5 January 2006

Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS DECEMBER 2005

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

1. Alzheimer's Drugs: The P&T Committee recommended that the status of tacrine be designate non-formulary, with donepezil, rivastigmine, galantimine, and memantine maintaining formulary status on the Uniform Formulary with the formulary cost share. The Committee voted to recommend an implementation period of 90 days.

Summary of Panel Comments:

- The Panel voted unanimously (12-0) to concur with the recommendation and implementation period.

- The Panel recommended that each of the five patients currently using tacrine be notified individually of the change in formulary status.

Director, TMA: ☑ These comments were taken under consideration prior to my final decision.

2. Nasal Corticorsteroids: The P&T Committee recommended that beclomethasone dipropionate, budesonide, and triamcinolone acetonide be designated classified non-formulary, and that flunisolide, fluticasone propionate and mometasone furoate be classified as uniform formulary agents. The P&T Committee recommended an implementation period of 90 days.

Summary of Panel Comments:

- The Panel voted unanimously (12-0) to concur with the recommendation of formulary status of the named pharmaceutical agents above.

- The Panel voted (10-2) to concur for the implementation period of 90 days.

- The Panel commented that a large number of beneficiaries would be affected by the move of the selected agents to non-formulary status and 90 days would not be enough time for them to be made aware of the change. The Panel's concern is that there seems to be a lengthy period between the time the TMA Director makes the decision and when the decision is actually made public. This especially affects beneficiaries using the retail (TRRx) and mail order (TMOP) pharmacies.

- Two panel members noted that now is a good time to be doing this since it is the off-season for allergies.

Director, TMA: BW

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

3. Macrolide/Ketolide: The P&T Committee recommended non-formulary status for telithromycin and the Zmax formulation of azithromycin, with erythromycin salts and base, all forms of clarithromycin and non-Zmax formulations of azithromycin maintaining formulary status on the Uniform Formulary at the formulary cost share. The P&T Committee recommended 60-day implementation period.

Summary of Panel Comments:

- Voted (12-0) to concur with the P&T Committee recommendations.
- Voted (6-6) regarding the implementation period.
- One of the reasons for the non-concurring votes was that it is extremely difficult to educate and contact the TRICARE Standard providers. There is no mechanism for doing so now and the group of people who are eligible for that benefit may be expanding to TRICARE Reserve Select.
- The civilian provider network is not being notified in a timely manner.

Director, TMA: BW

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

4. **Prior authorization for mecasermin (Increlex) Injection)**: The P&T Committee recommended placing a prior authorization on mecasermin. The Committee also recommended a 30-day implementation period.

Panel Comment:

- Voted unanimously (12-0) to concur with the recommendation to establish a prior authorization.
- Voted 11 for and one against to concur with the recommended implementation period.

Director, TMA: BW

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

5. Antidepressants (AD1): The P&T Committee recommend that fluoxetine (Sarafem) in special packaging for Premenstrual Dysphoric Disorder (PMDD), fluoxetine weekly (Prozac

Weekly), escitalopram and paroxetine CR, duloxetine, and bupropion XL be designated non-formulary, with bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlaxafine remaining on the uniform formulary. In addition, the P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued. The P&T Committee recommended a 180-day implementation

Panel Comment:

- The Panel voted was 7 concur and 4 non-concur (7-4) for changes to the uniform formulary.
- The Panel voted unanimously (11-0) to concur with the 180-day implementation period recommendation.
- Many members of the Panel were extremely concerned about changing an antidepressant drug for an active duty servicemember who was either within six months of deployment or actually in a hostile zone.
- All Panel members believe there should be an exception to the current policy for active duty servicemembers who are about to be deployed. The nonconcurring votes were strictly related to the active duty service member issue and not a reflection on the P&T recommendation as a whole

Director, TMA: BW

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

Meeting Summary
December 16, 2005
Washington, D.C.

Panel Members Present:

- Sydney Hickey, National Military Family Association, Chairperson
- John Class, Military Officers Association of America
- John Crum, Humana Military Healthcare Services, Inc.
- Deborah Fryar, National Military Family Association
- Marshall Hanson, National Military and Veterans Alliance
- Rance Hutchings, Uniformed Services Family Health Plan
- Lisa Le Gette, Express-Scripts, Inc.
- Martha Miller, Health Net Federal Services
- Charles Partridge, National Military and Veterans Alliance
- Jan Prasad, TriWest
- Marissa Schlaifer, Medical Professional
- Robert Washington, Fleet Reserve Association

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

Agenda

The December meeting of the Panel had the following agenda:

- Opening remarks and public comments
- Consideration of Acetylcholinesterase Inhibitor and N-Methyl D-Aspartate (NMDA) receptor antagonist drug class recommendations
- Consideration of Nasal Corticosteroids for Allergic Rhinitis drug class recommendations
- Consideration of Antidepressant I drug class recommendations
- Consideration of Oral Macrolide/Ketolide drug class recommendations
- Consideration of Prior Authorization (PA) requirements for mescasermin (Increlex) injection
- Wrap-up comments

Opening Remarks

MAJ Watson summarized the agenda, identifying the objectives as being to discuss and review the recommendations of the Department of Defense (DOD) Pharmacy and Therapeutic (P&T) Committee meeting held on November 15-17, 2005, in San Antonio, TX.

MAJ Watson stated that under 10 United States Code (U.S.C.) section 1074g the Secretary of Defense is required to establish a DOD Uniform Formulary (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 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 include:

- Reviewing and commenting on the recommendations of the P&T Committee concerning the establishment of the Uniform Formulary and subsequent recommended changes.
- Holding meetings in an open forum quarterly. The Panel may not hold meetings except at the call of or with the advance approval of the Chairperson of the Panel.
- Preparing minutes of the proceedings and preparing comments for the Secretary or his designee regarding the Uniform Formulary or changes to the Formulary.

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

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

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

MAJ Watson next reviewed the rules for 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. MAJ Watson announced that there are no private citizen comments on today's agenda.
- 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 next introduced two new members of the Beneficiary Advisory Panel: Marissa Schlaifer from the Academy of Managed Care Pharmacy and Dr. John Crum from Humana Military Healthcare Services. MAJ Watson also introduced the other Panel members present as well as individuals in the audience who may be participating in the session.

Private Citizen Comments

After reviewing the housekeeping considerations, MAJ Watson indicated that since there are no private citizen comments, discussion of all items on the published agenda would take place one hour earlier than planned.

MAJ Watson then turned the meeting over to the Panel Chair, Ms. Sydney Hickey.

Chairperson's Opening Remarks

At the request of the Chair, the two new members of the Panel outlined their background. Marissa Schlaifer introduced herself as the Director of Pharmacy Affairs of the Academy of Managed Care Pharmacy with a background in community pharmacy management and managed care. Her primary specialty is in managed care pharmacy, in which she has been engaged for about seven years. John Crum introduced himself as the Chief Medical Officer for Humana Military Health Care Services in Louisville, Kentucky, which administers the TRICARE program in the South region. He is a family practice doctor with 19 years experience in rural communities and managed care organizations (Health Maintenance Organizations (HMOs)). He has been affiliated with the TRICARE program since 1995.

Ms. Hickey then began the Panel proceedings by thanking MAJ Watson and Rich Martel for their strong support of the Panel. She also announced that a policy had been developed for dealing with delays due to inclement weather.

Ms. Hickey then called to the attention of the Panel a policy of which she had previously been unaware. That is that providers in the direct care system of military facilities are strongly encouraged, and perhaps more than strongly encouraged, to write prescriptions for medications that can be filled in their own pharmacy. She said in her own Association several beneficiaries have been refused a third-tier formulary script to be used in the retail or mail order pharmacy. She said her concern is not with policy - it is not the business of the BAP to talk about policy. However, as the Panel deliberates about putting drugs into the "non-formulary" class, it needs to understand that there may indeed be a group of beneficiaries other than active duty members - anyone being treated at a Military Treatment Facility (MTF) - who may be refused, or close to refused, the ability to use third tier drugs. That situation makes it not just an economic decision but also a closed formulary.

The Chair then turned the podium over to Lieutenant Colonel (Lt Col) Dave Bennett, Director of Clinical Operations at the DOD Pharmacoeconomic Center (PEC) to begin the presentation of drug class reviews.

Presentation on Acetylcholinesterase Inhibitor and N-methyl D-aspartate (NMDA) Receptor Antagonist Drug Class for the Treatment of Alzheimer's Disease

[Insert script pages 1-7]

Dr. Brian Crownover, a family physician from the training program at Eglin Air Force Base (in the Humana Region) and a physician member of the P&T Committee, addressed additional comments to the Panel. He said the Committee is acutely sensitive to the matter of making something "non formulary." He said that in the case of Alzheimer's drugs, the key point to keep in mind is that the medical community is seeing only a minimal gain with the drug – maybe five percent, which is a minimal impact. The system uses such drugs because it's all they have, but with over half the patients experiencing direct liver injuries they know that tacrine is not the best drug. In 1993, when tacrine first came out, the community was excited because they finally had a drug they could use for Alzheimer's. But it has to be taken four times a day and causes liver injuries, so patients have to be monitored frequently. Donepezil was the second Alzheimer's drug that came out and everyone became familiar with it and liked it because of its stark contrast with tacrine. He said no one in DOD will have any heartburn with taking tacrine off the formulary because they're not really using it - only five people across the entire DOD population of nine million. That plus the minimal clinical benefits warrant making the drug non-formulary.

Panel Questions on Alzheimer's Disease Agents

The Chairperson said the Panel appreciates having Dr. Crownover add a provider's perspective to the presentation. She then opened the floor to questions from the Panel prior to discussing the recommendations before voting.

Ms. Hickey said she understands there is a U.S. Food and Drug Administration (FDA) "black box" warning on tacrine and asked if this is correct. Drs. Moore and Crownover said that it is correct.

Ms. Hickey also asked about a patent challenge to galantamine and whether it would make any difference in the economic analysis. Dr. Moore replied that it would not have made any difference because the major use of these products is at the retail pharmacy. He said the makers of galantamine have told the PEC that they expect the drug to go generic. If this occurs, galantamine will be in an even more favorable position. The Committee voted to keep all of the other agents on the formulary so there is nothing to make galantamine go away.

