Uniform Formulary Beneficiary Advisory Panel (BAP)

Meeting Summary
January 10, 2008
Washington, D.C.

Panel Members Present:

- Robert Washington, Fleet Reserve Association, Chairman
- Kathryn Buchta, Health Net Federal Services
- John Class, Military Officers Association of America
- Deborah Fryar, Military Coalition
- Rance Hutchings, Uniformed Services Family Health Plan
- Lisa Le Gette, Express-Scripts, Inc.
- Kimberly Owens, Military Alliance
- 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 8:30 A.M.

MAJ Watson indicated this meeting of the Panel has been convened to review and comment on the recommendations of the Department of Defense (DOD) Pharmacy and Therapeutic (P&T) Committee meeting held during November 2007 in San Antonio, TX.

Agenda

The agenda for this meeting of the Panel is:

- Opening remarks and public comments
- Review and discussion of P&T Committee recommendations for drugs in the following drug classes:
  - Adrenergic Blocking Agents (ABAs)
  - BPH-Alpha Blockers (BPH-ABs)
  - Targeted Immunomodulatory Biologics (TIBs)
  - Designated Newly Approved Drugs
    - Exforge
    - Vyvanse
    - Lybrel
- Review and discussion of Recommendation for Reclassification of Amlodipine
- Review and discussion of non-formulary agents to be re-evaluated
- Additional information item: FY 2007 Uniform Formulary (UF) performance
- Wrap-up comments

Opening Remarks

MAJ Watson stated that Title 10 United States Code (U.S.C.) section 1074g requires the Secretary of Defense to establish a DOD UF 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 by the Director, TRICARE Management Activity (TMA) 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 the effective dates for changing drugs from "formulary" to "non formulary" status must be reviewed by the Director before making a final decision.
- To hold quarterly meetings in an open forum. 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 prepare 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 the Director, TMA (Dr. Casscells).

As guidance to the Panel regarding this meeting, MAJ Watson said the role of the BAP 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 chartered functions 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. The materials provided to the Panel are available on the TRICARE website.

Detailed minutes of this meeting are being prepared. The BAP minutes, the DOD P&T Committee meeting minutes and Dr. Casscells'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 briefly reviewed housekeeping considerations pertaining to the meeting and introduced the Beneficiary Advisory Members present. He also announced the death of one of the Panel Members, Dr. Jeffrey Lenow, since the last meeting. MAJ Watson spoke highly of Dr. Lenow's service and valuable contributions to the BAP.

Opening Comments by the Chairman

On behalf of the Panel, Chairman Washington also recognized with appreciation Dr. Lenow's many and valuable contributions to the BAP's deliberations since its establishment and noted how much they would be missed.

Private Citizen Comments

MAJ Watson opened the meeting for private citizen comments. There was no response from individuals present at the meeting.

Presentation of Drug Class Reviews

Major Wade Tiller began the presentation summarizing the P&T Committee's deliberations at its November 2007 meeting.

[Insert script, pages 1 and 2]

Review of the Adrenergic Beta-Blocking Agents (ABAs) Drug Class

Clinical Effectiveness Review

CDR Matt Carlberg provided the BAP with a summary of the P&T Committee's clinical effectiveness review of the Adrenergic Beta-Blocking Agents (ABAs) drug class.

[Insert script, pages 3 and 4]

Cost Effectiveness Review

Major Tiller next discussed the cost effectiveness review conducted for this drug class.

[Insert script, page 5, paragraphs 1 through 3]

P&T Committee Action and Recommendations

Major Tiller informed the Panel of the P&T Committee's recommendations regarding the agents in the ABA drug class.

[Insert script, page 5, paragraph 4]

P&T Committee Physician Perspective

The physician's perspective was provided by Lt Col (Dr.) Brian Crownover. He informed the Panel that there was no debate or controversy on this topic among the Committee. It was relieved that no "deal breaker" offers had to be considered. As clinicians, the Committee was interested in keeping the low priced generics available, but they were also able to keep Toprol XL and Coreg on formulary as heart failure agents. The Committee also was happy that Coreg ER came in at a very aggressive price that allowed it to be kept on formulary as well. These factors meant that the MHS would be able to keep all of the agents it has been using and that nothing would be excluded.

Panel Questions

The Panel had no questions for the presenters in this drug class.

Panel Discussion of P&T Committee Formulary Recommendations for the Adrenergic Beta-Blocking Agents (ABA) Drug Class

The Chairman read the P&T Committee's recommendations regarding the Adrenergic Beta-Blocking Agents (ABAs) drug class:

> "In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that:
>
> atenolol (Tenormin, generics), atenolol-chlorthalidone (Tenoretic, generics), metoprolol (Lopressor, generics), metoprolol succinate (Toprol XL, generics), propoanolol (Inderal, generics), propranolol-HCTZ (Inderide, generics), propranolol extended release (Inderal LA, generics), timolol (Blocadren, generics), timolol/HCTZ (Timozide), bisoprolol (Zebeta, generics), bisoprolol/HCTZ (Ziac, generics), nadolol (Corgard, generics), nadolol/bendroflumethiazide (Corzide, generics), acebutolol (Sectral, generics), betaxolol (Kerlone, generics), penbutolol (Levatol, generics), carvedilol IR (Coreg IR, generics), and carvedilol extended release (Coreg CR) be designated formulary on the UF."

There was no further Panel discussion of the recommendation.

Panel Vote on Formulary Recommendation for the Adrenergic Beta-Blocking Agents (ABA) Drug Class

Mr. Washington called for the Panel vote on the Adrenergic Beta-Blocking Agents (ABAs) drug class. The vote was:

9 Concur, 0 Non-Concur, 0 Abstentions.

Adrenergic Beta-Blocking Agents (ABAs) Drug Class Implementation Recommendations

Because all agents in the ABA drug class were recommended for inclusion on the Uniform Formulary, no implementation recommendations were necessary.

Review of the BPH Alpha Blockers (BPH-ABs) Drug Class

Clinical Effectiveness Review

CDR Carlberg next briefed the Panel on the results of the Committee's clinical effectiveness review of the BPH Alpha Blockers (BPH-ABs) drug class.

[Insert script, pages 6 and 7]

Cost Effectiveness Review

Major Tiller presented the results of the cost-effectiveness review conducted for this drug class.

[Insert script, page 8, paragraphs 1and 2]

P&T Committee Action and Recommendations

Major Tiller also discussed the P&T Committee's recommendations and the justification for them in the BPH-AB drug class.

[Insert script, page 8, paragraph 3 through page 9]

P&T Committee Physician Perspective

Lt Col Crownover, providing the BAP with the P&T Committee's physicians' perspective on the recommendations for this drug class, said there was again little debate or controversy about the recommendations. Important factors were the substantial relative price increase for Flomax over Uroxatral. Additionally, Flomax is already non-formulary. Finally, the automated PA criteria minimize the "hassle factor" for providers. His own experience was that making Flomax non-formulary met with some initial grumbling from providers because it was first to market and has a lot of name recognition. But the Military Health System (MHS) has already made the switch and most providers and patients are doing very well with it.

Panel Questions

Ms. Fryar asked when Flomax was made non-formulary. The answer was February 2006.

Mr. Hutchings asked about related products for females. Major Tiller said he would provide that information.

Mr. Partridge asked how many people are currently using Flomax and was told there are roughly 35,000 MHS users now. Mr. Partridge then asked about the basis for their usage, since Flomax is non-formulary. The answer provided was that users either could be paying the $22 co-pay or they could have met the medical necessity criteria.

Mr. Hutchings asked whether the term "adequate trial" period would be defined in the step therapy. He noted that his organization has had experience with patients who use an agent for a short period of time (e.g., three days) then want to go back to Flomax. For other drugs, specific time periods have been set. Dr. Crownover replied that the matter was discussed in the meeting and the problem was acknowledged, but that the specific time period to be included is still being evaluated by the PEC. A PEC staff member provided information by telephone in response to Mr. Hutchings question to the effect that it is technically impossible to do what he suggests. MAJ Watson clarified by stating that there is no way the MHS can set a minimum time patients would have to use a drug in order to qualify for making a change to another agent.

Dr. Schlaifer asked for an explanation of what happens during the implementation period for a drug that is already non-formulary. Major Tiller said the implementation period is an opportunity for TMA to get information out to the beneficiaries through the various channels already established. TMA has also recently begun to send out letters to the beneficiaries about change decisions, although that might be difficult to do for this particular class. Also, the new automated prior authorization process takes time to coordinate with ESI.

Dr. Schlaifer asked what is changing from the "old" non-formulary status to the "new" non-formulary status in this case. Major Tiller said the change is the automated prior authorization process.

Mr. Hutchings said he didn't see why a 60-day period is needed unless ESI needs 60 days. Dr. Crownover said someone with knowledge of the ESI process provides significant input to the Committee's deliberation regarding the implementation period to provide a "reality check" on what can and cannot be done.

Ms. Le Gette asked about figure 5 on page 11 of the handout, where a box at the bottom indicates "PA Approved for 12 Months." She noted that previous practice had been to approve an open-ended PA as long as the patient continued taking the second-tier medication. She asked if this was a change specific to this class. Major Tiller said he would have to go back and look at it before he could answer the question.

Mr. Class asked for further explanation, noting that usage initially dropped when the agent went to third tier but is now creeping back up. He asked if the PA is in response to the increased usage. Major Tiller answered that when the class was reviewed again, the Committee realized that there was now an opportunity to go after the Uniform Formulary Voluntary Rebate, which didn't apply in the previous decision. From earlier experience, the Committee has learned that

most folks can do extremely well if only one agent is available when there is a high degree of therapeutic interchangeability. The prior authorization process with step therapy is a very powerful tool that is used in the commercial sector to influence both patient and provider behavior in moving patients toward preferred agents. In this class, PEC tested several different condition sets (with and without PAs in place and one with all agents on the Uniform Formulary). The preference would be to have both agents available on the Uniform Formulary. However, there was a significant difference in MHS expenditures under a step therapy process. In the end, the Committee found the best value to be in having one agent on the formulary with a step therapy process for Flomax. Mr. Class asked what the anticipated drop in usage would be if Flomax were made available as second tier with step therapy. Major Tiller answered that the scenario had not been evaluated.

Mr. Hutchings commented that the step therapy has worked well for his organization's patients because it gave them a "heads up" about how to avoid the $22 co-pay. It was nice for them not to get stuck with the higher co-pay suddenly. That was especially true is this class, where Flomax is very well known and Uroxatral was not.

Mr. Class said the chart makes it looks like putting Flomax in the third tier didn't do much to the usage levels. His question is whether the earlier results justify the step therapy and how necessary is it to maintain Flomax on the third tier. Major Tiller noted that the Panel would be receiving a presentation after the drug class reviews to clarify the results of earlier step therapy decisions and their effectiveness in migrating patients toward preferred agents.

Panel Discussion of P&T Committee Formulary Recommendations for the BPH Alpha Blockers (BPH-ABs) Drug Class

Chairman Washington next read the P&T Committee's recommendations for agents in the BPH Alpha Blockers drug class:

"In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that:

1) Alfuzosin (Uroxatral) be maintained as the uroselective formulary AB, and that terazosin (Hytrin, generics) and doxazosin (Cardura, generics) be maintained as the non-uroselective fomulary ABs; and 2) tamsulosin (Flomax) be classified as non-formulary under the UF with a PA requiring a trial of alfuzosin (Uroxatral) for new patients.

BPH Alpha Blockers — PA Criteria. The P&T Committee agreed that the following PA criteria should apply to tamsulosin (Flomax). Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

   a) The patient has received a prescription for either tamsulosin (Flomax) or alfuzosin (Uroxatral) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

b) The patient has tried alfuzosin (Uroxatral) and had an inadequate response or was unable to tolerate treatment due to adverse effects.

c) Treatment with alfuzosin (Uroxatral) is contraindicated.

The Committee noted that in order for a patient to receive tamsulosin (Flomax) at the formulary cost-share, both the PA and medical necessity (MN) criteria must be met. If the PA criteria are met without an approved MN determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved PA for tamsulosin (Flomax) would NOT automatically receive it at the formulary cost-share." There was no further Panel discussion of the recommendations in this drug class.

Panel Vote on Formulary Recommendation for the BPH Alpha Blockers (BPH-ABs) Drug Class

The Beneficiary Advisory Panel vote on the BPH-AB drug class recommendations was:

8 concur; 0 non-concur; 1 abstain.

