrel should be classified as formulary on the UF formulary and did not believe that such a decision was inconsistent with the Nov 2005 decision to remove Norvasc (amlodipine) from the UF, which

was a value based decision. In that decision, Norvasc was located far up and to the right in the NE quandrant, and the Committee simply did not value Norvasc (amlodipine) enough to overcome its significantly increased cost (cost > 2-fold higher compared to nifedipine ER).

In regards to Catapress patches, the DoD P&T Committee agreed that the therapeutic niche of this dosage formulation (less risk of rebound hypertension upon withdrawal) overwhelmingly supported UF inclusion, despite the results of the cost-analysis.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 1 abstention, 1 absent) to accept the miscellaneous antihypertensive cost-analysis presented by the PEC. The P&T Committee concluded that Lexxel (felodipine/enalapril) and Tarka (verapamil/trandolapril) were not cost-effective relative to the other miscellaneous antihypertensive agents. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the miscellaneous antihypertensive agents, and other relevant factors, the P&T Committee recommended that Lexxel (felodipine/enalapril) and Tarka (verapamil/trandolapril) be classified as non-formulary under the UF. The P&T Committee also recommended that clonidine tablets, clonidine patches, Lotrel (amlodipine/benazepril), hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine be classified as formulary on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted 11 for, 4 opposed, 2 abstention, 1 absent) to recommend that Lexxel (felodipine/enalapril) and Tarka (verapamil/trandolapril) be classified as non-formulary under the UF, with clonidine tablets, clonidine patches, Lotrel (amlodipine/benazepril), hydralazine, minoxidil, methyldopa, guanabenz, guanfacine, reserpine, guanadrel, guanethidine, and mecamylamine remaining on the UF.

Implementation Plan: Due to the low number of beneficiaries who would be affected by this formulary action (5,946 patients known to be taking Lexxel and Tarka across the MHS), the P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval of the Director, TMA.

Committee Action: The P&T Committee voted (16 for, 0 opposed, 0 abstained, 2 absent) to recommend an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Dave Bretzke is up next to discuss the results of previous Uniform Formulary decisions

Dave Bretzke will present the GABA analogs drug class review

Background: We are going to call this drug class the GABA Analogs, or GABAs. This class includes three drugs that are used to treat seizures and neuropathic pain, a type of nerve pain. GABA stands for gamma-aminobutyric acid, which is a transmitter in the brain that inhibits pathways involved in pain and in seizure activity. Each of these medications slows down the transmission of nerve impulses, resulting in pain relief and treatment of seizures. The three GABA Analogs are listed in table 4 on page 8 of your handout and include gabapentin (which is available generically), pregabalin (Lyrica) and tiagabine (Gabitril). Also listed in the table are the initial FDA approval dates for the class. Lyrica is the newest GABA drug. Although it was approved by the FDA in December 2004, it didn't reach the market until August 2005. There are many other drugs from different classes that are used to treat nerve pain and seizures, however, we will focus on these drugs and their use in nerve pain. Their use for seizures will not be discussed.

Relevance to MHS and Utilization: In FY 2005, DoD spent $149 million dollars in all three points of service (retail, mail order, and military treatment facilities or MTFs) on the GABA drug class combined with the other seizure drugs. This makes it the 6th most expensive drug class in the DoD.

Let's also look at utilization -- please see the graph in Figure 7 on page 8 of your handout. Figure 7 shows the percentage of unique utilizers in the GABA drug class by month from Feb 2005 to Dec 31st 2005. A unique utilizer represents and individual patient. Since Lyrica came out on the market, its percentage of the GABA analog market share has increased, and in a few months it has gained 20% of the market of unique utilizers of the GABA analogs. For gabapentin, the percentage of the unique utilizers has decreased from almost 100% to about 80%. Gabitril makes up the remainder, at about 1% of the GABA analog unique utilizers. The purpose of this graph is to show how quickly Lyrica is making an impact in DoD.