Mr. Hutchings said that in looking back at a drug that was put on third tier, they found that the cost of that drug with the addition of a pharmacy dispensing fee was actually less than the co-pay. His understanding is that there isn't supposed to be a profit made on drugs and asked if that has been taken into consideration. MAJ Watson stated the beneficiaries would pay the lesser of the prescription cost or the copay.

Panel Discussion on Alzheimer's Disease Agents

Mr. Partridge asked about the policy requiring that non-formulary drugs must be written by an in-care provider to be accepted on a medical necessity basis (the policy that says MTFs do not have to fill a medical necessity prescription where the provider is not an MTF provider). Ms. Hickey replied that the BAP is not supposed to be dealing with policy - it is supposed to just review what the P&T Committee does. She also clarified that Mr. Partridge was not talking about the "you write it, you fill it" policy she was discussing earlier. The policy

recommendation Mr. Partridge is talking about was not made by the P&T Committee but by TMA, so it would fall outside of the Panel's purview. Mr. Partridge said, even so, he would like to lodge an objection to it.

Mr. Hutchings also commented that it seems to him that the drug in question in this instance might also have required a prior authorization (PA) in order to stop it initially. He said he would vote to concur with the recommendation, but he understood that this might not be necessary since there are so few DOD beneficiaries on tacrine

Ms. Hickey asked if any Panel members wished to offer additional comments. None did.

Panel Vote on Formulary Recommendation of Alzheimer's Disease Agents

The Chair then called for the vote on the P&T Committee's recommendation:

"Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the Alzheimer's drugs, the P&T Committee recommended that the status of tacrine be changed from formulary to non-formulary on the Uniform Formulary, with donepezil, rivastigmine, galantimine, and memantine maintaining formulary status on the Uniform Formulary with the formulary cost share. To address the safety concerns of tacrine, a Prior Authorization for tacrine was initially considered. However, due to the extremely low number of unique users (single digits) currently being treated with tacrine across the Military Health System (MHS) the P&T Committee felt the medical community was adequately aware of the risks associated with tacrine use, and safety concerns were already being appropriately addressed."

The Panel voted unanimously (12-0) to concur with the recommendation.

Panel Vote on Implementation Period of Alzheimer's Disease Agents

The P&T Committee recommended an implementation period of 90 days.

Mr. Class commented that even though there are only five individuals using tacrine, they should each receive notification of the change in status. Ms. Hickey concurred with the comment.

The Panel voted unanimously (12-0) to concur with the recommendation.

Panel Comments on Alzheimer's Disease Agents

The Panel recommended that each of the five patients currently using tacrine be notified individually of the change in formulary status.

Presentation on Nasal Corticosteroids Drug Class

The Chairperson introduced the next agenda item - nasal corticosteroids. Dr. Moore of the PEC began the presentation.

[Insert script pages 8-14]

Dr. Crownover next offered additional comments. In particular, he commented on the point made that fluticasone and mometasone were rated numbers one and two by providers. He said fluticasone is far and away the most commonly used agent. Regarding budesonide being "Category B" (for pregnancy), Dr. Crownover said that "Category C' is the default category in the absence of a study establishing the agent as "Category B". It is not uncommon for manufacturers not to want to do that to get FDA "Category B" approval. So even though budesonide is the only official "Category B" he said the topical application of the other agents minimizes their systemic absorption so the medical community is really not worried about the safety aspect.

Dr. Crownover also commented on the fact that the P&T Committee had recommended only three agents be kept on formulary in this class. He said the reason why patients come in and say they don't like a particular inhaler and want something different usually has to with factors like the smell of a drug, its taste or the way it feels when it hits the patient's nose. He said having three agents on the formulary should easily be enough to give patients a good sample.

Panel Questions on Nasal Corticosteroids Drug Class

Mr. Partridge asked which of the agents are the most popular with pediatricians. Dr. Crownover said that would be mometasone. He said some pediatricians prefer to use an agent in another drug class (cromolyn sodium agents) because, even though they are not as effective as a nasal steroid, there is more safety data.

Ms. Hickey asked how many providers responded to the survey. Dr. Moore answered "72."

Ms. Fryar commented that she noticed that this is the first time the P&T Committee has not had a unanimous vote and asked about that. Lt Col Bennett said that there were no P&T Committee votes against the recommendation, although there were abstentions (usually for legal reasons).

Panel Discussion on Nasal Corticosteroids Drug Class

Mr. Hutchings commented on flonase. He said a lot of people taking flonase (fluticasone) experience headaches because of the fragrance but he also agreed that having three agents on the formulary is sufficient.

Ms. Hickey wondered whether having an aversion to the smell, for example, wouldn't be sufficient to justify a medical necessity exception if that would cause the patient not to take the medication. That would make it a compliance issue.

Panel Vote on Formulary Recommendation on Nasal Corticosteroids Drug Class

The Chair read the P&T Committee recommendation:

"Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness evaluations, and other relevant factors, the P&T Committee recommended that beclomethasone dipropionate, budesonide, and triamcinolone acetonide be classified as non-

formulary under the UF, and that flunisolide, fluticasone propionate and mometasone furoate be classified as formulary on the UF."

The Panel voted unanimously (12-0) to concur with the recommendation.

Panel Discussion of Implementation Plan on Nasal Corticosteroids

The P&T Committee recommended an implementation period of 90 days.

Mr. Hanson expressed concern that there are over 30,000 people who will find that their current prescription will become non-formulary. He believes that 90 days is a rather short turnover period for such a large population, especially since the providers may have to go through some checks for such factors as smell. He suggested that a broader time period might be applicable in this case.

Dr. Miller said that now is a good time to be doing this since it is the off-season for allergies. She believes that 90 days will be just right before people come in with their spring allergies. She thinks that the 90-day period is a really good idea.

Mr. Class agreed with Mr. Hanson's comments.

Panel Vote on Implementation Plan on Nasal Corticosteroids Drug Class

The P&T Committee recommended an implementation period of 90 days. The Panel vote to concur was 10 for and 2 against.

Panel Comment on Nasal Corticosteroids Drug Class

The Panel commented that a large number of beneficiaries would be affected by the move of the selected agents to non-formulary status and 90 days would not be enough time for them to be made aware of the change. The Panel's concern is that there seems to be a lengthy period between the time the TMA Director makes the decision and when the decision is actually made public. This especially affects beneficiaries using the retail (TRRx) and mail order (TMOP) pharmacies.

The Panel also added a comment indicating that two Panel members believe the 90-day notification period is particularly efficacious because it will permit notification before the high allergy season.

Presentation on Macrolide/Ketolide Drug Class

MAJ Watson announced a change in the agenda, moving the consideration of the antidepressant I drug class to the afternoon session, taking up the macrolide/ketolide drug class next.

Lt Col Bennett delivered the PEC presentation on the macrolide/ketolide drug class.

[Insert script, pages 25-31]

Dr. Crownover also added his comments on this drug class. Regarding Zpaks, he said the industry is now marketing "tri-packs" - a three-day version of the former "five packs." He said the tri-pack packaging has been a fairly effective way to dispense azithromycin. Most patients do very well with it. The "one day" dosage of Zmax sounds even better. The problem, however, is the huge cost difference between Zmax and the tri-pack. He said that three days is fairly convenient and that the P&T Committee thought it would be sufficient without incurring the large cost difference of Zmax.

Regarding telithromycin, he said the applicable principle is POEM - Patient Oriented Evidence that Matters. Patients care about factors such as mortality, hospitalization rates and similar factors. He saw something that suggested there was a patient-oriented point that would give an advantage to telithromycin, so he pulled the original research article to check it out. The article that looked at pneumonia had what was called a "statistical trend" but it was not statistically significant, so it is not considered scientifically accurate and can't be used when making a decision. A second study was also looked at that was not very well done because it looked at a secondary, not a primary, end point. The results were analyzed only after-the-fact and the studies were "under-powered" in terms of their scope. Consequently, both of the studies that would have supported keeping telithromycin on the Uniform Formulary were very poorly done science. So telithromycin is not a first- or second-line choice.

Panel Questions on Macrolide/Ketolide Drug Class

Ms. Hickey asked how many providers responded to this survey; the answer provided was "33."

Mr. Hutchings asked whether the Committee discussed quantity limits for azithromycin. He said the therapeutical quantity limit is "10" but that is a clinical thing because the tri-packs and the Zpaks come in tablets of six and there are doctors writing refills all over the place which, in his opinion, never appropriate. But what happens is that patients send in to his organization for a refill and they have to tell the patient that they can only have four tablets on the refill because they are only allowed to fill to the quantity limit. Lt Col Bennett said that quantity limits were not discussed in the context of making this decision. But he agreed that from a management standpoint DOD has a quantity limit of 10. Mr. Hutchings pointed out that this is one pack plus a partial pack. Shana Trice of the PEC said that quantity limits had been discussed some time back by the PEC and that there was a reason for the quantity limit of 10 at the time that was set. It might be available from the minutes of that meeting. Mr. Hutchings said he has been unable to determine what indications, if any, would lead to a quantity limit of 10.

Panel Discussion on Macrolide/Ketolide Drug Class

Mr. Hanson complimented the PEC for the tables included in the handout and the information they contain. He said they are very helpful to the Panel.

Mr. Partridge asked Dr. Crownover about notification times. He noted that the recommendation in this instance calls for a 60-day implementation time. He asked what the time lag is between when a decision is made and when providers are notified of the change. Dr. Crownover said what happens is that the Surgeon General's Office receives notice and kicks it down to all the medical directors. Program directors also get it. These individuals pass the information along to MTF providers, who pass it along to the local doctors. There is enough time to see the decision

before the changes kick in. From his standpoint, he knows 45-50 days in advance when a change is coming. They can then factor it in when patients call in for refills.

Mr. Hanson asked the contractors on the Panel whether 60 days would give them enough time to make the changes they need to make. Mr. Hutchings said the answer is "yes," the 60 days notice would be enough in this case.