As a comment, Mr. Class said he would like the PEC to look at what the PA will do to change behavior and whether the result would warrant moving Flomax back from third tier onto the formulary. His reason is based on reliance on the medical necessity process for approval, which is tougher than most people think it is. Also people are starting to get charged for bringing in more forms for physicians to fill out.

Panel Discussion of P&T Committee BPH Alpha Blockers (BPH-ABs) Drug Class Implementation Recommendations

The Chairman read the P&T Committee's implementation recommendations for the BPH-AB drug class:

"The P&T Committee recommends an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA."

There was no additional BAP discussion of the implementation period recommendation.

Panel Vote on Implementation Recommendation for the BPH Alpha Blockers (BPH-ABs) Drug Class

The Beneficiary Advisory Panel vote on the BPH-AB drug class implementation recommendations was:

7 concur; 1 non-concur; 1 abstain.

Review of the Targeted Immunomodulatory Biologics (TIBs) Drug Class

Clinical Effectiveness Review

The next drug class review -- Targeted Immunomodulatory Biologics (TIBs) – was presented by CPT Josh Napier.

[Insert script, pages 11-14]

CPT Napier added that the P&T Committee vote on the clinical effectiveness recommendations was 16 for, 0 opposed and 1 absent.

Cost Effectiveness Review

Major Wade Tiller again presented the cost effectiveness review conducted for this drug class.

[Insert script, page 15, first two full paragraphs]

P&T Committee Action and Recommendations

Major Tiller also discussed the P&T Committee's TIB recommendations and their justification.

[Insert script, page 15, last three paragraphs through page 17]

P&T Committee Physician Perspective

Lt Col Crownover again provided the Panel with the P&T Committee's physicians' perspective on the recommendations for this drug class. He emphasized that the drug class has small volume with very high cost: $10,000 to $20,000 per patient per year. The Committee reached consensus that Humira had clinical effectiveness and efficacy across all of the multiple indications. Some concern was expressed about adopting a policy that tends to be overly exclusive of Enbrel given its high prescription volume. These concerns were addressed by the proposed medical necessity criteria that include approval for Enbrel if the patient is already on it and if "changing to a formulary agent would incur unacceptable risk." This will allow Enbrel for current patients who are stable and also approve Enbrel for juvenile rheumatoid arthritis, which is currently an FDA-approved indication but for which Humira does have pending studies.

Panel Questions

Ms. Owens asked for clarification on the trials that were done between Enbrel and Humira — that they were based only on placebos and that there were no head-to-head clinical trials of efficacy. CPT Napier confirmed that there were no head-to-head trials available. He also said that the placebo almost always included methotrexate. The comparisons would be the TIB alone, the TIB plus methotrexate versus methotrexate placebo.

Mr. Hutchings asked about the Prior Authorization (PA) recommendations and why the recommendations for Enbrel didn't include step therapy using Humira. He said he assumes that anyone who is filling out an Enbrel PA is a "new start." Major Tiller said there is already a Prior

Authorization requirement in place. While this is not really "step therapy" the patient will have to meet the time period requirements to be approved for treatment. The form will clearly state which agents are formulary agents and which are not. Mr. Hutchings said his concern was that the patient would fill out a form for Enbrel only to have to go back again and fill out a form for Humira. Major Tiller said there would only be one form and it will have a check box.

Mr. Class said it is hard for him to visualize how the PA criteria would work and asked if a flow chart was available similar to those for the other drug classes. Major Tiller answered that the Committee didn't change the PA criteria and they are already posted on the website.

Dr. Schlaifer asked about the pending Food and Drug Administration (FDA) decision (for Humira with psoriasis and JRA) and whether there is a timeline available. CPT Napier said they didn't have one but that the trials have been out for some time and are currently under review. He doesn't know exactly what the holdup is but the evidence looks pretty good.

Dr. Schlaifer asked whether, if the FDA came back with a surprise and didn't approve the decision, the P&T Committee would revisit its recommendation at that time. CPT Napier said the PA criteria would allow Enbrel to be used for psoriasis in that case. Dr. Schlaifer asked if the PA criteria currently on the form specify that the agent has to be used for an FDA indication. CPT Napier said the PA criteria don't require on-label prescribing — that isn't usually part of the PA. The criteria are that it has to be prescribed by a rheumatologist and that the patient does have the disease that the agent is being prescribed for.

Mr. Hutchings noted, regarding implementation, that patients who are notified of the change will be calling back to a rheumatologist, which is likely to create a large burden at the MTFs. His concern is whether the recommendation allows enough time for this process to occur. Major Tiller said he is unsure how willing a provider would be to change therapy on a patient that is stable, so he doesn't foresee a huge influx of patients trying to get changed over, although he recognizes that it is a possibility. He also said that, since the establishment of the Uniform Formulary two and a half years ago, MTFs have been very creative and successful in establishing non-formulary requests within the facility and he believes they will be able to address the situation if it comes up.

Ms. Owens agreed with concerns expressed about the 90-day implementation period. She is especially concerned that the age and mobility of the patients using these agents will affect their ability to obtain the needed medical necessity determinations. She doesn't think 90 days is enough; 120 days should be allowed. Major Tiller said one member of the P&T Committee is a rheumatologist and his opinions were expressed and taken into consideration.

Mr. Partridge asked whether Enbrel and Humira are generally prescribed in a similar ratio for each of the conditions or whether one is favored over the other. CPT Napier said that about 50 percent of the current users are taking Enbrel for RA, but that for new users the shift is toward Humira.

Panel Discussion of P&T Committee Formulary Recommendations for the Targeted Immunomodulatory Biologics (TIBs) Drug Class

Chairman Washington read into the record the P&T Committee's recommendations for agents in the Targeted Immunomodulatory Biologics (TIBs) drug class:

"Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the TIBs, and other relevant factors, the P&T Committee, based on its collective professional judgment, voted to recommend that Humira, Raptiva and Amevive be maintained as formulary on the UF and that Enbrel and Kineret be classified as non-formulary under the UF.

The P&T Committee recommends that 1) no changes be made to PA criteria for Enbrel, Humira, Kineret and Raptiva; 2) that a PA be required for Amevive under the PA criteria outlined above; and 3) that the effective date for the Amevive PA be timed to coincide with that established for the UF decision in this class."

Ms. Owens stated she has a problem with Enbrel being made non-formulary. She has had personal experience working with patients who use Enbrel for this debilitating disease and there is a difference between it and Humira. Many are on Medicare and have to pay the various differences. Often they have tried Humira and it isn't effective for them. She recognizes the cost is high but the number of users is low. She intends to non-concur on this basis.

Mr. Hutchings commented that Enbrel has a very good name, whereas Humira does not necessarily have that. But if Humira doesn't work for the type of patients Ms. Owens has worked with, medical necessity can be used to decrease the co-pay.

Mr. Partridge commented that he is concerned about the number of people on Enbrel who would have to change, so he will also non-concur.

Panel Vote on Formulary Recommendation for the Targeted Immunomodulatory Biologics (TIBs) Drug Class

The Beneficiary Advisory Panel vote on the formulary recommendations for the Targeted Immunomodulatory Biologics (TIBs) drug class was:

5 concur; 4 non-concur.

Mr. Class commented that with the FDA approval pending he would prefer not to move Enbrel to the third tier only to have to re-evaluate it and change back in a short time. He would prefer that both beneficiaries and providers have a choice.

Mr. Washington commented that the Panel's non-concurring votes were based on the recommendation to make Enbrel non-formulary.

Mr. Hutchings said he wants to make sure that the PA form is clear that Humira requires a lower co-pay.

Panel Discussion of P&T Committee Implementation Recommendations for the Targeted Immunomodulatory Biologics (TIBs) Drug Class

The Chairman read the implementation recommendations for this drug class:

"The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA."

Several panelists expressed concern about the adequacy of the recommended 90-day implementation period. Ms. LeGette said a minimum of 60 days is required for notification, which leaves people only 30 days to respond. Mr. Class asked whether MHS has reached the point where individuals will automatically be notified and was assured that MHS has a notification mechanism in place. Ms. Owens repeated her belief that the implementation period should be at least 120 days to allow patients the time to go through the PA process.

Panel Vote on Implementation Recommendation for the Targeted Immunomodulatory Biologics (TIBs) Drug Class

The BAP vote on the 90-day implementation period recommendation for the TIBs drug class was:

4 concur; 5 non-concur.

The BAP comment was that non-concurrence was based on a preference for 120 days versus the recommended 90 days.

Recently-Approved Drugs in Previously-Approved Drug Classes

Major Tiller introduced the discussion of new drugs in previously-reviewed drug classes.

[Insert script, page 18, first paragraph]

(1) Valsartin/Amlodipine (Exforge)

Clinical Effectiveness Review

[Insert script, page 18 – paragraphs headed "Background," "Utilization," and "Exforge."]

Cost Effectiveness Review

[Insert script, page 18, last two paragraphs].

P&T Committee Action and Recommendations — Exforge

[Insert script, page 19 first three full paragraphs]

P&T Committee Physician Perspective

Lt Col Crownover commented that combination drugs are great – practitioners love combinations because they decrease the pill burden. But MHS already does have available an ACE combo agent with an amlodipine (Lotrel). ACEs and ARBs are very similar in a lot of

ways, and MHS also has ARBs. Three have been added to the formulary, including a heart failure ARB (candesartan) which is similar to the valsartan agent in Exforge. Those are available individually. If Exforge had been in the ballpark price-wise, the Committee would love to have had it. But there are several very strong alternatives in this category.

Panel Questions

The BAP had no questions of the presenters regarding the Exforge review.

Panel Discussion of Exforge Formulary Recommendation

Chairman Washington read the P&T Committee's recommendation:

> "Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of Exforge, and other relevant factors, the P&T Committee, based on its collective professional judgment, voted to recommend that Exforge be designated as non-formulary on the UF."

Dr. Schlaifer asked if 60 days is the quickest that the recommendation can be implemented. Mr. Hutchings asked if the recommendations couldn't be implemented earlier and the use a "grandfather" period to notify patients. His concern is that the number of users will double in the next 60 days and he would like to avoid problems in notifying additional new users. MAJ Watson explained that the recommendation is what it is, but if the Panel believes a shorter period is merited, that should be included in the comments. The precedent has been that, when there is a new drug to market, it's better to make the implementation period shorter because the co-pay change affects fewer people that way.

Ms. LeGette said that, in a perfect world, their commercial recommendation is to give the beneficiaries 30 days to make the change (for doctors' appointments, etc.). Another 30 days is required to make address changes and such. So the 60 day period sounds about right for her organization.

Mr. Hutchings asked how quickly the use of this drug is growing. The answer was there isn't yet a lot of data to show how fast the usage is growing, but most of the usage has developed in the past couple of months. Mr. Hutchings then wondered whether it is even worth notifying the patients because there may be even more patients on Exforge by then and the notification would be after the fact, if at all.

Ms. Fryar asked whether new medications that come out like this will automatically be put on the Uniform Formulary. Dr. Crownover said when new drugs come out they are, by definition, on the Uniform Formulary until the Committee acts. That is why the PEC monitors the marketplace and looks for agents likely to be impact players in terms of dollars and might represent significant financial outlays. Major Tiller added that all new drugs don't fit this pattern. He cited Coreg CR as an example, where the Committee valued the drug at the price submitted by the manufacturer and elected to keep the drug on the Uniform Formulary. The drugs being used today were offered the same opportunity to submit pricing for Uniform Formulary status. So the outcome isn't automatic; every drug is reviewed on a case-by-case basis as to both the clinical and relative cost effectiveness.

Panel Vote on Exforge Formulary Recommendation

The BAP vote on the Exforge formulary recommendation was:

9 concur; 0 non-concur.

Panel Discussion of Exforge Implementation Recommendation

The Chairman read the P&T Committee's implementation recommendation for Exforge:

> "The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA."

Mr. Hutchings asked if it would be possible to separate the points of service so that implementation would be 30 days in the Mail Order program and the MTFs. MAJ Watson said MHS generally doesn't do that. Co-pay changes are made across all points of service to maintain consistency. The BAP could recommend immediate implementation if it wants to — changing the co-pay to $22 is very simple. But the mechanics involved in notifying beneficiaries and the call centers takes longer.

Ms. LeGette said the text of the changes is posted on the web 30 days in advance of the actual change date so a lot of people are getting their advance notice that way.