If you turn to page 9 and look at Figure 8, this is our typical utilization slide, which details the numbers of prescriptions dispensed at the MTF, TMOP and Retail Network. It shows that from the period of Feb 2005 to Jan 2006, that there were approximately 52,000 gabapentin prescriptions dispensed each month, 10,000 Lyrica prescriptions (since August 2005), and about 1,000 Gabitril prescriptions.

FDA Indications: Please go back to page 8 in your handout and look at table 5. This table provides a summary of the FDA-approved indications of the GABA analogs, and also provides evidence of efficacy for other indications (so called "off-label" uses). Gabapentin and Lyrica are both approved by the FDA for treating pain caused by shingles (the medical term is post-herpetic neuralgia). As we'll discuss later, there are no published studies with Gabitril in shingles.

Patients with diabetes commonly experience numbness, and dull achy pain in their hands and feet; this is called diabetic nerve pain (or diabetic neuropathy). Lyrica is FDA-approved for treating the nerve pain caused by diabetes. Although gabapentin is not approved by the FDA for treating diabetic nerve pain, there are several studies supporting its use, which we'll discuss later. There are no published studies with Gabitril for diabetic nerve pain.

There are several other types of nerve pain, including pain experienced in patients who have had limbs amputated, or pain caused by spinal cord injury. We've lumped all these other types of

pain together in the category of "other types of nerve pain". This type of pain is important in DoD, given the types of injuries being seen in soldiers returning from Iraq. None of the GABA analogs are FDA-approved for treating other types of nerve pain. However, there are published studies supporting the use of gabapentin in these other types of pain, and there is one small study of Gabitril. However, there are no published studies with Lyrica. The last column shows which GABA analogs are approved for treating seizures in children; they are all approved for treating seizures in adults.

(Data Source): Our relative clinical effectiveness analysis evaluated information about the GABA analogs from published meta-analyses, systematic reviews, and randomized placebo-controlled trials. A review of the published trials of the GABA analogs compiled by a group from the University of North Carolina as part of the Oregon Health & Science University Drug Effectiveness Review Project (OHSU-DERP) was also particularly useful.

As usual, I'm now going to discuss the key points concluded by the Committee and then go back and discuss the details.

1) For treatment of pain caused by shingles or pain caused by diabetes , the DoD P&T concluded that there was no evidence to suggest that gabapentin or Lyrica are more efficacious than the other. For Gabitril, there are no published studies looking at pain associated with shingles or diabetes.
2) For other types of nerve pain, there is published evidence to support efficacy of gabapentin, but only anecdotal (or "word of mouth") evidence to support efficacy of Gabitril, and no published studies with Lyrica.
3) In terms of safety and tolerability issues, Gabitril has been associated with the most side effects. All three GABA analogs should be slowly tapered when therapy is discontinued, rather than abruptly stopped, because there is a risk of causing seizures. For common side effects, Gabitril is more frequently associated with nervousness and tremor, while Lyrica and gabapentin are associated with dizziness, sleepiness (somnolence) and leg swelling (peripheral edema).
4) In terms of FDA-approved indications, there are differences among the GABA analogs, however there are several published studies supporting use for non-FDA approved indications, as seen in table 5.
5) In terms of pediatric uses, gabapentin and Gabitril are both approved for treating seizures in children.
6) In terms of controlled substance scheduling by the Drug Enforcement Agency (DEA), Lyrica is the only product that is a controlled substance, which suggests it has a higher potential for abuse than the non-scheduled drugs.
7) There are differences in the pharmacokinetic profiles (which deals with drug levels achieved in the body) between Lyrica and gabapentin. The linear kinetics with Lyrica have not translated into improved pain relief of Lyrica compared to gabapentin.
8) Lyrica can be dosed twice daily in pain due to shingles, while gabapentin requires three times daily dosing. In pain associated with diabetes, the manufacturer of Lyrica does not recommend twice daily dosing.
9) Lastly, Lyrica is easier to initiate therapy and change doses ("titrate" therapy) than gabapentin, however the onset of pain relief is similar between the two products.