Ms. Hickey also read the applicable portion of a letter submitted by Dr. Jeffrey Lenow, a panel member who was unable to attend today's session:

"I do have one observation in the macrolide review section. Again, it was very thorough and the proper academic entities and publications were identified. In the category of acute bacterial sinusitis (ABS) it is plainly evident to those of us in practice that most of these will resolve on their own with supportive measures, drainage, etc. Expensive broad spectrum antibiotics simply are not showing that much of a difference. It's not that they are not good medications, but often they only reduce the duration of symptoms by a brief amount, a day or so. For patients who smoke, it probably makes NO difference. Zitromax (azithromycin) is an amazing story - rarely have I seen patients flat out ask for a branded drug like they have with this agent. Probably due to clever packaging (the Zpak parlance) - what is really amazing is that this was NEVER approved for sinusitis until recently - but Docs used it anyway - easy to write and innocuous in terms of side effects.

Problem here is resistance. What I did NOT see discussed all that much is resistance data that does differentiate the classes. Zithromax is technically an azolide, Biaxin (clarithromycin) is a macrolide as is generic erythromycin, and Ketek (telithromycin) is a new class of medication, the ketolide class. If it is to be believed, the architecture of the ketolide resembles the clarithromycin molecule closely but for a few ribosomal modifications that confer resistance that otherwise has begun to manifest in the macrolide class and azolide class.

The Ketek (telithromycin) brand has cleverly promoted the brand in its relatively new launch mode (the last year and a half or so) as the 'tailored' drug, i.e. built to limit what they term 'collateral damage', i.e. the breeding of resistance as is the big concern for all antibiotics that are broad spectrum.

While I don't have great problems with the groups recommendations, I do feel some discussion about the differentiating features of the ketolide class vs. the others is warranted and certainly should be watched. If true, then the economic analysis ahead will have to factor that into the equation."

Lt Col Bennett pointed out that what Dr. Lenow saw was probably the summary of the actual clinical reviews presented at the P&T Committee meeting - a very thorough clinical review and analysis by subject matter experts. The reviews address the resistance issues with the macrolide/ketolide class of antibiotics that Dr. Lenow was talking about. The minutes of the Committee meeting don't allow for publication of the clinical reviews as they are too lengthy. The reviews indicated however, that while the *in vitro* (in a test tube) tests seem to show some benefit with telithromycin, the *in vivo* tests show no evidence that one is better than the other.

Lt Col Bennett, referring back to an earlier question regarding quantity limits, stated that the quantity limits for azithromycin were removed at the February 2005 P&T Committee meeting.

Ms. Hickey said she thought Dr. Crownover had also addressed the resistance issue effectively. She believes Dr. Lenow's comments were meant to suggest that the agent be watched and revisited if the "test tube" results prove to be true.

Panel Vote on Formulary Recommendation on Macrolide/Ketolide Drug Class

The Chairperson read the recommendation of the P&T Committee regarding the macrolide/ketolide drug class:

"The P&T Committee, based upon its collective professional judgment, voted to recommend non-formulary status on the Uniform Formulary for telithromycin and the Zmax formulation of azithromycin, with erythromycin salts and base, all forms of clarithromycin and non-Zmax formulations of azithromycin maintaining formulary status on the Uniform Formulary as the formulary cost share."

The Panel voted unanimously (12-0) to concur with the recommendation.

Panel Discussion of Implementation Plan on Macrolide/Ketolide Drug Class

The Chairperson stated that the P&T Committee recommended an implementation period of 60 days for the oral ketolide/macrolide drug class recommendations.

Ms. Hickey commented that, like others on the Panel, she is concerned about the brief implementation times because it has been taking at least two weeks, and sometimes more, to get a press release out of the TRICARE Management Agency (TMA). She also noted that while DOD notifies its pharmacy contractor and, now, the Uniformed Services Family Health Plan, she doesn't believe there is a requirement to notify managed care support contractors. Looking at where the prescriptions for the two drugs in this class that are going non-formulary are being written shows they are being filled in the retail pharmacy. That means it is the network providers or the regular standard providers that are writing these prescriptions. Her recommendation would be that the managed care support contractors be notified as soon as the pharmacy contractor and the Uniformed Services Health Plan are notified. They do have letters that go out to their providers and notification would be especially helpful with the 60-day time span.

Mr. Class agreed, saying he doesn't see any difficulty with getting the word to the network providers or to the MTFs. That can happen very quickly in this case. But - concerning TRICARE Standard patients and their providers - there is still no communications plan for how TMA will get the word out. This issue goes back to the Panel's first meeting. An annual standard newsletter goes to all beneficiaries once a year, but he said he still hasn't seen a plan.

Dr. Crum commented on the managed care support contractors and notifying community providers. He said the production, review and approval cycle on the provider newsletter is way more than 60 days. So there isn't an existing vehicle for notifying community providers. In response to a question from the Chair about the newsletter review and approval process, Dr. Crum said there is a marketing contractor with which each of the managed care support contractors coordinates. He also said that his lead time for communicating with providers using the newsletter is 6-9 months.

Dr. Miller said her organization (Health Net Federal Services, Inc - a TRICARE contractor) can post the information on their website and the information is also on the TMA website. Ms. Hickey said it would be helpful if all parties were notified in a timely manner so they could put it up on their own websites. She would also suggest that the network providers check the website more often to get the important information.

Mr. Hutchings observed that the non-network providers are seeing a whole host of patients. He believes that information like this coming across their desks is regarded as a piece of "trash mail" - just one more thing to remember. He said he doesn't believe that extending the implementation time period would actually notify any more providers. He also asked whether the Uniform Formulary is on ePocrates or any other downloadable formulary where physicians could see updates.

Dr. Crownover said ePocrates is probably the number one thing he uses as a physician. It is one of the top two or three drug guides. It has a nice feature in that the ePocrates Company can make your formulary downloadable from their website if it is submitted to them. He said as far as he knows the DOD formulary is not yet listed as one of the downloadable options. He is not sure who would have the authority to open negotiations with ePocrates to make that happen, but that would be a good idea.

Mr. Hanson offered another comment concerning non-network providers and their treating notices as a piece of "junk mail." He cited a comment by Chairman Duncan Hunter on C-SPAN two days ago (i.e., December 14) indicating that TRICARE Reserve Select is going to be expanded to members of the Guard and Reserve. This means there is going to be an extension of TRICARE Standard, since that's their only option under the current law (unless a change is made in the next National Defense Authorization bill). To discount getting information to a non-network doctor isn't the right approach when that part of the system is being expanded. Those beneficiaries need to be considered as well as those who take Prime. A traditional conflict between many of the associations and the health care contractors has been that they are emphasizing one program over another.

Panel Vote on Implementation Plan on Macrolide/Ketolide Drug Class

The Chairperson again read the P&T Committee recommendation: an implementation period of 60 days.

The Panel vote was: 6 concurring and 6 non-concurring.

Comments on Macrolide/Ketolide Drug Class Implementation Plan

The Panel commented that one of the reasons for the non-concurring votes was that it is extremely difficult to get the necessary information to the TRICARE Standard providers. There is no mechanism for doing so now and the group of people, particularly Reservists, who are eligible for that benefit, may be expanding due to TRICARE Reserve Select.

Additionally, the civilian provider network is not being notified in a timely manner.

The Panel also suggested that TMA consider adding the formulary to ePocrates if it has not already done so.

Mr. Hutchings commented that the six "concur" votes came from clinicians. His view is that timely notification, or the lack thereof, is a non-issue for the clinicians, based on the vote. In reply, Ms. Hickey said she would remind everybody that this is the beneficiary Panel and that it is supposed to represent the interests of beneficiaries. Mr. Hanson pointed out that all of the people representing the beneficiaries voted to not concur with the recommendation. Mr. Hutchings said his point was that no matter how much notice is given the physicians it is not going to have a substantial impact.

Mr. Class again commented that he is concerned that there is no plan to notify providers outside the network. He said this is the first time he has heard about a program on the web that physicians can use. He said he would be satisfied if TMA were to use something like that and say it is their plan for notifying non-network physicians. He said he would continue to oppose 60-day implementations until there is a plan, which they have asked for since February.

Presentation on Prior Authorization Requirement for Mecasermin (Increlex) Injection

Chairperson Hickey next turned the podium over to Dr. Shana Trice of the PEC for the presentation on the Prior Authorization Requirement for Mecasermin (Increlex) Injection.

[Insert script, pages 32-33]

Panel Questions on Mecasermin Prior Authorization

Ms. Hickey asked how many patients in the Military Health System are currently on mecasermin. Dr. Trice said she doubts that there are any MHS patients currently on the drug. In fact, she is not sure that the drug is even commercially available yet. Ms. Hickey said mecasermin was approved by the FDA on August 30, so it is a new drug. She applauded the P&T Committee for moving so quickly to require prior authorization for a drug that obviously has some side effects that are potentially very dangerous.

Dr. Crum asked whether it is anticipated that the distribution of this drug would be through the retail pharmacy and MTF or would it be given by providers in their offices. He asked how the program would operate. Dr. Trice said she doubts that it would be given very often by providers in their offices. She understands that while there are some special distribution provisions, there are no indications from the company that they would limit its availability to one specific pharmacy or do something that would make it unavailable. As far as she knows, it will be available through the retail pharmacy or through mail order.

Ms. Le Gette said she doesn't think the product has actually been launched. The company has said it wasn't going to release it until January. She also applauded the P&T Committee for moving so quickly on this item.

Dr. Trice clarified her earlier statement by stating that if and when the drug becomes available the P&T Committee isn't anticipating that it will be used by a lot of patients.

Panel Discussion on Mecasermin Prior Authorization

There was no additional discussion of this agenda item by the Panel.

Panel Vote on Mecasermin Prior Authorization

The Chair read the P&T Committee recommendation:

"Based on the need for careful patient selection to ensure safety and effectiveness, the P&T Committee recommended that a PA be required for mecasermin."

The Beneficiary Advisory Panel voted unanimously (12-0) to concur with the recommendation.

Panel Discussion and Vote on Mecasermin Prior Authorization Implementation Period

The P&T Committee recommended that the PA should have an effective date no later than the first Wednesday following a 30-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

There was no Panel discussion of the implementation period.

The Panel voted 11 for and one against to concur with the recommended implementation period.

Panel Comments on Mecasermin Prior Authorization Implementation Period

There were no Panel comments included in the record on this item.

Presentation on Antidepressants I (AD1) Drug Class

Consideration of this agenda item was deferred from the morning session until the afternoon session.

The Chair announced that Mr. Washington would not be present for the afternoon session.