Panel Vote on Exforge Implementation Recommendation

The BAP vote on the Exforge 60-day implementation recommendation was:

9 concur; 0 non-concur.

(2) Lisdexamfetamine (Vyvanse)

Vyvanse Clinical Effectiveness Review

The clinical effectiveness review for the new drug Vyvanse was presented by Dr. Dave Meade.

[Insert script, page 19, last two paragraphs through page 20, first five paragraphs]

Vyvanse Cost Effectiveness Review

Major Tiller presented the cost effectiveness evaluation.

[Insert script, page 20, header at paragraph 6 and next two paragraphs]

P&T Committee Action and Recommendations — Vyvanse

[Insert script, page 20, last paragraph through page 21, first three paragraphs]

P&T Committee Physician Perspective

Lt Col Crownover characterized the deliberations on this drug as a "a bit of a head scratcher." It has similar benefits and similar costs. During the discussion it became clear that if Vyvanse weren't added to the UF, nothing would be lost because the NHS already has agents on the formulary that do exactly what this one does. In fact, Adderall XR is the exact same type of agent and it is expected to go generic within the next year. If the Committee were to allow folks to migrate over to the new agent, the system would lose potential cost savings when Adderall XR does go generic. Although no one can accurately predict the generic market, Adderall is already on formulary and is likely to go generic. Consequently, the Committee had a fairly broad consensus about making the new drug non-formulary.

Panel Questions

Ms. Owens asked whether the Committee discussed the claim that the new product had less potential for abuse. Dr. Crownover said the Committee examined the data behind that marketing claim and found it to be very tenuous. Dr. Schlaifer clarified that the "lack of abuse" claim had to do with "lack of addiction," which is totally different. Ms. Owens said she just wanted to make sure it was taken into account. Dr. Crownover assured her that it was and that Committee carefully examined the evidence behind those marketing claims.

Mr. Class commented that he was having a lot of difficulty with this recommendation. It seems like going down a dangerous path: saying an agent hasn't been determined to be clinically better or worse and costs about the same, but we're going to put it on the third tier because we have a medication that is potentially going to go generic. His view is this would be the time to use a PA or step therapy as opposed to putting the agent on third tier. He can't see where this approach is going to end and it appears as though an agent is being put on the third tier without regard to either clinical effectiveness or cost.

Major Tiller agreed that in situations like this, prior authorization or step therapy requirements might be applicable. However, using step therapy in this case would require PEC to do a review of the entire therapeutic class again, which they will probably do anyway in the near future. Additionally, the Uniform Formulary rule clearly states that the Committee may elect not to add something to the Uniform Formulary if it does not represent a clinically meaningful or therapeutic advantage.

Dr. Crownover added that practitioners have a wide range of agents they can use for ADHD. The Committee members didn't feel as though they were losing anything clinically by making Vyvanse non-formulary.

Panel Discussion of Vyvanse Uniform Formulary Recommendation

Chairman Washington read the P&T Committee's formulary recommendation for the new drug Vyvanse:

> "Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of lisdexamfetamine (Vyvanse), and other relevant factors, the P&T Committee, based on its collective professional judgment,

voted to recommend that lisdexamfetamine (Vyvanse) be designated as non-formulary on the UF. This recommendation was primarily based upon the determination that lisdexamfetamine (Vyvanse) offers no clinically meaningful therapeutic advantage over other once daily ADHD stimulants."

There was no further discussion of the formulary recommendation.

Panel Vote on Vyvanse Formulary Recommendation

The Beneficiary Advisory Panel vote on the Vyvanse formulary recommendation was:

4 concur; 5 non-concur.

Mr. Class asked that a comment be included to the effect that since there is no clinical advantage or disadvantage and not much difference in cost, this agent appears to be a good candidate for step therapy rather than third tier.

Panel Discussion of Vyvanse Implementation Period Recommendation

The Chairman read the implementation period recommendation:

"The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA."

Ms. Owens commented that her personal experience trying to get an appointment at an MTF suggests that a 60-day implementation period is too short and thinks 90 days would be better.

Panel Vote on Vyvanse Implementation Recommendation

The Panel vote on the implementation period recommendation for Vyvanse was:

6 concur; 3 non-concur.

(3) Ethinyl Estradiol 20 MCG/Levonorgestrel 90 MG (Lybrel)

Clinical Effectiveness Review

CPT Napier presented the clinical effectiveness review for the third new drug, Lybrel.

[Insert script page 21, header at paragraph five and remainder of page through first two full paragraphs of page 22]

Cost Effectiveness Review

Major Tiller presented the cost effectiveness evaluation for Lybrel.

[Insert script, page 22, paragraphs three and four]

Committee Action and Recommendations — Lybrel

Major Tiller informed the Panel of the Committee's recommendations regarding this new drug.

[Insert script, page 22 paragraph five through page 23, first two paragraphs]

P&T Committee Physician Perspective

Lt Col Crownover explained that the concept of using oral contraceptives on a continuous use basis is not new. MHS has been doing that off label for a long time with standard monophasic contraceptives. As with Seasonale and Seasonique, the packaging is pretty but the Committee didn't value the price of this convenience. The formulary already include monophasics that offer a comparable mix of hormones. The only advantage offered by Lybrel is the pretty and convenient packaging.

Panel Questions

Ms. Owens commented that the normal prescription is for 12 refills for a normal menses cycle. She asked if there was a problem with the doctor writing a prescription for longer term use when the person hits the end of their 12 refills so they don't have to go back. Dr. Crownover said the monophasic pill pack includes 21 active days. The 90-day regimen includes four packs instead of three, so it hasn't been an issue. Additionally, there is a check block on the form for "continuous use."

Mr. Hutchings asked about the packaging. Major Tiller replied that it looks like a Pez dispenser with a "turn and click" mechanism. It is a 30-day wheel that the patient rotates under the opening to dispense the pill.

Mr. Class asked about the dissenting votes on the Committee. Major Tiller said two members preferred a 90-day implementation period.

Panel Discussion of Lybrel Uniform Formulary Recommendation

Chairman Washington read the P&T Committee's formulary recommendation for Lybrel:

> "Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the M20 EE contraceptive agents, and other relevant factors, the P&T Committee, based on its collective professional judgment, voted to recommend that Lybrel (Ethinyl Estradiol 20/levonorgestrel 0.09) be designated as non-formulary on the UF."

There was no further discussion of the formulary recommendation.

Panel Vote on Lybrel Formulary Recommendation

The Benficiary Advisory Panel vote on Lybrel was:

9 concur; 0 non-concur.

Panel Discussion of Lybrel Implementation Recommendation

The Chairman read the Lybrel implementation period recommendation:

> "The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRICARE Retail Pharmacy Network (TRRx), and at the Military Treatment Facilities (MTFs) no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TMA."

There was no further discussion of this topic.

Panel Vote on Lybrel Implementation Recommendation

The Panel vote on the Lybrel implementation recommendations was:

9 concur; 0 non-concur.

Presentation on Status of Amlodipine (Norvasc, Generics) On the Uniform Formulary

Major Tiller next presented to the Beneficiary Advisory Panel additional recommendations from the P&T Committee regarding the previously reviewed drug amlodipine (Norvasc and generics). The presentation included both clinical and cost effectiveness evaluations and Uniform Formulary and implementation recommendations.

[Insert script, page 23, paragraphs five through nine]

P&T Committee Physician Perspective

Lt Col Crownover told the Panel that the Committee recognized that Norvasc has always been a good drug. However, when under patent, it couldn't be offered at competitive pricing. Now as a generic with generic level pricing, the Committee views reclassification to Uniform Formulary status as a "no brainer" decision and was eager to add it.

Panel Discussion of Amlodipine Formulary Recommendation

The Chairman read the P&T Committee recommendation:

"In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the Dihydropyridine Calcium Channel Blockers, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that amlodipine (Norvasc, generics) be reclassified as formulary on the UF."

Mr. Partridge complimented the P&T Committee on their quick action on this agent.

Panel Vote on Formulary Recommendation

The BAP vote on the Norvasc formulary recommendation was:

9 concur; 0 non-concur.

Panel Discussion of Implementation Period Recommendation

Chairman Washington read the implementation period recommendation:

"The P&T Committee recommends an effective date as the date the Director, TMA, signs the minutes."

Mr. Hutchings asked if it could be done quicker.

Panel Vote on Norvasc Implementation Recommendations

The Panel vote on the Norvasc implementation recommendation was:

9 concur; 0 non-concur

Presentation on Re-Evaluation of Non-Formulary Agents

Major Tiller then presented to the Panel a proposed new procedure for re-classifying drugs from non-formulary to formulary status. A list of the drugs to be reevaluated using this new procedure, and on which the BAP is voting today, is attached as Appendix 2.

[Insert text, pages 24-26, first two paragraphs]

Mr. Class asked if there is a brief summary or flow chart available on the process so that he can be sure he is stating matters correctly when he sends information out to his beneficiaries. A PEC staff member said that such a document would be prepared.

P&T Committee Physician Perspective

Lt Col Crownover said that the proposed reevaluation process is a perfect example of one of the ways the Committee depends upon the members of the PEC. The Committee wants to recognize this. He said the Committee is certainly in favor of using this work by the PEC to recognize

opportunities and act on them. There was no dissent at all about the proposal and the Committee strongly endorsed the process.

Panel Questions

Ms. Owens asked whether the information would be marketed to beneficiaries by TMA or just released to providers and hope there is a migration. Major Tiller said the list includes drugs approved for evaluation, but stressed that they have not yet been evaluated. Ms. Owens asked what would happen after the evaluation and was told that on the event of approval, the co-pay would be reduced but that letters would not be sent. Ms. Owens suggested that the change should be publicized on the website for the population at large, not just provided to the BAP.

Panel Vote on List of Medications Presented

Major Tiller explained that the Beneficiary Advisory Panel is being asked to comment on and approve the list of medications to be reevaluated (Appendix 2). The process has already been approved; the concept now is to pre-approve the list so that once the drugs become available generically they can be added back on the Uniform Formulary with further action by the BAP. In future meetings, the changes will be presented as "information only" items.

Chairman Washington called for a Panel vote on the list of "Non-Formulary Agents for Re-Evaluation" (see Appendix 2). The Panel vote was:

9 concur; 0 non-concur.

Information Presentation on Results of 2007 Uniform Formulary Decisions

Dave Meade next gave the Beneficiary Advisory Panel a slide presentation on the performance effects of Uniform Formulary decisions implemented over the past 18 months. The review encompassed the following eight drug classes:

- Antilipidemics II
- 5-ARIs
- ARBs
- PPIs (including the automated PA on omeprazole or esomeprazole)
- Opthalmic Glaucoma Agents
- Newer Sedative Hypnotics
- ADHD/Narcolepsy Agents, and
- LIP1s.

He said the data are presented in terms of 30-day equivalents (to balance out the different amounts that can get dispensed at different points of service). Automated prior authorizations include only the retail (TRRx) and mail order (TMOP) points of service. Data also do not include numbers for the voluntary rebate (UF VARR), which means that the prices are conservative. The data look back 6 months prior to the Statin decision to get flat-line data for use in developing trends and looking at how the trends change as the decision progresses.

The first data slide (#5) showed non-formulary prescriptions dispensed for all three points of service (POS) combined. The chart shows that the ARBs and the PPIs are now coming down (after the signing and implementation dates), but most of the other classes are pretty much flat-lined. Slide #6 shows the same data broken out for the retail sector alone. This data shows no change immediately after the signing date, but a noticeable decline in the use of non-formulary agents after the implementation date. (especially noticeable in the PPIs and RBs, but also the Newer Sedative Hypnotics). Slide #7 shows the data broken out for MTFs only. The data show that the decline in usage by MTFs begins immediately after signing because MTFs are supposed to have as many folks as possible moved off on non-formulary agents by the implementation date. The data for mail order (slide #8) largely mimics what happens in the retail sector. By point of service (slide #9), the data show that the MHS uses significantly more non-formulary agents in the retail sector and mail order than in the MTFs. But by statute, the MTFs can't have these agents available unless someone meets the medical necessity criteria. At the other points of service, people can still get the drug if they pay the higher co-pay. Overall (slide #10) the decline in usage of non-formulary drugs amounts to about 26 percent (mostly in PPIs and ARBs). Slide #11 shows comparative data in the cost per day of non-formulary agents by point of service. The data for the eight agents (again excluding VARR dollars) shows a decrease of 14 percent.