Endpoints: I want to briefly discuss endpoints for pain studies. Pain is a subjective measure since pain tolerance differs between people. The studies that we evaluated for the GABA analogs all used standardized tests to measure pain relief of the products. Many of these pain scales ask a patient to rate their pain on a scale of 1-10, both before and after they receive one of the GABA analogs. Other endpoints that we looked at included the percentage of patients responding to therapy, and the numbers needed to treat. I'll talk about NNT later.

Key question #1 is: What is the relative clinical effectiveness of gabapentin, Lyrica or Gabitril in the treatment of the different types of nerve pain, including pain caused by shingles, diabetic nerve pain, and other types of nerve pain. This question is broken up into three parts.

a) **Post-herpetic neuralgia (Shingles)**: Lets talk about shingles pain first. Look again at table 5 on page 8. There are no published studies evaluating usefulness of Gabitril in treating shingles pain. There are no published trials directly comparing gabapentin with Lyrica for shingles pain. Because of this, the DoD Committee evaluated two placebo controlled trials with gabapentin, and three placebo controlled trials with Lyrica for shingles pain. These studies showed that both gabapentin and Lyrica provided better pain relief than the placebo. Since there are no head-to-head trials with Lyrica and gabapentin, one attempt to try determine how they differ in pain relief is to calculate the "number needed to treat" for each drug. The NNT is the number of patients who need to be treated for one patient to achieve a 50% reduction in pain. For gabapentin, the NNT for shingles pain ranged between 3.4 and 5.1. In other words, for every 3-5 patients treated with gabapentin, you get 1 positive response. For Lyrica, the NNT for shingles pain ranged between 3.3 and 6.3. As you can see, the NNTs are similar and overlap for gabapentin and Lyrica, which suggests that they have similar efficacy for treating shingles pain.

Based on the primary efficacy measures of change in mean pain score at baseline, the percentage of patients responding to therapy, and the NNTs, the Committee concluded that there is no evidence of superiority of either gabapentin or pregabalin in treating pain associated with shingles, when the individual results from the placebo controlled trials are compared. There are no trials evaluating efficacy of Gabitril in pain due to shingles.

b) **Diabetic Peripheral Neuropathy (diabetic nerve pain):** Keep looking at table 5 on page 8 of your handout. There are no trials evaluating efficacy of Gabitril for diabetic nerve pain. There are no head-to-head clinical trials comparing Lyrica with gabapentin for treatment of diabetic nerve pain. Some of the studies that the Committee evaluated included a Cochrane review of four placebo controlled trials with gabapentin; and three placebo controlled trials with pregabalin.

The four trials evaluated in the Cochrane review reported that gabapentin was significantly better than placebo at relieving pain. The NNT to treat for gabapentin was 2.9. For Lyrica, the number of patients needed to be treated (NNT) ranged from 3.4 to 4.0 for the three studies.

Based on the primary efficacy measures of change in mean pain score at baseline, the percentage of patients responding to therapy, and the NNTs, the Committee concluded that there is no evidence of superiority of either gabapentin or Lyrica in treating diabetic nerve pain. There are no trials evaluating efficacy of Gabitril in pain due to diabetes.

c) **Other types of nerve pain:** The P&T Committee evaluated the efficacy of GABA analogs for treating other types of nerve pain syndromes. Keep referring to table 5 on page 8. There is evidence from two studies to support use of gabapentin in other types of nerve pain. One of these studies was in patients with amputee pain. For Gabitril, there is one published trial, but it's difficult to know with certainty how useful Gabitril works for other types of nerve pain since this trial only enrolled 17 patients and ½ of the patients dropped out of the study due to side effects. There are no published studies with Lyrica this time.