She then turned the podium over to Dr. Shana Trice for the PEC presentation on the antidepressant I drug class.

[Insert script, pages 15-24]

Dr. Crownover next added comments to the presentation. He stressed that the Committee had not engaged in a cost minimization exercise. It selected ten drugs for depression to be kept on the Uniform Formulary - a wide variety from which to select. He cited Zoloft as an example to show this was not a cost minimization exercise. The Committee looked at Zoloft very closely. It has a very high per-fill cost, but it has multiple indications, it's popular with both doctors and patients, it's a very clean drug in terms of drug interactions and it's effective. Therefore, it was kept on the formulary despite its high cost.

Dr. Crownover then addressed the discussions regarding the drugs recommended for non-formulary status, starting with Paxil. He said the situation is a little confusing, especially in regard to Paxil IR. Unlike Bupropion IR, which is a three-times a day drug, Paxil IR is a once-a-day drug, as is the CR formulation. There was only a one percent gain in the discontinuation rate due to nausea with Paxil over paroxetine IR for a substantial difference in cost. Regarding Bupropion XL, which is a once-a-day drug, again there is a big difference in cost for the convenience of once-a-day dosing rather than two or three times a day.

Regarding Duloxetine, it has a second indication that none of the other agents have - diabetic peripheral neuropathy. However, the established treatment already in place to provide for diabetic peripheral neuropathy includes three groups of agents that are going to be used, so Duloxetine would be a fourth line of treatment. The Committee felt that leaving three standard, proven treatments in place for diabetic peripheral neuropathy would be sufficient.

Regarding Escitalopram, there is maybe a 10-15 percent difference in the response rate compared to Citalopram (Celexa). However, the Committee was concerned about having a branded product under patent and with marketing pressures in the MTF. In the end, it considered the gain in response rates to be outweighed by the differences in cost.

Panel Questions on the Antidepressant I (AD1) Drug Class

Mr. Hanson asked about figure 2 on page 5 of the Panel handout. He noted that with Lexapro there is a marked increase in use from the time of its introduction to where it is now the second most used prescription and asked about the reasons for that. Dr. Crownover explained that the year before Lexapro was introduced (2002), the same people that were pushing Citalopram (Celexa) started pushing Escitalopram (Lexapro), saying it was even better.

As a follow-on question, Mr. Hanson called attention to figure 4 on page 6, which shows Paxil CR falling off dramatically and asked for an explanation of that. Dr. Trice answered that the reason is that it was off the market for a while (March through June, 2005) because of some trouble with the controlled release formula. She said the graph also looks like providers put people on Paroxetine IR immediately.

Dr. Prasad said the only problem he has with the recommendations concerns Wellbutrin XL, which is recommended for non-formulary status. He said the graph (figure 6) shows that the Wellbutrin XL formulation is at about the same use level as the SR and IR formulations. He said as a physician he prefers to use once-a-day drugs to improve compliance. Dr. Trice acknowledged the convenience of the once-a-day dosing, but said that it was taken into account in the cost analysis, which shows that the gain is not enough to warrant the increase in cost. Dr. Crownover agreed, saying that he, too, would prefer the once-a-day formulation but the manufacturer is simply not cooperating on price - the cost is almost twice that of the other formulations. Dr. Trice added that she believes some of the increase in use is due to off label uses of the agent.

Ms. Hickey said she is concerned about the number of providers responding (42). She asked if the pediatrician and OB/GYN providers had been included in the survey. Dr. Trice said that they had not been included. She said she thinks it is predictable what the pediatricians would have said because fluoxetine is the only one with an indication. Ms. Hickey said is looks like a number of the providers who responded were not comfortable with what they prescribe

themselves, or maybe they just felt that whatever they said wasn't going to make any difference. Her point is that for such a large class of drugs the provider response appears to very small. Dr. Trice said the way the surveys are sent out is through the Pharmacy Services consultants and from there to individual providers. Because of this, one response may reflect the views of an entire group of physicians at one location. Dr. Trice also said that one specific thing they did in connection with the cost effectiveness modeling was they went to Wilford Hall Medical Center and talked to the providers there in psychiatry to get more information about their actual practices (how long do they give a drug, how long do they wait before they switch to another drug, how many patients would end up in specialty care?). That form of feedback can't be captured in a survey.

Mr. Class asked how much the secondary cost of non-compliance figures in to the PEC cost study. Dr. Trice said it is very difficult to determine the impact of noncompliance for specific anti-depressants because there is so much non-compliance anyway. Probably half the patients don't fill their prescription after the first time. The patient populations included in clinical trials, who are typically patients with mild to moderate major depressive disorder, are most likely different from patients in the community, who may have dysthymia or minor depression. Patients in the community may be even less likely to continue taking antidepressants than those in clinical trials. There is no way to turn the lack of compliance into a number, but the P&T Committee did assess that as they went along. Dr. Crownover said they have generalized compliance numbers across the board (for twice-a-day versus four-times-a-day, for example) but they have no data for antidepressant medications. Mr. Class said that without data, the Committee could be adding quite a lot of cost to the MHS and not know it. The figures may show a cost reduction in the drug itself, but the analysis may be doubling or tripling the cost of treatment. Dr. Crownover agreed with the point, but added that the Wellbutrin SR is also being marketed for smoking cessation. Some patients don't want the extended release versions because they need the "bump" from the SR for attention deficit disorder (ADD) or even smoking cessation. A lot of first time users of Wellbutrin SR are using it for smoking cessation.

Ms. Schlaifer asked, regarding Fluoxetine and Escitalopram, whether being controlled on a specific SSRI is considered a justification for medical necessity. Dr. Trice said the Committee did discuss this question. The actual wording of the formulary rule has to do with whether it would incur risk to the patient. If a patient has actually been controlled on one of these drugs for a long time, she believes the Committee would agree that would be considered a reason to qualify for the medical necessity. Ms. Hickey asked what is considered "long term." Dr. Trice answered that, given the rate of non-compliance, filling a prescription for the second or third time could pretty much be considered "long term." Whether or not antidepressants are truly used long-term would also depend on whether it is the patient's second episode or third episode. Certainly a third episode of depressions would be treated with long term therapy.

Ms. Hickey asked if there is information about what percentage of patients receiving anti-depressant drugs at the MTF are active duty. Dr. Trice said this analysis was not done. Ms. Hickey followed up by asking if that means that the PEC also doesn't know what percent of those deployed are on one of the drugs that are going to go non-formulary. Dr. Trice did not know, but said they could get the figure. MAJ Watson disagreed, stating this figure was not available. Ms. Hickey said she has a very strong concern with the active duty folks that are either in country or within six months of going. She suggested there should be a blanket medical necessity allowed for those situations.

Mr. Hanson asked what drugs in this class are being given to the troops when they come back - are there one or two preferred drugs or is it pretty much a "cocktail mix." The answer given was that it is generally the latter, a cocktail mix. Mr. Hanson followed up by asking about the dosing frequency. Dr. Crownover replied by saying that there are five SSRIs on the Uniform Formulary. It is a very substantial menu.

Ms. Hickey clarified that what she is talking about is not the "menu" but about individuals who are in country (in a hostile environment) or somebody who is now getting ready to go. She thinks it is ridiculous to add one more thing on their back, i.e., changing their medication a month before they leave. Dr. Crownover said he agrees. But he pointed out that the only potential problem is with patients who are on Duloxetine. Patients on the others would have access to alternative formulations of the same agent. The majority of those on Duloxetine are coming from non-network providers. Active duty folks who are being treated at MTFs are not being put on Duloxetine.

Mr. Hanson said one thing he noticed that would be applicable is Prozac Weekly. If you're out in the field it makes more sense to have a weekly drug than a daily drug. Any warrior coming back will tell you that the timeframe is entirely off. They will go for a period where they miss three or four meals and suddenly it catches up with them. Under these conditions, a patient isn't going to know that it's time to take the medication. He said it could be very detrimental to the missions in the field to deny a medication that has extensive use by making it non-formulary. Another Panel member pointed out that it would be just as difficult to remember what day of the week it is. Dr. Trice replied that if there had been any evidence of Prozac Weekly having equal efficacy with the daily product, the outcome might have been different. However, the evidence doesn't support that finding. She also agreed that remembering to take the medication could be more problematic with the weekly.

Mr. Hutchings said that the Prozac Weekly is just a novel formulation that happened to come out. It doesn't really last for 40 hours; only two or three. The extended release is more of a marketing ploy. Dr. Trice agreed that the agent is only a delayed release; they don't yet know how to really make it last a week yet. Fluoxetine, however, has the advantage of lasting a long time in the body so a patient could skip a day or two and probably not be in trouble. Dr. Crownover agreed, noting that Fluoxetine is the only drug like that, i.e. if you stop it abruptly it hangs around a long time.

Ms. Hickey asked about active duty personnel who become ill or are injured in theater, require long-term recuperation and have to be sent back home. She pointed out that "back home" for most active duty reservists is not by an MTF, so they are being treated by civilian providers in their home town. Because they are active duty, they get their medications for free at the TMOP or the retail pharmacy. But because they are active duty and the provider is not an MTF provider, it means that the provider cannot use the medical necessity for that active duty person.

MAJ Watson answered that as long as the provider is following the criteria they can go ahead and perform the medical necessity, but it has to be approved prior to the active duty person getting the prescription filled at any other points of service, i.e. by the contractor if the mail order or retail is being used or by the MTF. Ms. Hickey asked if Express-Scripts, Inc. (ESI) does medical necessity for the active duty servicemember who is getting their prescriptions filled at a retail pharmacy or a mail order pharmacy because they do not live near a Military Treatment Facility. MAJ Watson replied that is correct. Ms. Hickey said she apparently had been

misinformed because she was under the impression that ESI could not do medical necessity for active duty members.

Mr. Hanson said there would also be an issue with transition. The same people get access to U. S. Department of Veterans Affairs (VA) for two years, so there might be a potential conflict between the VA Formulary and this Formulary because individuals may be using two systems. Dr. Trice said that the VA and the DOD do have different formularies. In this case, the same drugs are likely to be available on both formularies. However, if a non-formulary medication is medically necessary for a given patient, it should be available from either the VA or DOD - both systems have mechanisms to handle non-formulary medications.