The factors affecting utilization and cost (slide #12) include a combination of UF decisions, the impact of a drug going generic, and implementation of the automated PA. To refine the data on impacts, four classes were looked at individually: statins (the number one drug class until six months ago); the Newer Sedative Hypnotics (NSH) (the first class with the automated PA); Proton Pump Inhibitors (PPIs) which have an automated PA and also took over as the number one drug class; and attention deficit hyperactivity disorder (ADHD), where a larger number of drugs were not made non-formulary.

Statin utilization for all points of service (slide #13) shows usage of Zocor (and generics), Lipitor, Vytorin and others compared with Crestor, the non-formulary agent. In the retail sector (slide #14) the data show a decline in Lipitor and a corresponding increase in Zocor and generics. This was a well-publicized generic offering with the insurance companies in particular waiting for generic Zocor to come out. Vytorin and Zetia trail both in usage, followed by Crestor. At the MTFs (slide #15), Zocor and generics is number one by a large margin. MHS had an exclusive contract for Zocor for a significant amount of time, so this result was expected. Vytorin usage has increased, and MHS is happy about that. The results here are just what MHS wanted to see. For mail order (slide #16), the usage pattern has remained about the same. There is a little bit of a rise in Crestor because the mail order program is being used for non-formulary drugs instead of the MTFs, which is what was supposed to happen. The statins average cost per day for all points of service (slide #17) show a drop of 33 percent on average (Caduet and Crestor are the non-formulary drugs in this class) with the biggest drops occurring between the signing and implementation dates (when the co-pay changed). Lipitor is the least cost effective agent on the UF and the dips in it, Vytorin and Zetia are the result of negotiated prices. Pravachol and Zocor prices dropped because the drugs went generic. The data also show the importance of making sure that there is an adequate supply available when a drug goes generic so that prices don't start jumping around. The next slide (#18) looked at whether the decisions to make something non-formulary were making so that beneficiaries can't get the drugs that they need. The slide shows that statin usage went from 1.1 million 30-day equivalents to 1.25 30-day equivalents between May 2006 and November 2007 — an increase of 12 percent. Accordingly, it appears that beneficiaries are able to get what they need.

The Newer Sedative Hypnotics (NSH) utilization for all points of service (slide #19) shows that Ambien use is going up, Ambien CR use went up and is starting to come down, Lunesta use is about flat as are the other two products. The drop in Ambien CR is attributable first to the MTF usage and second to the automated PA. In the retail sector (slide #20), the Ambien CR use also dropped once the automated PA went into effect. In the MTFs (slide #21) Ambien was the preferred agent, so Ambien CR began dropping markedly after the signing date. There has been a slight rise in Lunesta, which is the preferred agent after Ambien. In the mail order sector (slide #22) there has been growth across the board, probably due to the availability of non-formulary agents. The average cost per day slide (#23) shows a significant drop, starting when Ambien went generic. For the class as a whole, the average cost per day has dropped by 47 percent and continues to go down (again excluding VARR dollars for Lunesta). Slide #24 shows there has been a 22 percent increase in NSH drugs over the past six months, indicating that the PA requirement has not led people not to use the drug class.

Proton Pump Inhibitor (PPI) usage for all points of service (slide #25) shows very significant growth in Nexium usage since the signing date (Nexium went from non-formulary status to being a preferred agent). There has also been a significant drop off in non-formulary agents (particularly Aciphex) and there has been an ever sharper decrease since the automated PA went into effect. In the retail sector, Nexium usage has also increased, partly because letters were sent out (the frist such usage) and partly because of an aggressive marketing campaign by Nexium. There has been a significant drop in the use of other agents after the PA requirement took effect. The MTF slide (#27) shows the sharp drop in the use of Aciphex (previously the preferred agent) and Prevacid and a corresponding increase in the use of Nexium. The mail order data (slide #28) largely mirrors that for the retail network. In terms of average cost per day (slide #29), the cost of Aciphex has tripled as the price of Nexium has decreased, raising the average cost for the class as a whole. The average cost per day for Omeprazole has also begun dropping as more competing drugs have come on the market. Across all points of service, there has been an 11 percent increase in usage (slide #30) over the past 18 months.

In the ADHD class for all points of service (slide #31), Concerta was and remains number one and is number one in the MTFs. About a year ago, Concerta lost its patent protection but has not gone generic because of production considerations resulting from a special manufacturing process. Accordingly, there has been no price change and no utilization change in Concerta. Adderall is number two overall and number one in the retail network. It will continue to have patent protection for about a year. Strattera is number three in terms of usage. All of these drugs are required on the UF for clinical reasons. Drops and increases in usage shown on the chart are attributable to seasonal fluctuations (summertime). The average cost per day for the ADHD drugs (slide #32) is pretty flat — an eight percent increase overall. The overall trend over the past 18 months (slide #33) shows a 10 percent increase (with the seasonal fluctuations noted above).

In conclusion, Dr. Meade stressed that only eight classes were discussed with only an 18 month time frame and VARR savings not included. Overall the data show:

- Significant savings with aggressive formulary management.
- Growth in the utilization of each class. Formulary management techniques do not appear to be inhibiting the use of the benefit.

- Step therapy is guiding beneficiary utilization to the most desired drug products.
- At times, the medical requirements and class makeup prevent significant movement within the class (and also prevent significant savings).

Questions

Asked about overall savings since the inception of the Uniform Formulary, Dr. Meade indicated that the result would be a "real tight graph" crowded with data, but that he would see what can be devised.

A Panel Member asked if the utilization figures include all medications dispensed, including those in combat zones and overseas. Dr. Meade said that PEC doesn't have access to those numbers, although not all classes get used overseas (e.g., ARBs and glaucoma).

Closing Comments

Major Tiller thanked the Panel for its attentiveness and turned the meeting over the MAJ Watson.

With no further discussion or questions from the Panel, MAJ Watson adjourned the meeting at 12:00.

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.

- ABAs — Adrenergic Blocking Agents (a drug class)
- ABs — Alpha blockers
- ACE inhibitors — Angiotensin-converting Enzyme inhibitors (a drug class)
- ADHD — Attention deficit hyperactivity disorder
- APR — Automated Profile Review
- ARB — Angiotensin Receptor Blocker (a drug class)
- BAP — Uniform Formulary Beneficiary Advisory Panel (the "Panel" referred to above)
- BCF — Basic Core Formulary
- BIA — Budget Impact Analysis
- BPA — Blanket Purchase Agreement
- BPH-ABs — Benign Prostatic Hypertrophy – Alpha Blockers (a drug class)
- CCBs — Calcium Channel Blockers (a drug class)
- CEA — Cost-effectiveness analysis
- C.F.R — Code of Federal Regulations
- CMA — Cost-Minimization Analysis
- CR — Controlled Release (a drug formulation)
- DEA — U.S. Drug Enforcement Administration
- DFO — Designated Federal Officer
- DHP — Dihydropyridine (a type of CCB)
- DOD — Department of Defense
- 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
- GHD — Growth hormone deficiency
- GSA — Growth Stimulating Agents (a drug class)
- HMO — Health Maintenance Organization
- IR — Immediate Release (a drug formulation)
- JRA — Juvenile rheumatoid arthritis
- LIP-2 — Antilipidemic agents (a drug class)
- LM — Leukotriene Modifiers (a drug class)
- MHS — Military Health System
- MN — Medical Necessity
- MTF — Military Treatment Facility

- NA — Newer Antihistamines (a drug class)
- NIH — National Institutes of Health
- NNH — Number Needed to Harm
- NNT — Number Needed to Treat
- OTC — Over the counter
- PA — Prior Authorization
- P&T Committee — DOD Pharmacy and Therapeutics Committee
- PDTS — Pharmacy Data Transaction Service
- PEC — DOD Pharmacoeconomic Center
- POS — Point of Service
- RA — Rheumatoid arthritis
- RAAs — Renin Angiotensin Antihypertensives (a drug class)
- RCTs — Randomized Control Trials
- SGA — Second generation newer antihistimines
- TIBs — Targeted Immunomodulatory Biologics (a drug class)
- TMA — TRICARE Management Activity
- TMOP — TRICARE Mail Order Pharmacy
- TNF — Tumor necrosis factor
- TRRx — TRICARE Retail Pharmacy Program
- UF — DOD Uniform Formulary
- U.S.C. — United States Code
- VA — U.S. Department of Veterans Affairs
- VARR — Uniform Formulary Voluntary Rebate

Table 5 — Non-Formulary Agents for Re-Evaluation

10 Jan 2008 BAP Meeting

(Major Tiller) Good Morning,

I'm Major Wade Tiller, Deputy Director of the PEC. Joining me today from the PEC Clinical Operations staff are CPT Josh Napier, our army physician, CDR Matt Carlberg, our Navy physician, and Dr. Dave Meade, one of our clinical pharmacists. One of our DoD P&T Committee members, Lt Col Brian Crownover, is also here to give the physician perspective and comment on the recommendations made by the Committee. Also joining us today from TMA are RADM McGinnis, the Director of Pharmaceutical Operations, CAPT Blanche, Director of Pharmacy Programs and LTC Kelly Director of the PEC.

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).

CPT Napier, CDR Carlberg, Dr. Meade, 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 the Uniform Formulary based upon both relative clinical effectiveness and 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. These 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 adrenergic beta-blocking agents, alpha blockers for BPH, and the targeted immunomodulatory biologics; and three new drugs in previously reviewed classes.
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.
5) The DoD P&T Committee's recommendation regarding UF status of amlodipine (Norvasc), a currently non-formulary medication that recently became generically available at a substantially reduced cost.
6) The DoD P&T Committee's recommendation concerning a process to be followed to facilitate reclassification of non-formulary medications when they become generically available and cost effective relative to similar drugs on the UF.

We've given you a handout which includes the Uniform Formulary recommendations for all the drugs discussed today; this is found in Table 1, on pages two and three. There are tables and

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

CDR Carlberg will now present the adrenergic beta-blocking agents relative clinical effectiveness evaluation.

ADRENERGIC BETA-BLOCKING AGENTS (ABAs) CLINICAL EFFECTIVENESS

***(CDR Carlberg)*: Background and members in the class:** The relative clinical effectiveness evaluation was conducted by Dr. Angela Allerman, a PEC clinical pharmacist, and me. As you can see from Table 1 on page 2 of your handout, the adrenergic beta-blocking agent or ABA drug class was subdivided into two general categories for purposes of the clinical effectiveness evaluation. These categories were ABAs evaluated (but not necessarily FDA-approved) for treating chronic heart failure (HF) and ABAs not evaluated for HF. Several of these ABAs have been on the market for decades, and are used primarily for high blood pressure and include combinations of ABAs with diuretics such as hydrochlorothiazide.

All of the ABAs are available in generic formulations except carvedilol extended (or controlled) release (Coreg CR), which was introduced to the market in March 2007. Generic formulations of carvedilol immediate release (Coreg) and metoprolol succinate extended release (Toprol XL) were launched in mid- to late-2007.

Relevance to MHS and Utilization: Expenditures for the ABAs exceeded $140 M in FY 2007, placing the class in the top 15 MHS classes.. Of the ABAs not evaluated for HF, atenolol (the generic for Tenormin) and metoprolol tartrate (the generic for Lopressor) accounted for the great majority of use—about 225,000 30-day equivalent prescriptions per month for atenolol and 100,000 for metoprolol tartrate. There was relatively little use of other non-heart failure ABAs.

Utilization of the ABAs evaluated for HF is shown as Figure 1 on page 8 of your handout. As you can see, metoprolol succinate (as either branded Toprol XL or its generic) accounts for 150,000 to 160,000 prescriptions per month, followed by carvedilol immediate release (mostly as brand name Coreg) at about 60,000 prescriptions per month. You can also see initial use of generic carvedilol immediate release and the new extended version of carvedilol (Coreg CR).

Indications: Cardiovascular indications evaluated by the Committee included high blood pressure, angina (chest pain) and chronic heart failure.

- All ABAs and ABA/diuretic combinations are approved for the treatment of high blood pressure, with the exception of sotalol, which is used for the treatment of cardiac arrhythmias.
- Two ABAs are FDA-approved to reduce the risk of death from chronic heart failure: carvedilol (both Coreg immediate release and its generics as well as Coreg CR) and metoprolol succinate (Toprol XL). Coreg IR and Coreg CR are also approved to reduce the risk of death following heart attack in patients with left ventricular systolic dysfunction. Bisoprolol (Zebeta) is not FDA-approved for treating heart failure, but has evidence of a mortality benefit from one clinical trial.
- Niche uses for ABAs include sotalol for cardiac arrhythmias, labetalol for severe high blood pressure and use in pregnancy, and propranolol for various non-cardiovascular uses (such as migraine prevention).