The Committee concluded that gabapentin demonstrated modest clinical efficacy for other types of nerve pain, based on two placebo controlled trials. No conclusion can be made concerning the efficacy of Gabitril here, due to limited evidence from one poorly designed study. Lyrica has not been evaluated in other types of neuropathic pain syndromes.

Key question #2: What are the comparative safety issues (serious or life threatening adverse reactions and mild side effects), and tolerability issues (those that may adversely effect compliance) with the GABA analogs?

The Committee assessed the comparative safety and tolerability of gabapentin, Lyrica and Gabitril, including rare but serious adverse effects, common adverse effects, the potential for drug interactions, and safety in special populations.

Serious adverse effects: With regards to serious adverse effects, all three GABA analogs should be gradually tapered when therapy is discontinued, to decrease the risk of causing seizures. Gabitril has been associated with more side effects in the class, including prolonged seizures in patients who did not previously have seizures, and effects on the brain, such as impaired concentration, or speech and language problems. There are reports of sudden unexplained death in patients with epilepsy taking Gabitril or gabapentin; however, it is unknown whether the unexplained deaths were a direct result of gabapentin or Gabitril therapy. Lyrica has not been on the market long enough to determine if sudden unexplained death can occur with it too. Lyrica has been associated with cause elevations in creatinine kinase, and there have been three reports of muscle injury leading to kidney problems (rhabdomyolysis).

Side Effects: The most commonly reported side effects associated with all three GABA analogs include dizziness, somnolence, and general weakness. These adverse effects appear to be dose related (in other words, as you increase the dose, you increase the risk of the side effect), and tend to decrease over time. Based on clinical trial experience, Gabitril appears more commonly associated with nervousness and tremor, while gabapentin and Lyrica are associated the weight gain, dizziness, sleepiness (somnolence) and swelling of the legs (peripheral edema). It is difficult to determine if one GABA analog is more likely to cause these mild side effects (weight gain, dizziness, leg swelling, sleepiness) because we don't have any head to head trials.

One method that the Committee uses to determine differences in side effects or tolerability profiles is to look at the differences between the GABA analogs in the numbers of patients who have to drop out of the clinical trial due to a side effect. Numbers needed to harm (NNH) is another way of measuring adverse events, and for the purpose of this review it was defined as the number of patients being treated with a drug that experienced any adverse effect leading to withdrawal from a study. So, higher numbers mean less people dropping out of a study. NNH

could be calculated for two of the trials assessing pain due to shingles. For gabapentin, the NNH was 11 (which means that for every 11 patients treated, 1 would drop out due to side effects); while for pregabalin the NNH was 4 (for every 4 patients treated 1 would drop out due to side effects). Although the NNH to harm was smaller with Lyrica, which indicates that the drug may be less tolerable than gabapentin, the titration period with Lyrica was faster (over 1 week) compared to the gabapentin trial (over 4 weeks). A longer titration period may have led to a more favorable NNH in the gabapentin trial. In a clinical trial evaluating Lyrica in patients with either shingles pain or diabetic nerve pain where a longer titration schedule was used, the NNH was 11, which is more in-line with the NNH of 11 reported with gabapentin.

Let's move on to Drug interactions: Drug interactions with gabapentin and Lyrica are rare, as these two drugs are not metabolized by the liver. Gabitril is primarily metabolized by the liver, thus drug interactions have been reported when other anticonvulsant drugs are used at the same time, for example, carbamazepine, phenytoin, phenobarbital, primidone.

In summary, the Committee concluded withdrawal seizures occurring with sudden discontinuation of therapy have been reported with all three GABA analogs. Gabitril is associated with infrequent, but serious adverse events. Dizziness and somnolence are the most commonly reported adverse effects with Lyrica and gabapentin, while tremors and nervousness are more commonly reported with Gabitril. Indirect comparisons, based on NNH and the percentage of patients discontinuing therapy due to adverse effects, show only minor differences in tolerability between gabapentin and Lyrica. Gabitril has a greater drug interaction potential compared to gabapentin and Lyrica, due to liver metabolism.