Ms. Le Gette, referring to the table on page 4 where the drug class is broken down by drug and point of service, said three of the drugs recommended for non-formulary status - Wellbutrin XL, Cymbalta and Paxil CR - have huge amounts of users in retail. This supports Dr. Crownover's point about the amount of marketing going on. The MTFs obviously have much tighter control.

Mr. Partridge commented that the cost of making an exception for those about to go in theater would be negligible, although he understands that the administration of it might be difficult. He really believes that DOD needs to make an exception for these people. It is very difficult to manage this in a combat zone.

Panel Discussion of the Antidepressant I (AD1) Drug Class

Chairperson Hickey began the discussion period by reading that portion of Dr. Lenow's letter that deals with the antidepressant I drug class:

"I must note my conflict on the antidepressant category as my company does event planning work for the Effexor XR brand (Venlaxafine). But for what it's worth, I have a very strong background and expertise in this category. I would note that the P&T review effort was spot on in my estimation and I found little to argue with in their summary conclusions and recommendations in this area."

Mr. Hanson said he feels uncomfortable with the situation with deployment and the potential complications that would occur. Because the things discussed might happen, he feels forced into taking a negative position on these recommendations.

Ms. Hickey added she also intends to vote negatively because of the active duty implications. If there was a resolution of these questions, she would not go that way.

Mr. Hutchings asked if it might be possible to formulate a comment before the vote. He said he intends to vote to concur. He expressed the view that sometimes the Panel's votes to concur and non-concur are actually the same vote and he believes that a comment might help to clarify the situation.

Ms. Hickey agreed to formulate a comment and give Panel members the opportunity to sign on to the comment, whether or not they vote to concur or non-concur on the P&T Committee recommendations.

After a brief discussion, the comment agreed to was:

Many members of the Panel were extremely concerned about changing an antidepressant drug for an active duty servicemember who was either within six months of deployment or actually in a hostile zone. Some members of the Panel non-concurred with the recommendations of the P&T Committee for that reason. Some members of the Panel concurred with the recommendations of the P&T Committee but were equally concerned about the active duty issue. Panel members believe there should be an exception to the current policy for active duty servicemembers who are or are about to be deployed."

By show of hands, all members of the Panel agreed to sign on to the above comment.

Panel Vote on the Antidepressant I (AD1) Drug Class Formulary Recommendation

The Chairperson read the P&T Committee recommendation:

"The P&T Committee, based upon its collective professional judgment, voted to recommend that fluoxetine (Sarafem) in special packaging for Premenstrual Dysphoric Disorder (PMDD), fluoxetine weekly (Prozac Weekly), escitalopram and paroxetine CR, duloxetine, and bupropion XL be classified as non-formulary under the UF, with bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlaxafine remaining on the UF. In addition, the P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued."

The Panel vote was 7 concur and 4 non-concur.

Panel Comments on Antidepressant I (AD1) Drug Class

The Panel added the comment already agreed to (see "Discussion" above).

Mr. Class commented that the Wellbutrin XL analysis should be revisited to reconsider the question of compliance and the secondary cost of non-compliance.

Mr. Hanson commented that if a similar case to that just reviewed comes up, i.e., one where a drug has utilization within a combat arena, he hopes that the P&T Committee would use their expertise to provide some explanation or recommend exceptions that might be made in order to help the Panel with its future decisions.

Dr. Prasad asked that the P&T Committee start using brand names in place of generic drug names except where "generic only" will be filled. As a provider he is more familiar with the brand names. Several other Panel members indicated their agreement with this request.

Panel Discussion and Vote on the Implementation Plan for Antidepressant I (AD1) Drug Class

The Chair read the P&T Committee recommendation:

"The P&T Committee recommended an effective date no later than the first Wednesday following a 180-day implementation period."

Ms. Hickey pointed out that the 180-day period is the longest that the law allows.

Mr. Hanson asked the Chair if her impression was that a longer period would be helpful. Ms. Hickey replied that the original law states that the implementation period can be no longer than 180 days.

Ms. Hickey asked whether those Panel members who voted to non-concur on the formulary recommendation ought to vote on the implementation period recommendation. MAJ Watson advised the Chair that all Panel members should vote on the recommendation because it is a separate issue.

The Panel voted unanimously (11-0) to concur with the 180-day implementation period recommendation.

Closing Comments

The Chairperson noted that several letters from the public had been submitted to the Panel for consideration. They are available on the BAP website and members should read them.

She indicated that the Panel anticipates and expects that read-ahead materials for the meetings will be received two weeks before the meeting date in the future.

She announced that the next meeting of the Beneficiary Advisory Panel is scheduled for March 30, 2006. The Panel anticipates looking at three categories of drugs at that time: medications for overactive bladder, miscellaneous hypertension agents and anticonvulsants used for the treatment of neuropathic pain.

Ms. Fryar expressed her appreciation for the additional information provided with the read ahead materials, especially the extended tables. She said she would also like to see the introductory page designate what categories the individual Panel members are representing. She also asked if a chart could be developed showing the overall rankings of drugs in the system in terms of their utilization, perhaps the top 100. It would also be helpful to have a ranking in terms of their cost to the MHS.

Lt Col Bennett said the difficulty is that there are pre-defined classes of drugs that have been in place for years. These are changing as the Uniform Formulary is developed. So the information may not be readily available, although it has been up until now. He said the PEC would do the best they can.

Mr. Class asked about the matter of conducting re-reviews where there is any change, such as when a medication that is currently third tier goes generic or there is a substantial price change. He said it would be helpful to him if the Panel could get some information about what the process is for doing that. He doesn't want to make a decision now, have the situation change and be stuck with it for four or five years until we look at it again.

Lt Col Bennett said that part of the critical review is trying to forecast as best they can what is happening in the generic market. Even so, it isn't always clear what the patent rights for these

medications are. All classes are re-reviewed on a periodic basis anyway. Classes where there are a lot of changes would be reviewed more often.

Mr. Class repeated that a communications plan for TRICARE Standard providers is urgently needed.

Mr. Class also said it would be interesting to look and see if the migrations forecast by the group for the earlier classes have actually happened - if the cost mechanism has actually panned out. The Chairperson replied that a review of two earlier classes considered by the Panel is on the agenda for the March meeting.

Mr. Hanson asked, following up on Mr. Class' earlier question, whether, if an individual drug goes generic and there are big changes in its cost, the P&T Committee is required to look again at the whole class or can it just revisit the particular drug as an interim measure until the whole class gets reviewed. Lt Col Bennett said that if a new drug enters the market, they can review it and compare it to the top effective drugs already on the Uniform Formulary. If a drug goes generic, they would have to look at things on a case-by-case basis and see what makes sense for that particular class. The P&T Committee has the latitude to do that and would deliberate about it.

Mr. Hutchings commented on the Chair's statement regarding MTF providers not writing non-formulary prescriptions. He said he works with 120 physicians who have ways of handling situations where patients ask for non-formulary medications. He said it isn't that they are forbidden from writing the non-formulary prescriptions, but there are often good reasons for not doing so. Ms. Hickey said the Panel is obliged to go by the letter of the law, which states that third-tier drugs should be available to beneficiaries who wish them and whose provider is willing to prescribe them, regardless of internal policy considerations.

The Chairperson adjourned the meeting at 1:45 P.M.

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.

- ABECB — Acute Bacterial Exacerbation of Chronic Bronchitis
- ABS — Acute Bacterial Sinusitis
- AD1 — Antidepressant I (a drug class)
- ADD — Attention Deficit Disorder
- ADHD — Attention Deficit Hyperactivity Disorder
- BAP — Uniform Formulary Beneficiary Advisory Panel (the "Panel" referred to above)
- BCF — Basic Core Formulary
- BIA — Budget Impact Analysis
- CCOHTA — Canadian Coordinating Office of Health Technology Assessment
- CEA — Cost-effectiveness analysis
- C.F.R — Code of Federal Regulations
- CMA — Cost-Minimization Analysis
- CR — Controlled release (a drug formulation)
- DFO — Designated Federal Officer
- DOD — Department of Defense
- DPNP — Diabetic Peripheral Neuropathic Pain
- ER — Extended Release (a drug formulation)
- ESI — Express-Scripts, Inc.
- FACA — Federal Advisory Committee Act
- FDA — U.S. Food and Drug Administration
- GAD — Generalized Anxiety Disorder
- HIV — Human Immunodeficiency Virus
- HMO — Health Maintenance Organization
- IGF-1 — Insulin-like Growth Factor-1
- IR — Immediate release (a drug formulation)
- MAUT — Multi-Attribute Utility Table (an analytical tool for quantifying effectiveness differences)
- MHS — Military Health System
- MAOIs — Monoamine Oxidase Inhibitors
- MDD — Major Depressive Disorder
- MTF — Military Treatment Facility
- NICE — British National Institute for Clinical Excellence
- NMDA — Acetylcholinesterase Inhibitor and N-Methyl D-Aspartate (a drug class)
- OCD — Obsessive Compulsive Disorder
- IHSU-DERP — Oregon Health & Science University Drug Effectiveness Review Project
- OTC — Over the counter

- PA — Prior Authorization
- P&T Committee — DOD Pharmacy and Therapeutics Committee
- PD — Panic Disorder
- PEC — DOD Pharmacoeconomic Center
- PMDD — Premenstrual Dysphoric Disorder
- PTSD — Post-Traumatic Stress Disorder
- SAD — Social Anxiety Disorder
- SNRIs — Serotonin Norepinephrine Reuptake Inhibitors (a sub-class of the antidepressant I drug class)
- SR — Sustained release (a drug formulation)
- SSRIs — Selective Serotonin Reuptake Inhibitors (a sub-class of the antidepressant I drug class)
- SUI — Stress Urinary Incontinence
- TCAs — Tricyclic antidepressants
- TMA — TRICARE Management Activity
- TMOP — TRICARE Mail Order Pharmacy
- TRRx — TRICARE Retail Pharmacy Program
- UF — DOD Uniform Formulary
- U.S.C. — United States Code
- VA — U.S. Department of Veterans Affairs

16 December 05 BAP Script

Good Morning,

I'm LtCol Dave Bennett, Director of Clinical Operations at the PEC. Joining me today from the clinical PEC clinical operations staff are Shana Trice and Eugene Moore - Staff Clinical Pharmacists and analysts, and Maj Wade Tiller Pharmacoeconomic Analyst.