Summary of the Clinical Effectiveness Evaluation

With respect to efficacy:

1. Labetalol was not considered to be clinically comparable to carvedilol (Coreg or Coreg CR), despite exhibiting alpha-blocking properties, since it has not been evaluated for chronic HF.

2. Sotalol was not considered to be clinically comparable to the other ABAs, since it is not FDA-approved for treating chronic HF.
3. For treating hypertension, there is no evidence of clinically relevant differences in efficacy between the ABAs, when titrated to effect (that is, after doses are adjusted to provide maximum reduction in blood pressure with minimum adverse effects).
4. For treating chronic HF, metoprolol succinate extended release (Toprol XL and generics), carvedilol immediate release and extended release (Coreg and Coreg CR), and bisoprolol (Zebeta) have been shown to reduce mortality. Bisoprolol is not FDA-approved for this indication. Based on the available evidence, there are no data to suggest that there are differences in the reduction in mortality between these three medications.

With respect to safety and tolerability:

5. Clinically relevant differences in the safety and tolerability profile of the ABAs are not apparent. There is insufficient evidence to determine if there are clinically relevant differences in the adverse event profile between carvedilol immediate release (Coreg) and carvedilol extended release (Coreg ER).

Overall

6. Despite the convenience of once daily dosing of carvedilol extended release (Coreg CR), there is no compelling clinical evidence to suggest a benefit of Coreg ER over carvedilol immediate release (Coreg).

Overall Relative Clinical Effectiveness Conclusion: The DoD P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the clinical effectiveness conclusions stated above.

Major Tiller will now discuss cost-effectiveness for the ABAs.

ADRENERGIC BETA-BLOCKING AGENTS (ABAs) COST EFFECTIVENESS

(Maj Tiller) The relative cost-effectiveness evaluation for the ABAs was conducted by Eugene Moore. For the economic evaluation, the ABAs were functionally divided into three groups, based on predominant use: 1) ABAs for hypertension, 2) ABAs for chronic HF, and 3) ABAs used for other conditions (e.g., labetalol for severe hypertension and sotalol for arrhythmias).

Since the relative clinical effectiveness evaluation concluded that: 1) for high blood pressure, ABAs are highly clinically interchangeable when titrated to effect, and 2) for chronic HF, there is insufficient evidence to suggest clinically significant differences between agents or immediate vs. extended release formulations, cost minimization analyses (CMAs) were conducted for each of the subgroups. The agents were evaluated on their weighted average cost per day of therapy across all three points of service.

Relative Cost Effectiveness Conclusion: Based on the results of the CMAs, and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

1) All ABAs used primarily to treat hypertension are cost effective, with atenolol (Tenormin, generics), metoprolol tartrate (Lopressor, generics), and propranolol IR (Inderal, generics) being the most cost-effective.
2) All of the ABAs with clinical evidence for heart failure are cost effective, with carvedilol IR (Coreg IR, generics) being the most cost-effective agent.
3) The ABAs for other indications, sotalol (Betapace, generics), sotalol AF (Betapace AF, generics), and labetalol (Normodyne, generics) are cost effective.

A budget impact analysis (BIA) was performed to examine the potential budget impact of a UF scenario with carvedilol ER designated as formulary on the UF versus a one with carvedilol ER designated as non-formulary on the UF. The BIA showed that the scenario that designated carvedilol ER as formulary on the UF resulted in significantly lower MHS expenditures versus the scenario which designated carvedilol ER as non-formulary on the UF.

COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ABAs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstention, and 2 absent) to recommend that all ABAs be designated formulary on the UF.

LtCol Crownover will now provide the physician perspective from the meeting.

(LtCol Crownover) *(Whatever you're going to say)* That concludes the ABA presentation. CPT Napier, Major Tiller and I will gladly answer any questions that you may have.

(Major Tiller) Now we'll move on to the alpha blockers for BPH clinical effectiveness evaluation.

BPH ALPHA BLOCKERS (BPH-ABs) CLINICAL EFFECTIVENESS

(CDR Carlberg) **Background:** The relative clinical effectiveness evaluation for the alpha blockers used for the treatment of benign prostatic hypertrophy (BPH) was conducted by Dr. Julie Liss, one of the PEC clinical pharmacists, and LtCol Jim McCrary, the Air Force physician at the PEC. If you look at the bottom of Table 1 on page 2 of your handout, you'll see that the class includes four agents: terazosin (Hytrin, generics), doxazosin (Cardura, generics; Cardura ER), alfuzosin ER (Uroxatral), and tamsulosin (Flomax). Tamsulosin (Flomax) is currently non-formulary under the UF. All four agents are FDA-approved for treating the signs and symptoms of BPH (urinary difficulties caused by progressive enlargement of the prostate and obstruction of the urethra, most commonly seen in men over 50 years of age).

Pharmacology: The BPH-ABs can be divided into the uroselective agents (Uroxatral and Flomax) and non-uroselective agents (terazosin and doxazosin) based on whether they preferentially bind to alpha-1 receptors found in the prostate or whether they affect alpha receptors throughout the body. The uroselective agents are associated with a generally lower incidence of adverse effects such as dizziness and drops in blood pressure upon standing compared to the uroselective agents, which historically have been used to treat high blood pressure.

Relevance to MHS and Utilization: Expenditures for the BPH-ABs were about $135 M in FY 2007, placing the class in the top 15 MHS classes by expenditure. Figure 2 on page 8 of your handout shows the relative utilization of the BPH-ABs by number of prescriptions, including changes that have occurred since the class was last reviewed by the Committee in August 2005. As you can see, designating Flomax as non-formulary resulted in an initial decrease in use across the system, followed by a gradual increase. Uroxatral utilization markedly increased after Flomax was designated non-formulary in August 2005. Use of the two non-uroselective agents, terazosin and doxazosin, has remained steady.

Summary of the Clinical Effectiveness Evaluation

With respect to efficacy:

1. Based on randomized placebo-controlled trials, terazosin (Hytrin, generics), doxazosin (Cardura, generics), tamsulosin (Flomax), and alfuzosin (Uroxatral) were found to produce clinically significant and comparable symptom improvements when compared to placebo.
2. Based on limited head-to-head trials and indirect comparisons between the agents, existing evidence does not support clinically significant differences in efficacy between alfuzosin (Uroxatral) and tamsulosin (Flomax).

With respect to safety and tolerability:

3. There appear to be few differences in the incidence of adverse effects with alfuzosin (Uroxatral) and tamsulosin (Flomax), based on placebo-controlled trials and limited comparative data. Both agents are well tolerated. The most common adverse events are related to dilation of blood vessels (dizziness, weakness/fatigue, headache, and drops in blood pressure).
4. Major differences in withdrawal rates due to adverse events have been reported during clinical trials with the uroselective agents (Flomax and Uroxatral; 4-10%) vs. the non-

uroselective agents (terazosin and doxazosin; 8-20%). Withdrawal rates reported in clinical trials were low overall for Flomax and Uroxatral.

5. The package labeling for Uroxatral contains cautions for QT prolongation effects. The effect of Flomax on the QT interval has not been studied
6. Uroxatral is contraindicated for use with drugs that potently inhibit hepatic metabolism by the cytochrome P450 3A4 isoenzyme, such as ketoconazole (Nizoral), itraconazole (Sporanox), and ritonavir (Norvir). Flomax has potential drug interactions with cimetidine and warfarin.
7. Doxazosin (Cardura, generics; Cardura XL) should be used with caution in men with hepatic failure. Uroxatral is contraindicated in men with moderate to severe hepatic impairment (Child-Pugh categories B and C), whereas Flomax may be used in men with moderate hepatic dysfunction without the need for dose adjustment.
8. Package labeling for all four BPH-ABs contains information regarding a potential increase in the risk of intraoperative floppy iris syndrome (IFIS), a rare complication of cataract surgery. Consultation with an ophthalmologist is recommended prior to cataract surgery for patients receiving Uroxatral and Flomax.

Overall:

9. The non-uroselective BPH-ABs, (terazosin and doxazosin) have a low degree of therapeutic interchangeability with the uroselective agents (Uroxatral and Flomax) in terms of safety/tolerability, due to higher withdrawal rates during clinical trials and a higher incidence of vasodilatory effects seen with the non-uroselective agents.
10. Uroxatral and Flomax have a high degree of therapeutic interchangeability; either drug could be expected to meet the needs of the majority of DoD BPH patients requiring an uroselective agent.
11. Review of the clinical literature since 2005 does not add substantial new information or support changes in current clinical practice for the treatment of lower urinary tract symptoms in men with BPH, or for safety profiles between the uroselective BPH-ABs.
12. Based on clinical issues alone, there are no compelling reasons to classify any of the BPH-AB agents as non-formulary under the UF.

Overall Relative Clinical Effectiveness Conclusion - The P&T Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) to accept the clinical effectiveness conclusions stated above.

Major Tiller now will discuss the relative cost effectiveness of the BPH-ABs.

BPH ALPHA BLOCKERS (BPH-ABs) COST EFFECTIVENESS

(Major Tiller) The relative cost effectiveness evaluation for the BPH-ABs was conducted by LTC Chris Conrad, an Army clinical pharmacist stationed at the PEC. Given the overall clinical conclusion that there was insufficient evidence to suggest that the uroselective BPH-AB agents differed with regard to efficacy, safety, tolerability, or clinical outcomes data in the treatment of BPH, a CMA was performed to compare the relative cost effectiveness of potential UF scenarios for the two uroselective agents. The CMA compared the weighted average cost per day of treatment for each potential UF scenario across all three points of service.

Relative Cost Effectiveness Conclusion: Based on the results of the CMA and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that:

1. The most cost effective UF scenario was the one that designated Uroxatral as the single uroselective agent on the UF and BCF (with Flomax designated as non-formulary) and included a prior authorization (step therapy) process that would require all new users of an uroselective BPH-AB to complete an adequate trial of Uroxatral.
2. The next most cost effective UF scenario was the one that designated Uroxatral as the single uroselective agent on the UF and BCF (with Flomax designated as non-formulary), but did not require prior authorization for new users of Flomax. However, under this UF scenario, the weighted average cost per day of therapy increased by 53% over the most cost-effective UF scenario.
3. Any scenario that included tamsulosin on the UF was more costly based on the weighted average cost per day of therapy compared to baseline (what DoD pays today).

COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the BPH-ABs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 2 absent) to recommend that: 1) alfuzosin (Uroxatral) be maintained as the uroselective formulary BPH-AB, and that terazosin (Hytrin, generics) and doxazosin (Cardura, generics) be maintained as the non-uroselective formulary BPH-ABs; and 2) tamsulosin (Flomax) be classified as non-formulary under the UF with a PA requiring a trial of alfuzosin (Uroxatral) for new patients.

NF Justification:

The P&T Committee recommended that Flomax be classified as non formulary under the UF, with prior authorization required for new users of uroselective BPH-AB agents. The Committee's recommendation was based on the following:

1) Results of the clinical effectiveness evaluation did not support clinically significant differences in efficacy or incidence of adverse effects between the two uroselective agents (Uroxatral and Flomax).
2) Availability of Uroxatral on the UF meets the clinical needs of the vast majority of DoD patients for an uroselective agent. Minor clinical differences between the two uroselective agents with regard to the potential for drug interactions and use in patients with hepatic failure are unlikely to affect a large number of patients and can be adequately addressed by the medical necessity process.

3) The results of the cost effectiveness analysis showed any scenario that placed Flomax on the UF would increase costs for DoD. Of the two possible scenarios that designated Flomax as non-formulary, the scenario that included a prior authorization (step therapy) requiring all new users of an uroselective BPH-AB to try Uroxatral showed about a 50% reduction in costs compared to no such requirement.

COMMITTEE ACTION: PA CRITERIA / STEP THERAPY – The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) the following PA criteria for Flomax. Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

   a) The patient has received a prescription for either Flomax or Uroxatral at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days. This represents the automated part of the process, which is often referred to as "step therapy." Please see Figures 4 and 5 on pages 10 and 11 of your handout for a visual explanation of this process.

2) PA criteria if automated criteria are not met. These criteria are intended to make Flomax available to patients who have not been treated with a uroselective product in the last 180 days, but who require treatment with Flomax rather than Uroxatral because:

   a) They have tried Uroxatral in the past and had an inadequate response or were unable to tolerate treatment due to adverse effects.

   b) Treatment with Uroxatral is contraindicated.

COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (14 for, 1 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday following a 60-day implementation period in the TRICARE Mail Order Pharmacy (TMOP) program and TRRx, and at the MTFs no later than a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

The Committee member casting the one opposing vote cast preferred a 90-day implementation period.

Since Flomax is currently non-formulary under the UF, no beneficiaries will incur increased copays as a result of the recommendation. On an annual basis, about 43,000 new users presenting prescriptions for Flomax would be required to try Uroxatral or validate medical necessity for Flomax.

MTFs will not be allowed to have Flomax on their local formularies. MTFs will be able to fill non-formulary requests for Flomax only if both of the following conditions are met:

1) The prescription must be written by a MTF provider, *and*

2) MN is established. MTFs may (but are not required to) fill a prescription for Flomax written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

LtCol Crownover will now present the DoD P&T Committee's perspective.
(LtCol Crownover) *(Whatever you're going to say)* That concludes the BPH-AB presentation, CDR Carlberg, Major Tiller, and I will now gladly answer any questions you may have.

(Major Tiller) Next on the agenda is the Targeted Immunomodulatory Biologics (TIBs) clinical effectiveness evaluation.

TARGETED IMMUNOMODULATORY BIOLOGICS (TIBs) CLINICAL EFFECTIVENESS

(CPT Napier) **Background:** The clinical evaluation of this class was performed by Dr. Shana Trice, a PEC clinical pharmacist, and me. As you can see on page 3 of your handout, the TIB class includes five medications covered as part of the DoD pharmacy benefit: adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel), efalizumab (Raptiva), and alefacept (Amevive). All of these are injected subcutaneously (under the skin) except for Amevive, which may be given intra-muscularly or by intravenous (IV) injection.

If you will now turn to page 9 of your handout, table 7 lists FDA-approved indications and frequency of administration for the TIBs. It also includes three similar biologic agents that are not part of the pharmacy benefit because they must be given IV: abatacept (Orencia), infliximab (Remicade), and rituximab (Rituxan). The IV agents were included in the TIB evaluation for comparative purposes only. I'd like you to particularly note Remicade, which works by the same mechanism of action as Enbrel and Humira and in many respects directly competes with these two medications.

Indications and Administration

As you can see from Table 7, the TIBs are used for a variety of rheumatological, dermatological, and gastrointestinal conditions. Based on an analysis of DoD prescriptions and diagnostic codes over a six-month period (Jan to June 2007), the most commonly treated condition treated with TIBs in DoD is rheumatoid arthritis (RA). About 73% of TIB patients are being treated for RA. Other conditions include plaque psoriasis (15%), psoriatic arthritis (7%), ankylosing spondylitis (4%), as well as Crohn's disease, juvenile rheumatoid arthritis, and ulcerative colitis (all less than 1% each). In most cases the TIBs are indicated as treatment for moderate to severe cases of these conditions, usually following an inadequate response to initial therapy with other medications. In rheumatological conditions such as RA, they are frequently given along with other so-call disease modifying drugs, such as methotrexate.

Three of the five agents are approved by the FDA for a single condition and are rarely used for other conditions. These include Amevive and Raptiva for plaque psoriasis and Kineret for RA. Enbrel and Humira are approved for multiple indications. The red "P"s listed in Table 7 for Humira represent potential new indications currently under review by the FDA.

I'd also like you to note the frequency of administration for these medications. Enbrel is typically given once weekly by subcutaneous injection for most indications, while Humira is given every other week or every week, depending on indication. Remicade is typically given by IV infusion every 8 weeks, although it may be dosed more frequently. The single indication RA mediation Kineret must be given on a daily basis. The two single indication psoriasis medications, Amevive and Raptiva, are given on a weekly basis, although Amevive is only given for 12 weeks, followed by at least a 12-week drug-free period.

Relevance to MHS and Utilization: Since the FDA lacks regulatory authority to approve generic versions of biologic medications, generic formulations for the TIBs are not likely to appear in the near future. The TIB class accounted for approximately $136 million dollars in MHS expenditures in FY 2007, primarily at the retail point of service (66%), followed by MTFs (19%) and mail order (15%). This estimate does NOT accurately represent utilization of the IV agents (primarily Remicade), since these medications are commonly administered in clinic or

office settings. They are not available in retail or mail order and are included on outpatient pharmacy profiles only in MTFs that choose to maintain such a record.

The cost of treatment with TIBs is high (on the order of $10,000 to $20,000 annually). There were approximately 11,500 DoD beneficiaries receiving TIBs in the most recent quarter (Jun to Aug 2007), not including patients receiving IV agents. As you can see in Figure 3 on page 9 of your handout, the majority of use of TIBs in DoD (more than 96%) is for the two multi-indication agents (Enbrel and Humira), of course again not taking into account the unknown number of patients receiving IV agents. Over the entire patient population, Enbrel and Humira are consistently used in about a 2:1 ratio, although utilization in the last quarter (Jun to Aug 2007) shows increased uptake of Humira among new users (new users only: 44% use of Humira vs. 54% use of Enbrel, 2% other TIBs).

Relative Clinical Effectiveness Summary

With respect to efficacy, the DoD P&T Committee concluded that:

1. Across all disease states reviewed, all of the TIBs that are FDA-indicated for a particular condition have sufficient evidence from placebo-controlled trials to demonstrate efficacy. TIBs are typically added to standard therapy in patients with moderate to severe disease. In general, combination treatment of rheumatologic conditions with TIBs plus another commonly prescribed drug, methotrexate, offers better efficacy than TIBs or methotrexate alone. In addition, clinical trial data showed that beneficial effects on quality of life and productivity are generally associated with improvements in clinical response.
2. There is a lack of direct comparative evidence (that is to say, head-to-head clinical trials) across all disease states. In all disease states except RA, trials were too small in number or too varied in the way that they were designed and carried out to make adequate indirect comparisons. With two exceptions, treatment effect across agents appeared similar. The two exceptions are as follows:
    a. In RA, Kineret appears to be less efficacious than Enbrel, Humira, and Remicade (known collectively as the TNF inhibitors) with respect to effects on symptoms (ACR response) based on indirect comparison of data from placebo-controlled trials.
    b. In psoriasis, the PASI 75 score is a commonly measured response to treatment. It refers to a 75 percent improvement in the severity of disease and body surface area involved compared to the pre-treatment baseline. The PASI 75 scores for Remicade appeared consistently higher than with other TIBs used for psoriasis (Enbrel, Amevive, and Raptiva), although there is insufficient direct comparative evidence to draw a definitive conclusion. Some evidence suggests diminishing effect with Remicade as continuous use approaches 1 year. PASI 75 response rates for Amevive, Raptiva, and Enbrel appear similar in 12- to 24-week trials. An indication for Humira for the treatment of plaque psoriasis is under consideration by the FDA; one published trial and additional unpublished data available from the manufacturer supports its efficacy for this condition.
3. The multi-indication self-administered TIBs (Humira and Enbrel) compare favorably to one another, but there are some differences with regard to their FDA-approved indications. Humira is FDA indicated to treat Crohn's disease, while Enbrel did not

appear to be efficacious in Crohn's disease based on one clinical trial. Humira lacks published evidence in juvenile rheumatoid arthritis and has limited published evidence in psoriasis; however, the manufacturer has unpublished data suggesting efficacy in both disease states and both are under consideration by the FDA. Enbrel is FDA-approved for the treatment of both psoriasis and juvenile rheumatoid arthritis. For disease states in which both Humira and Enbrel are indicated, there is little evidence to suggest any clinically relevant difference in treatment effect.

4. Amevive and Raptiva are FDA-indicated only for psoriasis; they appear to compare favorably to Enbrel in terms of treatment effect. Their place in therapy relative to Enbrel and Remicade (and potentially Humira) in the treatment of psoriasis is probably influenced by individual provider and patient preference, and may be negatively affected by factors such as the intramuscular route of administration of Amevive, the additional recommended lab monitoring with both agents, and greater familiarity among providers with the TNF inhibitor agents (Enbrel, Humira, and Remicade).

With respect to efficacy, the DoD P&T Committee concluded that:

5. Overall, TIBs were well-tolerated during clinical trials; the most common and consistently reported adverse events are injection site or infusion reactions (depending on whether they are given by injection or by IV infusion). Kineret may cause more injection reactions than Humira and Enbrel based on one systematic review. In addition, Kineret is given once daily, as opposed to weekly or every other week dosing for Humira and Enbrel.

6. The primary safety concerns with TIBs are related to the potential for increased risk of serious adverse events (for example, infections, malignancies, autoimmune disorders, etc), most of which are associated with the drugs' effects on the immune system. These effects are rare and cannot be assessed reliably during clinical trials, although the overall occurrence of serious adverse events tends to be higher with TIBs compared to placebo. There is insufficient evidence to draw conclusions about comparative risk of any of these serious adverse events.

    a. There is fair evidence of an increased risk of serious infections (including tuberculosis) for TIBs compared to placebo.

    b. Observational evidence indicates a higher risk of lymphoma for patients treated with Remicade or Enbrel. Results of studies addressing other malignancies are mixed.

    c. Evidence concerning the safety of TIBs in patients with chronic heart failure and the effects of TIBs on the development of chronic heart failure is mixed. However, observational studies have reported lower rates of cardiovascular events in RA patients on TNF inhibitors compared to those on conventional therapy.

    d. All TNF inhibitors (Enbrel, Humira, and Remicade) appear to cause the development of autoantibodies to some extent. Cases of drug-induced lupus, lupus-like syndromes and other autoimmune disorders have been reported with Enbrel, Humira, and Remicade.

    e. Humira, Enbrel, and Remicade may be associated with nerve demyelination. Liver toxicity has been reported with Remicade and Amevive.

f. Laboratory monitoring is required or recommended for Kineret (neutrophil counts), Amevive (CD4+ T lymphocyte counts), and Raptiva (platelet counts) due to reports of blood cell abnormalities.

7. There is little substantive information concerning potential drug interactions with the TIBs, which are in general considered safe for use with the large number of drugs used concurrently in clinical trials. Based on two combination trials (one with Kineret plus Enbrel and one with Orencia plus Enbrel), the additive negative effects on the immune system appear to prohibit simultaneous treatment with more than one TIB at a time.

With respect to the use of TIBs in special patient populations,

8. Overall, they do not appear to have major differences in terms of efficacy or safety/tolerability in specific subsets of patients (e.g., based on age, gender, race, or in patients with multiple health conditions), with the exception of a reported higher risk of death among chronic heart failure patients treated with Enbrel or Remicade. Potential differences include varying pregnancy categories (B vs. C) across drugs (Amevive, Orencia, and Rituxan are Category C); the need for dose reduction of Kineret in patients with impaired renal function; and availability of data in pediatric patients (Enbrel for JRA; Remicade for pediatric Crohn's disease).

This concludes the clinical effectiveness discussion. Major Tiller will now discuss the relative cost effectiveness of the TIBs.

(Major Tiller) **TARGETED IMMUNOMODULATORY BIOLOGICS (TIBs) COST-EFFECTIVENESS**

(Maj Tiller) The relative cost-effectiveness evaluation for this class was conducted by Major Josh Devine. The cost effectiveness evaluation compared the estimated cost of treatment by disease state for RA and plaque psoriasis, the two most common indications. The analyses compared the expected cost per year of treatment for each drug product by indication across all three points of service.

Relative Cost Effectiveness Conclusion: Based on the results of the CMA and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, and 1 absent) that:

1. For RA, the clinical effectiveness evaluation concluded that Kineret appears to be less effective for the treatment of RA than the multi-indication TIBs. A cost effectiveness analysis comparing the expected cost per year of treatment across all three points of service for Enbrel, Humira, and Kineret showed that Humira was the most cost effective TIB for treatment of RA. Enbrel was more costly than Humira with similar effectiveness, while Kineret was both more costly and less effective.
2. For psoriasis, there was insufficient evidence to definitely conclude that treatment effectiveness differed among agents. A cost analysis comparing the expected cost per year of treatment across all three points of service for Raptiva, Enbrel, and Amevive showed similar cost effectiveness profiles for all three agents.
3. The UF scenario that placed Humira as the sole multi-indication TIB on the UF was the most cost effective scenario.

COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the TIBs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 2 opposed, 1 abstained, and 1 absent) to recommend that:

- Humira, Raptiva, and Amevive be maintained as formulary on the UF and
- Enbrel and Kineret be classified as non-formulary under the UF.

There were two committee members who cast votes opposing the UF recommendation. One member opposed the recommendation to make Enbrel non-formulary since the decision would affect approximately 60% of the patients using a TIB. The other member casting an opposing was not only concerned about the number of patients affected by the recommendation but was also concerned that the drugs were not 100% therapeutically interchangeable in disease states outside of RA.

NF Justification:

The P&T Committee recommended that Enbrel and Kineret be classified as non-formulary under the UF. For Enbrel, the Committee's recommendation was based on:

1. For disease states in which both Humira and Enbrel are indicated, there is little evidence to suggest any clinically relevant difference in treatment effect.
2. While Humira lacks an FDA indication for juvenile rheumatoid arthritis and plaque psoriasis, the manufacturer has submitted data supporting both indications to the FDA for

consideration. Enbrel lacks the indication for and does not appear to be efficacious in Crohn's disease, based on one clinical trial.

3. Humira is the most cost effective agent for RA, the most common indication for the TIBs.

For Kineret, the Committee's recommendation was based on:

1. Evidence suggesting that it is less effective for RA than Enbrel, Humira, and Remicade.
2. The need for daily dosing vs. weekly or every other week dosing with other TIBs.
3. The potentially higher risk of injection reactions with Kineret.
4. Recommendations or requirements for lab monitoring and dosage adjustment for patients in renal failure receiving Kineret.
5. Findings from the cost effectiveness analysis suggesting that Kineret is both more costly and less effective than Humira or Enbrel for the treatment of RA

COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee recommended (15 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday following a 90-day implementation period at the TMOP and TRRx, and at the MTFs no later than a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA. The P&T Committee also recommended that letters be sent to educate patients receiving non-formulary TIBs about the change in formulary status. Approximately 11,500 DoD beneficiaries filled a prescription for a non-formulary TIB in the previous quarter.

MTFs will not be allowed to have Kineret and Enbrel on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met:

1) The prescription must be written by a MTF provider, *and*
2) Medical necessity is established. MTFs may (but are not required to) fill a prescription for a Kineret or Enbrel written by a non-MTF provider to whom the patient was referred, as long as MN has been established.

COMMITTEE ACTION: CONTINUATION OF PA REQUIREMENTS FOR ENBREL, HUMIRA, KINERET, AND RAPTIVA AND A NEW PA REQUIREMENT FOR AMEVIVE – The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) to recommend 1) that no changes be made to the current PA requirements and PA criteria for Enbrel, Humira, Kineret, and Raptiva; 2) that a PA be required for Amevive; and 3) that the effective date for the Amevive PA be timed to coincide with that established for the UF decision in this class.

The P&T Committee agreed that the following PA criteria should apply to Amevive, consistent with FDA-approved labeling and PA requirements for the other TIBs:

1) Coverage would be approved for the treatment of:
   - Adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy
2) Coverage would NOT be approved for:

- Patients with HIV, patients with a CD4+ T lymphocyte count below normal at start of treatment, immunocompromised patients or those receiving other immunosuppressive agents or phototherapy
- Children (age < 18 years)

The P&T Committee agreed that the PA criteria for Enbrel, Humira, Kineret, and Raptiva reflect current FDA labeling and published clinical literature and require no substantive changes.

COMMITTEE ACTION: CONTINUATION OF QUANTITY LIMITS FOR ENBREL, HUMIRA, AND KINERET – Currently, quantity and/or days supply limits apply to Enbrel, Humira, and Kineret. In general, patients are limited to a 4-week supply of these medications at retail network pharmacies at any one time (no multiple fills for multiple copays) and a 6- to 8-week supply at the TMOP, based on product labeling and packaging. The intent is to limit potential wastage if medications are discontinued or changed.

The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) to recommend 1) that no changes be made to existing quantity / days supply limits for Enbrel, Humira, and Kineret.

LtCol Crownover will now present the DoD P&T Committee's perspective on the UF recommendation for the TIB class…

(LtCol Crownover): … *(Whatever you're going to say)* That concludes the TIB presentation, we will now gladly answer any questions you may have.

(Major Tiller): Now we will discuss the clinical and cost effectiveness for three new drugs that fall into classes that were previously reviewed for UF placement. Please turn to page 3 of your handout, and look at Table 2. First we'll discuss a new blood pressure medication falling into the renin angiotensin antihypertensive or RAA drug class, then a new medication for attention deficit hyperactivity disorder (ADHD), and finally a new oral contraceptive.

VALSARTAN/AMLODIPINE (EXFORGE) CLINICAL EFFECTIVENESS

(Dr. Carlberg): **Background:** The clinical effectiveness evaluation for this product was conducted by Dr. Angela Allerman. Exforge is a fixed dose combination product containing valsartan (available separately as Diovan) and amlodipine (available separately as Norvasc, which is now generically available). It is indicated only for treating high blood pressure.

Utilization: As of the DoD P&T Committee meeting in mid-November, 2,376 DoD beneficiaries had filled prescriptions for Exforge. All of these prescriptions were in the retail network.

Exforge: Treatment with Exforge has been shown in two randomized trials to produce additive BP lowering and superior BP control compared to placebo and the individual components administered alone. It showed similar BP lowering as the fixed dose combination of the ACE inhibitor lisinopril given with the diuretic HCTZ in one trial.

The adverse event profile of Exforge reflects that of the individual components. In clinical trials, the incidence of peripheral edema with the combination of valsartan/amlodipine is less than that seen when amlodipine is administered alone. Studies evaluating the effect of Exforge in terms of patient convenience have not been conducted. Potential benefits of fixed dose combination drugs include reduced tablet burdens, simplified medication regimens, and improved adherence.

Clinical effectiveness conclusion: The P&T Committee concluded (15 for, 0 opposed, 0 abstained, 2 absent) that, while the combination valsartan/amlodipine product Exforge offers a slight convenience to the patient in terms of decreased tablet burden and simplified medication regimen, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other antihypertensive agents included on the UF.

This concludes the Exforge clinical effectiveness discussion. Major Tiller will now discuss the cost effectiveness section for Exforge.

VALSARTAN/AMLODIPINE (EXFORGE) COST EFFECTIVENESS

(Major Tiller) The relative cost-effectiveness evaluation for this drug was conducted by LtCol Conrad. A cost minimization analysis was employed to evaluate the cost effectiveness of Exforge. The cost-effectiveness of Exforge was evaluated relative to the following combinations of single agents: telmisartan (Micardis)/amlodipine (the most cost-effective UF ARB), candesartan (Atacand)/amlodipine (chronic HF indication UF ARB), and valsartan (Diovan)/amlodipine (single agents of Exforge).The results of the CMA showed that the projected weighted average daily cost of Exforge was significantly higher than the weighted average daily cost of the combinations of UF ARBs with amlodipine.

Relative Cost Effectiveness Conclusion: The P&T Committee voted (13 for, 0 opposed, 3 abstained, 1 absent) that valsartan/amlodipine is not cost effective relative to the other agents in the RAA class. The weighted average cost of combined individual agents (UF ARBs and generic amlodipine) is more cost-effective relative to Exforge.

COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (12 for, 0 opposed, 3 abstained, 2 absent) to recommend that valsartan/amlodipine be classified as non-formulary under the UF.

NF Justification:

1) The fixed-dose combination of Exforge does not offer compelling benefits over other blood pressure medications on the UF. Although combining two medications with differing mechanisms of actions offers additive blood-pressure lowering and may be helpful in controlling high blood pressure, many such combinations are available. Unlike many of these other combination drugs, Exforge lacks a diuretic component, which is preferred based on national guidelines. (i.e., JNC VII).
2) There is no evidence to suggest that the valsartan/amlodipine combination offers enhanced BP lowering effects over other combination products (e.g., an ACE inhibitor plus hydrochlorothiazide).
3) There is no evidence to suggest enhanced adherence with this product compared to other blood pressure medications on the UF.
4) The combination valsartan/amlodipine product (Exforge) is not cost effective relative to the other agents in the RAA class. Specifically, the weighted average cost of combined individual agents (UF ARBs and generic amlodipine) is more cost-effective relative to Exforge.

COMMITTEE ACTION: IMPLEMENTATION PERIOD: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at military treatment facilities (MTFs) no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this decision. The implementation period will begin immediately following the approval by the Director, TMA.

LtCol Crownover will now present the DoD P&T Committee's perspective on the UF recommendation for Exforge.

(LtCol Crownover) *(Whatever you're going to say)* That concludes the Exforge presentation. We will now gladly answer any questions you may have.

(Major Tiller) Let's move on to our next newly approved drug, lisdexamfetamine, or Vyvanse.

LISDEXAMFETAMINE (VYVANSE) CLINICAL EFFECTIVENESS

(Dr. Meade) **Background:** Lisdexamfetamine (Vyvanse) is a new stimulant drug approved for treating attention deficit/hyperactivity disorder (ADHD) in children 6 to 12 years of age.

Utilization: As of the DoD P&T Committee meeting in mid-November, 2,200 DoD beneficiaries had filled prescriptions for Vyvanse. All of these prescriptions were in the retail network.

Vyvanse: The ADHD and narcolepsy drugs were evaluated at the November 2006 DoD P&T Committee meeting. Two ADHD medications—methylphenidate transdermal system (Daytrana

patch) and dexmethylphenidate (Focalin and Focalin XR)—are currently classified as non-formulary under the UF.

With regard to efficacy, there is insufficient evidence to suggest that clinically relevant differences exist between Vyvanse and other ADHD stimulant products. Unlike other drugs used for ADHD—including methylphenidate extended release (Concerta), mixed amphetamine salts extended release (Adderall XR), and atomoxetine (Strattera)—Vyvanse is not currently indicated for treating adolescents and adults.

With regard to safety, there is no evidence to suggest that the adverse event profile of Vyvanse differs clinically from other amphetamine formulations, although no comparative trials are available. Up to 33% of patients report appetite suppression. The package labeling for Vyvanse carries the same black box warning as the other stimulants for tolerance, dependence, abuse potential and sudden cardiac death in children with pre-existing structural cardiovascular abnormalities. The drug interaction profile is the same as other ADHD stimulants.

With regard to abuse potential, Vyvanse is a Schedule II controlled substance, as are the other ADHD stimulants (e.g., methylphenidate and amphetamines). Vyvanse is a pro-drug that is broken down in the GI tract to its active ingredient, dextroamphetamine, with the goal being lower potential for abuse, diversion and overdose toxicity than amphetamine. Based on "likeability" studies in drug abusers, Vyvanse doses of less than 100 mg were similar to placebo, while doses exceeding 100 mg were similar to dextroamphetamine. The maximum recommended Vyvanse dose currently marketed is 70 mg.

Relative Clinical Effectiveness Conclusion – The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that lisdexamfetamine (Vyvanse) does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other ADHD agents included on the UF.

Major Tiller will now discuss the cost effectiveness evaluation.

LISDEXAMFETAMINE (VYVANSE) COST EFFECTIVENESS

(Major Tiller): The relative cost-effectiveness evaluation for this drug was conducted by Eugene Moore, Pharm D. Since the relative clinical effectiveness evaluation concluded that there is insufficient evidence of a clinically meaningful difference between once daily stimulants for the treatment of ADHD, a cost minimization analysis was employed to determine the cost effectiveness of Vyvanse relative to the once-daily ADHD stimulants on the UF. Comparators included the UF once daily formulations ADHD stimulants: methylphenidate (Concerta, Metadate CD, Ritalin LA), and mixed salts of amphetamine extended release (Adderall XR). Results from the CMA revealed that the weighted average cost per day of therapy for Vyvanse was similar to the other UF once daily ADHD stimulants.

Cost Effectiveness Conclusion – The P&T Committee concluded (14 for, 0 opposed, 1 abstained, 2 absent) that Vyvanse had similar relative cost-effectiveness compared to the other UF once daily ADHD stimulants.

COMMITTEE ACTION – UF RECOMMENDATION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of Lisdexamfetamine (Vyvanse), and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 1 abstained, 2 absent) to recommend that lisdexamfetamine (Vyvanse) be designated as non-formulary on the UF. This

recommendation was primarily based upon the determination that lisdexamfetamine (Vyvanse) offers no clinically meaningful therapeutic advantage over other once daily ADHD stimulants.