Key question #3 What other factors may influence use of one GABA over another?

Other factors the Committee examined were whether or not a drug had FDA-approval for the different types of pain we've talked about, whether it is indicated for use children, whether it is designated controlled substance by the Drug Enforcement Agency, pharmacokinetic parameters with respect to dose response, frequency of dosing, and the time needed to get to the effective dose (or titration schedules).

a) Controlled Substance Scheduling: Lyrica is the only GABA analog that is a scheduled controlled substance (C-V). This means that there is a slight chance of abuse of the drug. In clinical studies, when Lyrica was abruptly discontinued, some patients reported symptoms of insomnia, nausea, headache, or diarrhea, suggesting dependence. Due to the schedule V status, no more than 5 refills of Lyrica can be obtained in a 6-month period. Gabapentin and gabitril are not controlled substances.

b) **Pediatrics:** For pediatric patients, gabapentin is approved in for use for epilepsy in patients as young as three years old. Gabitril is approved for use in patients as young as 12 years old for treatment of epilepsy. Lyrica has not been studied in pediatric patients.

c) **Pharmacokinetics:** Gabapentin exhibits non-linear pharmacokinetics; what this means is that as the dose of gabapentin is increased, less of the drug is absorbed into the body, and the response rate might by erratic at higher doses. In contrast, pregabalin exhibits linear pharmacokinetics, which means that as you give larger doses, more of the drug is absorbed and available in the body. However, a linear dose response has not resulted in significantly improved

pain relief when Lyrica is administered at higher doses (600mg/d) vs. lower doses (300 mg/d). In fact, the manufacturer of Lyrica does not recommend giving more than 300 mg/d for treating diabetic nerve pain.

d) **Dosing frequency:** Lyrica can be dosed twice daily for treatment of pain associated with shingles, while gabapentin requires three times a day dosing. For pain associated with diabetes, both Lyrica and gabapentin require three times a day dosing. Unpublished trials with Lyrica available from the FDA website showed that twice a day dosing of Lyrica in patients with diabetic nerve pain was not better than placebo, and therefore is not recommended by the manufacturer.

e) **Titration schedules:** The dosage initiation schedule for Lyrica is less complex and requires a shorter time period than the dosage titration recommended with gabapentin. However, improvements in pain relief have been seen within 1-2 weeks of starting therapy with both gabapentin and Lyrica. In other words, an easier dosage titration schedule has not translated into improved pain relief with Lyrica. Also recall that under the safety section, a faster titration schedule can lead to more patients dropping out of the study. One benefit of an easier titration schedule is that it may result in improved patient compliance.

With regards to these other factors, the Committee concluded that Lyrica is the only GABA analog that has restrictions in prescribing due to its controlled status. The linear pharmacokinetic profile of Lyrica has not resulted in significant improvement in efficacy with higher doses. Lyrica may potentially have improved patient compliance compared to gabapentin, due to an easier titration schedule and twice a day dosing in patients with shingles. However, three times a day dosing is recommended for pregabalin in patients with diabetic nerve pain. There is no published data evaluating the efficacy of Lyrica in children.

Provider Opinion: A survey of DoD providers ranked gabapentin first in terms of clinical efficacy for treating all types of nerve pain, due to more personal clinical experience, compared with Lyrica and Gabitril. Lyrica was ranked second in terms of clinical efficacy, primarily due to lack of clinical experience, but providers did prefer ease of titration and twice daily dosing in shingles. The majority of providers' therapeutic strategy would include a trial of gabapentin first, followed by Lyrica if therapy with gabapentin was not successful. Gabitril was rarely used in nerve pain, and if it was chosen, it was added on to other drugs, and was not used as an alternative to gabapentin or Lyrica.