Also joining us are CDR Richerson, PEC Director, CAPT Patricia Buss, Chairman of the DoD Pharmacy and Therapeutics Committee, and LtCol Brian Crownover, Physician member of the Pharmacy and Therapeutics Committee.

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).

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

1) A brief overview of the relative clinical-effectiveness analyses considered by the DoD P&T Committee.
2) A brief general overview of the relative cost-effectiveness analyses. This overview will be general in nature since we are unable to disclose the actual costs used in the economic models. This overview will include the factors used to evaluate the costs of the agents in relation to the safety, effectiveness, and clinical outcomes.
3) The DoD P&T Committee's Uniform Formulary recommendation based upon its collective professional judgment when considering the analyses from both the relative clinical and relative cost-effectiveness evaluations of the Alzheimer's medications (acetylcholinesterase inhibitors and n-methyl D-aspartate receptor antagonist), nasal corticosteroids, selected antidepressant medications, and the macrolide/ketolide class of antibiotics.
4) The DoD P&T Committees recommendation as to the effective date of the agents being changed from formulary tier to the non-formulary tier of the Uniform Formulary. Based on 32 C.F.R. 199.21, such change will not be longer than 180 days from the final decision date but may be less.

Mr. Eugene Moore will now present the first class review.

I'm going present the class review for the ALZHEIMER'S DRUGS, the ACETYLCHOLINESTERASE INHIBITORS AND N-methyl D-aspartate (NMDA) RECEPTOR ANTAGONIST)

Relative Clinical Effectiveness:

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

There are five drugs marketed in the US for the treatment of Alzheimer's disease. (See table 7 on page 10 in your handout). This category includes the acetylcholinesterase inhibitors donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne), and tacrine (Cognex), and the NMDA receptor antagonist memantine (Namenda). These drugs are used to treat the cognitive symptoms of Alzheimer's disease like memory and awareness.

Relevance to MHS and Utilization: Look at figure 8 on page 10 of your handout. Together the five Alzheimer's drugs account for approximately $65M annually in Military Health System (MHS) drug class expenditures. Donepezil is the most popular acetylcholinesterase inhibitor in the MHS; it is ranked #1 in utilization (number of prescriptions) at all three venues (MTF, mail order, and retail network). The NMDA receptor antagonist memantine is #2 in utilization at all three venues. In the twelve month period prior to the November 2005 meeting, there were approximately 69,940 unique utilizers of Alzheimer's drugs in the MHS; 56% of patients receiving an Alzheimers drug in the MHS are receiving donepezil, while 26% are receiving memantine. Among patients taking memantine, 64% took memantine alone, 24% took it in combination with donepezil, 7% took it in combination with galantamine and 5% with rivastigmine.

FDA Indications: All of the acetylcholinesterase inhibitors are approved for treating the memory and awareness symptoms of mild to moderate dementia of Alzheimer's disease. (Refer to table 7 on page 10 in your handout). Memantine is FDA-approved for the treatment of moderate to severe dementia of Alzheimer's disease, alone or in combination with acetylcholinesterase inhibitors.

Based on the relative clinical effectiveness review the DoD P&T committee concluded the following 8 points:

1) Tacrine has less clinical utility than the other acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease because it has been associated with liver toxicity.
2) The safety concerns related to liver toxicity with tacrine outweighed any cost benefit that might be obtained by keeping it on the Uniform Formulary.
3) The remaining acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) have similar relative clinical effectiveness for treating mild to moderate symptoms of dementia of the Alzheimer's type.
4) Memantine has a place in therapy for the treatment of moderate to severe dementia of Alzheimer's disease.

5) Donepezil and galantamine are more likely to cause drug interactions than the other Alzheimer's drugs. However, these drug interactions are not considered to be clinically important.
6) With regard to safety and tolerability, memantine has an adverse event rate similar to placebo.
7) While minor differences exist between galantamine, rivastigmine, donepezil and memantine, none were considered significantly different with respect to major contraindications, drug interactions or adverse reactions.
8) Donepezil and the extended release formulation of galantamine (Razadyne ER) have a clinical advantage in that they are dosed once daily, thus allowing for easier dosing adjustments in new patients, as compared to the other acetylcholinesterase inhibitors. DoD providers expressed a preference for donepezil due in part to its once daily dosing and ease of titration. However, there is no evidence to support clinical superiority of any one Alzheimer's agent over another based dosing and titration schedules or DoD provider opinion.

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

(Data Source): To answer the key questions (which we are going to discuss next), the Alzheimer's drugs relative clinical effectiveness analysis evaluated information from randomized, clinical trials (which were used to produce the Alzheimer's drug class review). Additional published clinical trials were found using a Medline Search, searching major medical journals table of contents, and manufacturer press releases. Systematic reviews from the Cochrane Collaboration, the Canadian Coordinating Office of Health Technology Assessment (CCOHTA), and the British National Institute of Clinical Excellence (NICE) were also consulted. The FDA website was monitored for new indications.

(Key question #1) What is the relative clinical effectiveness (between agents) of drugs used to treat symptoms of Alzheimer's disease: The Committee concluded that there is no evidence that any one Alzheimer's drug is preferable to the others with respect to clinical effectiveness. All of the drugs used for Alzheimer's disease show statistically significant changes in cognition rating scores compared to baseline. Whether these results are clinically significant is debatable. There are no direct comparative trials available, but there is no evidence to suggest that any one Alzheimer's disease drug is more efficacious than another, when used according to FDA indications.

In well-designed randomized controlled trials, involving donepezil vs. placebo, rivastigmine vs. placebo, galantamine vs. placebo and tacrine vs. placebo, all of the acetylcholinesterase inhibitors showed statistically significant differences compared to placebo in the endpoints used in the studies to evaluate memory/awareness. Systematic reviews by Cochrane, the British National Institute for Clinical Excellence (NICE), the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) and others have found that treatment with these drugs gave a small clinical benefit when compared to placebo.

Conclusion: The DoD P&T Committee agreed there is no evidence that any one Alzheimer's drug is preferable to the others with respect to clinical effectiveness.

Next, we're going to address questions #2 and #3 together.
Key question #2 What are the differences in side effect profiles (serious or life threatening or those that may adversely effect compliance) of drugs used to treat symptoms of Alzheimer's Disease:, and

Key question #3 Are there subgroups of patients based on demographics (age, gender), other medications, co-existing illnesses, or severity of illness for which one drug used to treat symptoms of Alzheimer's disease is more effective or associated with fewer adverse events:

Serious effects – liver toxicity: Tacrine is the only drug in the class that has been associated with serious liver toxicity. Almost ¾ of patients receiving tacrine at high doses may have to stop treatment due to lab tests showing decreased liver function. The FDA requires a black box warning for the possibility of severe liver failure and death, and frequent monitoring of lab tests is mandated for patients using tacrine.

Side effects: Rivastigmine and galantamine are associated with a higher incidence of gastrointestinal side-effects (nausea and vomiting) and consequently require more complex dosage adjustment than the other cholinesterase inhibitors or memantine. A complex dosage adjustment schedule possibly affects the likelihood that patients will be able to comply with these regimens. In clinical trials of memantine, the numbers of patients who stopped therapy due to side effects was the same with memantine and placebo. This shows that memantine has a relatively safe side effect profile.

Drug interactions: Donepezil and galantamine may be prone to more drug interactions than other agents. However, it should be noted that these interactions are not generally considered to be clinically significant.

Conclusion: The DoD P&T Committee agreed that among the acetylcholinesterase inhibitors, tacrine differed significantly in terms of safety due to its potential to cause liver injury. While minor differences exist among the other acetylcholinesterase inhibitors and memantine, none were considered significantly different with respect to major contraindications, drug interactions, or adverse drug reactions.

Key question #4 Is it feasible to designate one or more of these drugs as non-formulary on the Uniform Formulary: The four acetylcholinesterase inhibitors and memantine represent the only agents for the treatment of Alzheimer's disease available in the United States. Efficacy with these agents is measured in terms of slowing the progression of disease, rather than improving the patients' functioning. The four cholinesterase inhibitors and memantine all exhibit slight advantages in efficacy over placebo. Tacrine is associated with clinically significant, severe liver toxicity and would thus be a potential candidate for non-formulary designation. Based upon the available clinical evidence there is nothing that would preclude non-formulary designation for any of the other available agents.

Conclusion: The DoD P&T Committee concluded that it is feasible to designate one or more of the Alzheimer's drugs as non-formulary on the Uniform Formulary.

Overall Clinical Conclusion: Tacrine has serious liver safety concerns that limit the clinical utility of this drug. The remaining acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) have similar relative clinical effectiveness for treating mild to moderate symptoms of dementia of the Alzheimer's type. Memantine has a place in therapy for the treatment of moderate to severe dementia of Alzheimer's disease.

Committee Discussion: There was lengthy discussion among the DoD P&T Committee members regarding the potential for non-formulary designation of any of the acetylcholinesterase inhibitors or memantine. The results of the provider survey were presented to better understand how MHS providers use these drugs in clinical practice. The responders included neurologists, geriatricians, internists, and family practitioners. The majority of providers favored products with once daily dosing. (donepezil, galantamine ER) Most responders said they avoided tacrine because of liver toxicity; all preferred donepezil because it is easy to titrate and many providers were familiar and comfortable with using it. Most providers said that they add memantine or switch to memantine when acetylcholinesterase inhibitors fail to provide expected benefit. Most felt that these medications should not be discontinued, even if patients don't continue to respond, because it is felt that a rapid deterioration of their condition will occur.

There was significant discussion concerning the safety of tacrine since it is well known to cause liver problems. A key question in considering whether the status of tacrine should remain formulary on the UF was whether or not the potential problem of liver toxicity was self-limited by the low usage of this agent. Currently there are only five users of tacrine in DoD. The P & T Committee acknowledged that utilization was low, but felt that in the interest of safety, tacrine should not remain on the Uniform Formulary. Furthermore the safety concerns regarding the use of tacrine outweighed any cost benefit that might be obtained by keeping it on the Uniform Formulary.