The one opposing vote was cast due to the opinion that, given the similar cost per day of therapy for Vyvanse, NF status for Vyvanse unduly limited the choice of ADHD agents for providers.

NF Justification:

1) Vyvanse does not offer a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other ADHD agents included on the UF. While its formulation as a prodrug may potentially offer lower abuse potential relative to other amphetamine products, the actual clinical relevance is unclear. Vyvanse is designated as a Schedule II controlled product by the DEA, similar to other ADHD stimulant agents.
2) Vyvanse had similar relative cost effectiveness compared to the other once-daily ADHD stimulants on the UF.

COMMITTEE ACTION: IMPLEMENTATION PERIOD: The P&T Committee voted (14 for, 0 opposed, 1 abstained, 2 absent): 1) an effective date of the first Wednesday following a 60-day implementation period in TMOP and TRRx, and at military treatment facilities (MTFs) no later than a 60- day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TRICARE Management Activity (TMA). Approximately 2,800 DoD beneficiaries filled a prescription for Vyvanse in the previous quarter.

LtCol Crownover will now present the DoD P&T Committee's perspective on the UF recommendation for Vyvanse.

(LtCol Crownover) *(Whatever you're going to say)* That concludes the Vyvanse presentation. We will now gladly answer any questions you may have.

(Major Tiller) Let's move on to our next newly approved drug, Lybrel.

ETHINYL ESTRADIOL 20 MCG/LEVONORGESTREL 90 MG (LYBREL) CLINICAL EFFECTIVENESS

(Dr. Napier) **Background:** Lybrel is the first FDA-approved contraceptive formulation specifically packaged for continuous use. Active tablets are taken 365 days a year, with the intent of eliminating cyclical bleeding periods.

Utilization: As of the DoD P&T Committee meeting in mid-November, 290 prescriptions had been filled for Lybrel (~91% in the retail network).

Lybrel: The product consists of a 28-day pack containing active tablets only; oral contraceptives are conventionally packaged in 28-day packs typically containing 21 active tablets plus 7 placebo tablets. Conventionally packaged contraceptives are commonly used on a continuous or extended cycle basis: four conventional contraceptive packs are dispensed every 90 days, and the patient is instructed to discard the unneeded placebo tablets. This practice also provides access to the full array of oral contraceptive products, with varying estrogen levels and types of progestins.

Contraceptives containing 20 mcg of EE with 100 mcg of levonorgestrel are included on the BCF. The ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg formulation of Lybrel cannot be exactly duplicated by using conventional packages of ethinyl estradiol 20 mcg/ levonorgestrel

0.1 mg or its equivalents, due to the 10 mcg difference in the levonorgestrel component; however this difference in the progestin content is of questionable clinical relevance.

With respect to efficacy, there is no evidence to suggest that ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg would differ from other similar contraceptives containing low-dose estrogen. With respect to safety, as with other continuous regimens, breakthrough bleeding is common with ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg, but decreases over time.

Relative Clinical Effectiveness Conclusion – The Committee voted (15 for, 0 opposed, 0 abstained, 0 absent) that ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg did not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness or clinical outcome over other oral contraceptives included on the UF.

Major Tiller will now discuss the cost effectiveness evaluation.

ETHINYL ESTRADIOL 20 MCG/LEVONORGESTREL 90 MG (LYBREL) COST EFFECTIVENESS

(Major Tiller): The relative cost-effectiveness evaluation for this drug was conducted by Eugene Moore, Pharm D. The relative clinical effectiveness evaluation concluded that Lybrel does not show compelling clinical superiority over monophasic oral contraceptives containing 20 mcg of ethinyl estradiol. A cost minimization analysis comparing the cost effectiveness of Lybrel relative to UF monophasic oral contraceptives containing 20 mcg of ethinyl estradiol (Sronyx, Lutera, Levlite-28, Aviane, and Lessina-28) used on a continuous cycle basis revealed a significantly higher weighted average cost per day for treatment for Lybrel.

Relative Cost Effectiveness Conclusion – The Committee voted (13 for, 1 opposed, 0 abstained, 3 absent) that the weighted average cost per day of treatment for Lybrel is significantly higher than UF monophasic oral contraceptives containing 20 mcg of ethinyl estradiol, when used on a continuous cycle basis.

COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of ethinyl estradiol 20 mcg/levonorgestrel 0.09 mg (Lybrel) and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that Lybrel be designated as non-formulary under the UF.

NF Justification:

1) Results of the clinical effectiveness evaluation did not support clinically significant differences in the 0.09 mg levonorgestrel component in Lybrel vs. the 0.10 mg levonorgestrel component found in other oral contraceptives included on the UF.

2) Although Lybrel is indicated and packaged for continuous use, other conventional contraceptives are frequently used continuously or on an extended cycle basis.

3) Lybrel does not offer a clinically significant benefit over other monophasic contraceptives containing 20 mcg ethinyl estradiol included on UF, and is more costly than other contraceptives used in a continuous manner.

COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (12 for, 2 opposed, 1 abstained, 2 absent) to recommend: 1) an effective date of the first Wednesday following a 60-day implementation period in the TMOP and TRRx, and at military treatment

facilities (MTFs) no later than a 60-day implementation period; and 2) TMA send a letter to beneficiaries affected by this UF decision. The implementation period will begin immediately following approval by the Director, TRICARE Management Activity (TMA). Approximately 273 DoD beneficiaries filled a prescription for Lybrel in the previous quarter.

The two committee member casting opposing votes preferred a 90-day implementation period.

LtCol Crownover will now present the DoD P&T Committee's perspective on the UF recommendation for Lybrel.

(LtCol Crownover) *(Whatever you're going to say)* That concludes the Lybrel presentation. We will now gladly answer any questions you may have.

STATUS OF AMLODIPINE (NORVASC, GENERICS) ON THE UNIFORM FORMULARY

(Major Tiller) I would now like to discuss the UF status of amlodipine (Norvasc, generics) on the UF. On an ongoing basis, the PEC monitors changes in the clinical information, current costs, and utilization trends to evaluate whether the UF status of agents designated as non-formulary needs to be readdressed. Until recently, the price for amlodipine, even though it became available generically in early 2007, was similar to the price for brand name Norvasc and did not support a change in its UF status. However, the price has now dropped substantially, leading to a significant decrease in cost across all three points of service. Accordingly, the DoD P&T Committee re-evaluated the UF status of amlodipine.

Clinical Effectiveness Evaluation - At the August 2005 P&T Committee meeting, the Committee concluded that in general, amlodipine had similar clinical effectiveness relative to other similar agents (dihydropyridine calcium channel blockers) in the calcium channel blocker class in regards to efficacy, safety, and tolerability. Table 6 on page 7 of the handout includes the calcium channel blocker drugs and previous decision.

Cost Effectiveness Evaluation – In consideration of the Committee's previous relative clinical effectiveness conclusion, a cost minimization analysis was performed to determine the cost-effectiveness of amlodipine relative to the other dihydropyridine calcium channel blockers included on the UF. Based on the results of the analysis, the Committee voted (16 for, 0 opposed, 0 abstained, 1 absent) that amlodipine was the most cost-effective dihydropyridine calcium channel blocker.

COMMITTEE ACTION: UF RECOMMENDATION – In view of the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the dihydropyridine calcium channel blockers, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that amlodipine be reclassified as formulary on the UF.

COMMITTEE ACTION: UF IMPLEMENTATION PERIOD – The P&T Committee recommended immediate implementation upon signing of the November 2007 DoD P&T Committee minutes by the Director, TMA.

LtCol Crownover will now present the DoD P&T Committee's perspective on the UF recommendation for amlodipine.

(LtCol Crownover) *(Whatever you're going to say)* We will now gladly answer any questions you may have.

RE-EVALUATION OF NON-FORMULARY AGENTS

(Major Tiller) The example of amlodipine points out the need for a procedure that would allow the reclassification of a drug from non-formulary to generic in a more expeditious manner than can be accomplished through the normal quarterly P&T Committee cycle, when such a reclassification would be advantageous for both the MHS and its beneficiaries. The Committee has developed a process for the re-evaluation of non-formulary agents in circumstance similar to those demonstrated by amlodipine at its May 2007 meeting. This general process was briefed to the BAP at the June 07 meeting and has been approved by the Director, TMA.

At the last meeting, the PEC defined a list of non-formulary agents for Committee review that met the following criteria: 1) they were from drug classes in which UF status was NOT awarded based on condition sets that specified the number of similar agents on the UF (i.e., agents in the same class or subclass); and 2) they had been determined to have similar relative clinical effectiveness (i.e., similar efficacy, safety, and tolerability) compared to similar agents on the UF and were NOT excluded from the UF based on clinical issues alone.

Following the process, the UF status of non-formulary agents meeting the above criteria would be re-evaluated using the following pre-established criteria.

1) The non-formulary agent becomes generically available and:
    a) The generic product is "A-rated" as therapeutically equivalent to the brand name product according to the FDA's classification system
    b) The generic market supply is stable and sufficient to meet DoD MHS supply demands.
2) The non-formulary agent is cost effective relative to similar agents on the UF. A non-formulary agent becomes cost-effective when:
    a) The non-formulary agent's total weighted average cost per day of treatment is less than or equal to the total weighted average cost per day of treatment for the UF class to which they were compared.
    b) The non-formulary agent's total weighted average cost based on an alternate measure used during the previous review is less than or equal to that for the UF class to which they were compared. For example, antibiotics may be compared on the cost per course of therapy used to treat a particular condition.

When the pre-established criteria for reclassification were met, the Chairperson of the P&T Committee would call for an electronic vote by the members of the P&T Committee on the matter.

1) Upon a majority vote affirming that the non-formulary drug should be reclassified as generic, that agent will be changed from non-formulary status to formulary status as a generic.
2) Committee members will be briefed on any reclassification of a non-formulary agent at the next meeting of the P&T Committee. This information will be recorded as an information-only item in the meeting minutes. The item will be included in information provided for the BAP's next meeting; however, since the BAP will have already made any comments on the subject, the item will normally not be subject to further BAP comment.

COMMITTEE ACTION: The P&T Committee voted (15 for, 0 against, 1 abstained, 1 absent) to recommend that a list of current non-formulary drug agents be re-evaluated for UF status when the pre-established criteria are met.

The PEC will continue to monitor the cost effectiveness of non-formulary medications and will refer the matter to the Committee when non-formulary mediations become generically available and become cost effective relative to similar agents on the UF.

LtCol Crownover will now present the DoD P&T Committee's perspective on the process for re-evaluation of non-formulary agents.

(LtCol Crownover) *(Whatever you're going to say)* We will now gladly answer any questions you may have.

FY07 UF Performance Overview

(Major Tiller) – Dr. Meade will now provide an information only presentation of FY 07 UF Performance.

(Dr. Meade):

(Major Tiller) – (concluding remarks).

Table 5 – Non-Formulary Agents for Re-Evaluation

Generic Name	Brand Name	UF Class	Generics Shipping
EE 30 mcg; 0.15 mg levonorgestrel	Seasonale	BCs (M30)	Y
EE 30/10 mcg; 0.15 mg levonorgestrel	Seasonique	BCs (M20)	N
EE 35 mcg; 0.4 mg norethindrone	Ovcon-35	BCs (M35)	Y
EE 50 mcg; 1 mg norethindrone	Ovcon-50	BCs (M50)	N
EE 20 mcg; 0.1 mg norethindrone	Loestrin 24 FE	BCs (M20)	N
ciclopirox	Loprox	AF-DERMs	Y
econazole	Spectazole	AF-DERMs	Y
moexipril	Univasc	ACEs	Y
quinapril	Accupril	ACEs	Y
amlodipine	Norvasc	CCBs	Y
nicardipine	Cardene	CCBs	Y
nicardipine SR	Cardene SR	CCBs	N
isradipine IR	Dynacirc	CCBs	Y
isradipine CR	Dynacirc CR	CCBs	N
diltiazem ER HS	Cardizem LA	CCBs	N
verapamil ER HS	Verelan /Covera HS	CCBs	N
bupropion XL	Wellbutrin XL	AD1s	Y (300mg only)
paroxetine CR	Paxil CR	AD1s	N
escitalopram	Lexapro	AD1s	N
verapamil ER / trandolapril	Tarka	Misc HTNs	N
tramadol ER	Ultram ER	Narcotic analgesics	N
timolol maleate	Istalol	EYE-1s	N
timolol hemihydrate	Betimol	EYE-1s	N
tolterodine IR	Detrol IR	OABs	N