Overall, the Committee concluded that (1) the efficacy of gabapentin and Lyrica for treating pain associated with either diabetes or shingles appears similar; (2) gabapentin is the only GABA analog that has shown modest efficacy in treating other types of nerve pain based on published clinical trials; (3) there is insufficient data regarding the efficacy of Gabitril in patients with nerve pain syndromes to make definitive conclusions; (4) the safety and tolerability profiles of gabapentin and Lyrica are more favorable compared to Gabitril; (5) there appear to be only minor differences in the tolerability profiles of gabapentin and Lyrica, when evaluating the incidence of somnolence, dizziness, and peripheral edema; (6) there are minor differences in other factors between the drugs, including use in pediatrics, pharmacokinetic profiles, titration schedules, onset of effect, and controlled substance status. Overall the Committee agreed that

based on clinical usefulness alone, there is no basis for classifying any of the GABA analog as non-formulary.

Maj Wade Tiller will now present the cost effectiveness analysis for the GABA analog drugs.

Relative Cost Effectiveness:

The P&T Committee evaluated the relative cost-effectiveness of the GABA analogs 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).

The first step in determining the relative cost-effectiveness of the selected agents in this class was to conduct a cost-analysis to calculate the total weighted average cost per day of treatment for each agent. The second step was to conduct the appropriate pharmacoeconomic analysis taking into account the conclusions of the clinical review. A cost-effectiveness analysis was conducted using data from three well-designed randomized controlled trials to determine the relative cost-effectiveness of agents within the GABA analog therapeutic class. The trials studied Lyrica and gabapentin in diabetic peripheral neuropathy (diabetic nerve pain) and pain associated with shingles (post herpetic neuralgia). The principal outcome of interest was the mean reduction in weekly pain scores at the 12th week, and the primary cost input for the model was the weighted average cost per day of therapy across the MHS.

Results of the cost-effectiveness analysis (CEA) showed gabapentin at doses of up to 2400 mg to be the most cost effective GABA analog in the treatment of neuropathic pain with the lowest average cost per patient over twelve weeks of treatment, and no clinically significant differences in outcomes.

The results of the above analyses were then incorporated into a Budget Impact Analysis (BIA), which accounted for other factors and costs associated with a potential decision regarding formulary status of GABA analogs within the UF. These factors included: market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the budget impact analysis further confirmed the results of the CEA. Gabapentin was found to be the most cost-effective GABA analog overall in the treatment of neuropathic pain.

Conclusion: The P&T Committee agreed (16 for, 0 against, 0 abstained, 2 absent) with the relative cost-effectiveness analysis of the GABA analogs presented. The P&T Committee concluded that gabapentin was the more cost effective GABA analog for the treatment of neuropathic pain. The cost-effectiveness of Gabitril was also considered, and it was determined that nothing would be gained clinically or economically by making Gabitril non-formulary.

Based on the results of the two analyses, the P&T Committee concluded that Lyrica was much more costly, and had similar relative clinical effectiveness compared to gabapentin in both neuropathic pain and partial seizures. Gabitril also had similar relative clinical effectiveness in partial seizures as compared to gabapentin and Lyrica. However, due to its low utilization, and small, static market share, it was felt that Gabitril contributed minimally to the amount spent in this drug class. Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the GABA analogs, and other relevant

factors, the P&T Committee recommended that Lyrica be classified as non-formulary under the UF, with gabapentin and Gabitril remaining on the UF.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (14 for, 2 against, 0 abstained, 2 absent) to recommend non-formulary status for Lyrica, with gabapentin and Gabitril maintaining formulary status on the Uniform Formulary at the formulary cost share.

Implementation Plan: The P&T Committee recommended an effective date no later than the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

COMMITTEE ACTION: The P&T Committee recommended (15 for, 0 against, 0 abstained, 3 absent) an effective date no later than the first Wednesday following a 60 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

I'll discuss the quantity limit recommendations for the new drug, Nexavar.