This concludes the clinical presentation for the Alzheimer's drugs, next we're going to move on to the Relative Cost Effectiveness:

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

The first step in determining the relative cost-effectiveness of the selected agents in this class was to conduct a cost-analysis to calculate the total weighted average cost per day of treatment for each agent. The second step was to conduct the appropriate pharmacoeconomic analysis taking into account the conclusions of the clinical review. Because the clinical review concluded that all of the agents within the Alzheimer's drug class, with the exception of tacrine, had similar relative clinical effectiveness (efficacy, safety and tolerability), a cost-minimization analysis

(CMA) was selected. To adjust for the safety issues associated with the use of tacrine, the cost of monitoring liver function tests was added to the drug cost of tacrine in the CMA.

The cost analysis only considered drug costs. The results showed tacrine to be the acetylcholinesterase inhibitor with the lowest total weighted average cost per day of treatment across all points of service (MTF, Retail, Mail). The CMA, which considered lab costs for monitoring tacrine, showed that donepezil was the most cost-effective agent when the additional requirement of multiple liver function tests was taken into account.

The results of the above analyses were then incorporated into a Budget Impact Analysis (BIA), which accounted for other factors and costs associated with a potential decision regarding formulary status of Alzheimer's drugs within the UF. These factors included market share migration, cost reduction associated with non-formulary cost shares, medical necessity processing fees, and switch costs. The results of the budget impact analysis further confirmed the results of the CMA. Donepezil was found to be the most cost-effective Alzheimer's drug overall.

Conclusion: The P&T Committee agreed (17 for, 0 against, 1 abstained, 1 absent) with the relative cost-effectiveness analysis of the Alzheimer's drugs presented. The P&T Committee concluded that the safety concerns regarding the use of tacrine outweighed any cost benefit that might be obtained by keeping it on the Uniform Formulary. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the Alzheimer's drugs, the P&T Committee recommended that the status of tacrine be changed from formulary to non-formulary on the Uniform Formulary, with donepezil, rivastigmine, galantamine, and memantine maintaining formulary status on the Uniform Formulary with the formulary cost share. To address the safety concerns of tacrine, a Prior Authorization (PA) for tacrine was initially considered. However, due to the extremely low number of unique utilizers (five) currently being treated with tacrine across the MHS, the P&T Committee felt the medical community was adequately aware of the risks associated with tacrine use, and safety concerns were already being appropriately addressed.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (10 for, 6 against, 2 abstained, 1 absent) to recommend non-formulary status for tacrine, with donepezil, rivastigmine, galantamine, and memantine maintaining formulary status on the Uniform Formulary at the formulary cost share.

Implementation Plan: Because of the low number of beneficiaries that would be affected by this formulary action (five patients known to be taking tacrine across the MHS), the P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

This next section will apply to all the drug classes being discussed today, so we'll only mention it here. Patients wishing to fill prescriptions for Non-Formulary drugs at the Retail network pharmacies or the TMOP will have to pay the non-formulary cost share unless medical necessity for these agents are established by the beneficiary or their provider. MTFs are not allowed to have non-formulary pharmaceutical agents (tacrine) on their local formularies. MTFs will be able to fill non-formulary requests for non-formulary agents only if both of the following

conditions are met: 1) the prescription is written by a MTF provider and 2) the beneficiary and his or her provider has established medical necessity for the agent. MTFs may (but are not required to) fill a non-formulary prescription written by a non-MTF provider to whom the patient was referred as long as medical necessity has been established.

COMMITTEE ACTION: The P&T Committee recommended (17 for, 0 against, 1 abstained, 1 absent) an effective date no later than the first Wednesday following a 90 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

This concludes the clinical and cost presentations for the Alzheimer's drugs, we now would like to turn the meeting over to Ms. Hickey.

Next up are the **NASAL CORTICOSTEROIDS.**

We'll discuss the Relative Clinical Effectiveness first:

Members in the class: The nasal steroids were reviewed for placement on the Department of Defense (DoD) Uniform Formulary. Refer to Table 8 on page 11 of your handout. There are six different drugs in the nasal steroid class; however some of these drugs are available under more than one brand name. There are 8 branded products on the market, but we are only going to refer to the 6 active ingredients, beclomethasone (Beconase AQ, Vancenase AQ), budesonide (Rhinocort AQ), flunisolide (Nasarel), fluticasone (Flonase), mometasone (Nasonex), and triamcinolone (Nasacort AQ).

Generic Availability: Currently there is only one generic for this class, flunisolide (Nasarel). Fluticasone is the next nasal steroid expected to be generic, but the exact date of generic availability is unknown.

Table 1: Nasal steroids available in the U.S *(package inserts)

Generic	Brand (Manufacturer)	Generics available	Strengths & formulations	FDA approval date
Beclomethasone	Beconase AQ (GlaxoSmithKline)	No	42 mcg / dose	July 1987
	Vancenase AQ	No	42 mcg / dose	
	Vancenase AQ DS	No	84 mcg/ dose	June 1996
	Not marketed: Beconase, Vancenase			
Budesonide	Rhinocort AQ (AstraZeneca)	No	32 mcg / dose	October 1999
	Not marketed: Rhinocort			
Flunisolide	Nasarel (Ivax)	Yes	25 mcg / dose	March 1992
	Not marketed: Nasalide (Elan)			
Fluticasone	Flonase (GlaxoSmithKline)	No	50 mcg / dose	October 1994
Mometasone	Nasonex (Schering-Plough)	No	50 mcg / dose	October 1997
Triamcinolone	Nasacort AQ	No	55 mcg / dose	May 1996

Market Availability:
Beclomethasone, and budesonide where previously available in aerosol formulations, but these aerosols are no longer marketed by their manufacturers, due to declining popularity. Today, only aqueous (spray) products are available, since physicians and patients prefer the ease and convenience of the aqueous formulations.

Relevance to MHS and Utilization:

Look at figure 9 on page 11 in your handout. The nasal steroids currently rank #19 overall in terms of Military Health System (MHS) drug class expenditures. In FY 2004, $60.2 million dollars was spent in all three points of service (retail, mail order, and military treatment facility – MTF) on nasal steroids. Fluticasone is the most popular nasal steroid in the MHS; it is ranked #1 in utilization (number of prescriptions) at all three venues (MTF, mail order, and retail network). Mometasone is #2 in utilization at all three venues. There are 778,000 unique utilizers of nasal steroids in the MHS; 70% of patients receiving a nasal steroid in the MHS are receiving fluticasone, while 13% are receiving mometasone.

Once again, we're going to give the conclusion first, then go back and discuss the differences between the nasal steroids. Based on the relative clinical effectiveness review the DoD P&T committee concluded the following six points:

1) In comparable doses, the nasal steroids are equally effective at relieving symptoms of allergic rhinitis and have similar local side effect profiles.
2) All the nasal steroids have the risk of being absorbed systemically (into the bloodstream) and causing adverse effects. However, if the nasal steroids are used according to the package insert, this risk is extremely low.
3) Nasal steroids that are dosed once daily (budesonide, fluticasone, mometasone, and triamcinolone) may have advantages in patient preferences over products requiring multiple daily dosing (beclomethasone and flunisolide).
4) All of the available nasal steroids can be used in patients older than 6 years of age. Mometasone is indicated for use in pediatric patients as young as 2 years of age, while fluticasone can be used in children as young as 4 years old.
5) Budesonide is has a FDA pregnancy category B rating, while the other nasal steroids have a FDA pregnancy category C rating.
6) There is no evidence to support a clear difference between the nasal steroids in terms of patient preference and tolerability.

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

Key Questions:

1) What are the differences in efficacy amongst the nasal steroids?
2) How relevant are systemic effects of growth suppression, adrenal suppression (fight or flight response of the immune system), and cataract risk in the pediatric, adult, and elderly populations?
3) Do patient preferences and tolerability of local adverse events (nasal irritation, stinging, etc) affect patient compliance/adherence to therapy?

(Data Source): To answer the key questions, the nasal steroids relative clinical effectiveness analysis evaluated information from meta-analysis reviews, systematic reviews, and published head-to-head randomized clinical trials (which were used to produce the nasal steroid class review). Several sections of the review were also adapted from the Veterans Administration Pharmacy Benefits Management Strategic Healthcare Group Drug Class Review for Intranasal

Steroids in January, 2001. The published clinical trials were found using a Medline Search, searching major medical journals table of contents, and manufacturer press releases. Also, the FDA website was monitored for updates.

Key question #1 What are the differences in efficacy amongst the nasal steroids?: All of the nasal steroids are FDA-approved for the treatment of allergic rhinitis. Most of the clinical trials used endpoints that required a patient to score their allergic symptoms such as nasal congestion, sneezing, runny nose, nasal itching, and burning or tearing eyes. All levels of evidence, including head to head trials, placebo controlled trials, and systematic reviews concluded that all the nasal steroids were equally effective at relieving allergic rhinitis symptoms when used at comparable doses. Possible differences may lie in individual physician/patient preferences and population specific safety concerns.

Conclusion: The DoD P&T Committee agreed there is no evidence that one nasal steroid is more efficacious than another for treating allergic rhinitis symptoms.

Key question #2 What are the differences between the nasal steroids in systemic side effects, such as suppression of the adrenal gland, growth suppression in children, and eye cataract formation. Also, how relevant are these systemic effects in the pediatric or adult patient? AND What are the differences between the nasal steroids for local side effects such as nose bleeds and nasal irritation.

Although the nasal steroids are inhaled through the nose to work locally, there is a concern that long lasting side effects can occur if these products are absorbed into the body. The side effects we're going to talk about are also a concern with steroids used in asthma inhalers, and oral steroids, such as prednisone.

Adrenal gland suppression: As steroids build up in excess in the blood stream there is a risk of altering the release of a hormone called cortisol from the adrenal gland. Cortisol secretion increases in response to any stress in the body, whether physical (such as illness, trauma, surgery, or temperature extremes) or psychological. Excesses or deficiencies of this hormone can lead to various physical symptoms and disease states.

Two separate review articles, one evaluating 19 randomized clinical trials and the other 7 randomized clinical trials, found no significant differences between the nasal steroids in causing adrenal suppression. It is unlikely that the risks of adrenal suppression differ among the nasal steroids, but theoretically fluticasone and mometasone may confer lower risk since they are less likely to accumulate in the bloodstream than the other nasal steroids.