Background: One of the duties of the DoD P&T Committee, in addition to determining if a medication requires a prior authorization, is to decide if a drug should have a limited quantity of tablets or limited days supply. We call this "quantity limit determination." There are several potential reasons why a quantity limit is applied, for instance safety reasons (an example of this is triptan medications for treating migraine headaches where if you exceed the recommended dose you are at risk for side effects; or a drug with a high risk of side effects where the patient would have to stop therapy); cost issues; inappropriate use (an example of this is drugs used to treat growth hormone deficiency, as these drugs are sometimes used in appropriately in children who are short in stature but don't have growth hormone deficiency); or stockpiling (example asthma inhalers). This is the first time that the P&T Committee has recommended a quantity limit for a newly approved medication in the past year, thus it is the first time that you have seen this as members of the BAP.

Nexavar place in therapy and prognosis of Renal Cell carcinoma: We're now going to discuss the issues with the recommended quantity limits for Nexavar (sorafenib). Nexavar is a new oral drug that is approved to treat patients with kidney cancer (renal cell carcinoma). One of the advantages of the drug is that since it can be taken orally. Nexavar is a potential replacement for previous treatments for kidney cancer which required hospitalization in the Intensive Care Unit, and had many serious side effects, including infection, dangerously low blood pressure, and death. Patients diagnosed with kidney cancer have a bleak prognosis; only about 50% of patients are still alive 2 years after diagnosis. Nexavar is promising in that it has shown some benefit in delaying the progression of the disease, but studies are still being conducted by the FDA.

Nexavar ADRs: Nexavar can cause side effects such as nausea, vomiting and diarrhea. It can also cause blisters on the soles of the feet and some very distinctive painful rashes, which sometimes requires the drug to be discontinued. Other side effects are increases in blood pressure and changes in lab values.

Other new cancer drugs and cost / availability issues: I'd like to briefly mention some additional information about these new cancer drugs, since there are several that are expected to be approved by the FDA in the upcoming year, which the DoD P&T Committee will be evaluating. There are several new drugs for cancer that have been approved by the FDA. Some of these drugs are given by the IV route, while others are available in oral formulations. These drugs work within the cancer cell to prevent the tumor from growing or prevent the tumor from getting an adequate blood supply. Because these drugs are so specialized, they cost $10s of thousands of dollars for a year's treatment. Several companies have special programs set up to obtain the drug; these are called "restricted distribution" programs. The restricted distribution programs are often the only way to obtain the drug, and there is also help with insurance reimbursement. Nexavar costs $26.89/per tab, and 4 tablets are needed daily, at a cost of $107.56/day. This translates to a cost of $3,227 /month, and $38,000 per year.

Nexavar restricted distribution: Nexavar has a restricted distribution program. The drug isn't currently available from the mail order pharmacy (TMOP) however, the drug company, Bayer, is

trying to work with DOD to allow the drug to be available through the mail. The restricted distribution program developed by Bayer allows a 30 day supply to be dispensed each month. **Recommendation and Rationale**: The DoD P&T Committee recommended quantity limits of 120 tablets per 30 days, which is a 30-day supply, in the Retail Network (this is the same amount that the restricted distribution program allows anyway). The Committee also recommended a quantity limit of 180 tablets per 45 days (a 45-day supply) in the TMOP, if Nexavar becomes available from the TMOP. The usual recommendations for the TMOP are to dispense a 90-day supply of drug. The reasons why a quantity limit was recommended for Nexavar is because there is a high risk that a patient might not be able to continue therapy, either because they die during therapy or develop a side effect that would make them discontinue the drug. This recommendation is consistent with past decisions by the Committee, as there are similar quantity limits for other oral drugs used to treat leukemia and lung cancer.

Committee Action: The DoD P&T Committee voted (15 for, 0 against, 1 abstained, 2 absent) to recommend that Nexavar have quantity limits of 180 tablets per 45 days from the Tricare Mail Order Pharmacy (TMOP) should the product become available from the TMOP, or 120 tablets per 30 days from the Retail Network (TRRx).