Growth suppression in pediatrics: The FDA requires all asthma steroid inhalers and nasal steroids to include a warning label in their package inserts regarding the potential risk of growth suppression in children. Growth suppression has been demonstrated with oral steroids (prednisone) and inhaled steroids (asthma inhalers), but there has been no clear evidence to support the link to nasal steroids. The risk of growth suppression is more likely to occur if large amounts of steroids from any source are absorbed and accumulate in the body. Children who are receiving multiple steroid therapies (oral prednisone, asthma inhalers, and nasal steroids) should be routinely monitored by their physician for potential

growth suppression. In general, nasal steroids should be used at the lowest effective dose in children to minimize the risk of growth suppression. It is unlikely that any one nasal steroid has a larger risk of growth suppression, when used alone without any other steroid source.

Cataracts: If steroids are used in excess doses for long periods of time there is a concern for an increased risk of cataract formation. A large retrospective study in the United Kingdom in 300,000 patients found that there was no increased association between any single nasal steroid and formation of cataracts. However, an increased risk of cataracts was seen with oral prednisone. Excessive doses of nasal steroids can sometimes cause cataracts, but this is rare. There is not enough evidence to predict whether a single nasal steroid is more likely to cause cataracts than another

Local side effects: Nasal irritation, nose bleeds, and runny noses are the most common local adverse events, and are equally likely to occur with any of the nasal steroids.

Conclusion: It is unlikely that any one nasal steroid has a higher risk of causing local side effects than another. For systemic effects (adrenal suppression, growth suppression, and cataract formation), there is no definitive evidence that one nasal steroid is more likely to cause these effects than another. According to the package inserts of all the nasal steroids, the risk of systemic effects are increased when higher than normal amounts of nasal steroids are used.

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

Dosing frequency: Most of the products are marketed for once daily administration. Theoretically once daily dosing may result in improved patient compliance vs. products requiring multiple daily dosing. Budesonide, fluticasone, mometasone, and triamcinolone are dosed once a day, while beclomethasone and flunisolide require at least twice to three times daily dosing. When initiating therapy with a nasal steroid, the budesonide package labeling states that it has a starting dose of 1 spray in each nostril, daily, vs two sprays in each nostril daily with the other steroids. Whether this fact is an important difference is debatable.

Pediatric Populations: All the nasal corticosteroids are indicated for use in children as young as 6 years of age, but mometasone is indicated for use in children as young as two years, and fluticasone can be used in children as young as 4 years old.

Pregnancy: All of the nasal corticosteroids are rated FDA pregnancy category C (risk cannot be ruled out) except budesonide which has a FDA Category B rating (low risk in humans). In rat studies, when certain nasal corticosteroids were administered in doses that were at least 4 times the maximum daily dose recommended in adults, birth defects like cleft palate were seen. But, one study in humans showed that fluticasone was safe when given to pregnant women, as there were no differences in pregnancy outcomes compared to placebo. However, in discussions with OB/GYN physicians, including a P&T Committee member who is an OB/GYN, they felt that these differences in the FDA labeling do not reflect any real or

observed safety differences in the nasal steroids. It was felt that there is a class effect amongst the nasal steroids and any of them could be used in a pregnant patient.

Patient preference/tolerability: Patients' concerns about features such as taste, odor, irritation, and moistness may effect how compliant they are with nasal steroid therapy. Although an individual patient might prefer one nasal steroid over another due to these factors, clinical trials have not shown any one nasal steroid to be preferred over another when this issue has been specifically evaluated. More well-designed head-to-head randomized controlled trials are needed to support that one nasal corticosteroid is superior to another in tolerability or compliance.

Conclusion: The DoD P&T Committee agreed there are some small differences between the nasal steroids in terms of dosing frequency, use in pregnancy, or use in pediatric patients. There is no evidence that any one nasal corticosteroid is preferable to the others with respect to patient tolerability and preferences.

Provider Opinion: MTF providers were surveyed regarding their opinions on the nasal steroids. Overall, a product that was dosed once daily was preferred, with fluticasone specifically mentioned. Providers, including two pediatrician members on the P&T Committee, did consider mometasone and fluticasone to be preferred in children younger than 6 years of age. When providers were asked to rank the nasal steroids from the greatest clinical usefulness to the least useful, fluticasone was ranked first, followed by mometasone, budesonide, triamcinolone, beclomethasone, and lastly flunisolide.

As stated earlier, fluticasone is the most popular nasal steroid at the MHS (used in 70% of patients). However, providers did indicate that the preference for fluticasone could be overcome with a significant difference in cost from one of the other products dosed once a day (budesonide, mometasone or triamcinolone). Overall providers felt there was a class effect in efficacy and safety amongst the nasal steroids.

Overall Conclusion to Relative Clinical Effectiveness: The DoD P&T Committee concluded that the nasal steroids show similar efficacy and safety profiles, when doses do not exceed the recommendations in the package inserts. As mentioned early, minor differences are apparent between the products in terms of other factors, such as dosing, use in pregnancy, or used in pediatrics.

Maj Tiller will now present the next portion of the Nasal steroid presentation.

Nasal Steroid Relative Cost Effectiveness:
Nasal Corticosteroids Uniform Formulary Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the agents within the Nasal Corticosteroid therapeutic class in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21 (e) (2).

The DoD P&T Committee agreed with the preceding evaluation that the nasal corticosteroids have similar relative clinical effectiveness (efficacy, safety, tolerability, and clinical outcomes), but acknowledged that small differences exist between agents in clinical utility (dosing frequency, pregnancy and pediatric indications, and DoD provider preferences). Since the agents were determined to have similar relative clinical effectiveness, a simple cost-analysis was performed. To account for the difference in clinical utility, a cost-effectiveness analysis (CEA) was performed based on the results obtained via a Multi-attribute Utility Theory Analysis (MAUT). The MAUT analysis quantified differences between the agents in regards to switch rate, persistence of use, general DoD provider preference, willingness to use in pregnancy, willingness to use in children ages 0-6, dosing frequency, and general efficacy. The source data for the MAUT analysis consisted of data obtained from the DoD Provider Nasal Corticosteroid Survey and the DoD Nasal Corticosteroid Prescription Utilization Data Analysis.

The results from the cost analysis revealed that overall flunisolide had the lowest total weighted average cost per day of treatment. Among the agenets dosed once-a-day, fluticasone had the lowest total weighted average cost per day of treatment, followed by mometasone, triamcinolone, and budesonide. The results from the CEA based on the MAUT analysis paralleled those of the cost analysis. Among the agents dosed once-a-day, fluticasone was the most cost-effective agent.

The results of the analyses were incorporated into a budget impact analysis (BIA). The goal of the BIA was to assist the Committee in determining which group of NCS best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical considerations, the Committee agreed that a group of Nasal Corticosteroids that included: flunisolide, fluticasone, and mometasone best achieved this goal when compared to other combination groups of Nasal Corticosteroids and thus were determined to be more cost-effective relative to other combination groups.

The DoD P&T Committee readily endorsed placement of fluticasone and mometasone on the Uniform Formulary, given that fluticasone and mometasone were the most cost-effective once-a-day dosed nasal corticosteroids and they currently rank #1 and #2 in MHS Nasal Corticosteroid utilization, respectively. The Committee also agreed that flunisolide should be maintained on the Uniform Formulary, even though the agent requires multiple daily dosing. The Committee realized that if flunisolide was designated non-formulary, patients currently stabilized on the most cost-effective nasal corticosteroid would likely migrate to a higher cost agent.

There was some discussion among DoD P&T Committee members regarding the potential non-formulary designation of budesonide. The Committee evaluated budesonide's safety in pregnancy (Category B versus Category C) and dosing convenience (starting dose of 1 spray in each nostril daily versus two sprays in each nostril daily) at an increased cost relative to the other

agents dosed once-a-day. As was discussed in the relative clinical effectiveness presentation with respect to safety in pregnancy the Committee determined differences in the FDA labeling do not reflect any real or observed safety differences in the nasal corticosteroids and that any of them could be safely used in pregnancy. In regards to dosing convenience, DoD utilization data did not support that budesonide was dosed any different compared to the other nasal corticosteroids dosed once-a-day. Ultimately, the DoD P&T Committee did not value budesonide's potential advantages enough to compensate for the significantly increased cost compared to the other nasal corticosteroids. With respect to the other two nasal corticosteroids, triamcinolone and beclomethasone, the Committee readily agreed with the proposed designation of non-formulary.

Conclusion: The DoD P&T Committee agreed with the relative cost-effectiveness analyses presented for the nasal corticosteroids. Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations of the nasal corticosteroids, the P&T Committee recommended Uniform Formulary status for the nasal corticosteroids.

Committee action: The P&T Committee, based on the collective professional judgment, voted (17 for, 0 opposed, 1 absent, 1 abstained) to recommend formulary status for flunisolide, fluticasone and mometasone; and non-formulary status for beclomethasone, budesonide and triamcinolone under the UF.

Implementation Plan: Because of the high utilization of fluticasone and the low utilization of the proposed non-formulary nasal steroids (beclomethasone, budesonide, and triamcinolone), the Committee determined that a 90-day implementation period would be adequate for this formulary action.

Committee Action: The P&T Committee voted (17 for, 0 opposed, 1 absent, 1 abstained) to recommend an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

This concludes the section for the Nasal Steroids. Dr Crownover do you have anything to add

ANTIDEPRESSANT I DRUG CLASS REVIEW

Background: This class of medications, which we are going to call the Antidepressant I class, or the AD1s, include all of the antidepressant medications marketed in the U.S. except those falling into two older classes (the tricyclic antidepressants or TCAs, and the monoamine oxidase inhibitors, or MAOIs), which will be reviewed later. I may also refer to this class as the "newer" antidepressants. Table 2—on page 3 in your handout—shows the brand and generic names of these medications and their pharmacological classifications, along with their initial FDA approval dates. The two major subclasses are the selective serotonin reuptake inhibitors, or SSRIs, and the serotonin norepinephrine reuptake inhibitors, or SNRIs.

The SSRIs are currently the first choice of therapy in depression and many other psychiatric conditions. There is a lot of variability in patient responses to antidepressants in general, and with the SSRIs in particular. In other words, individual patients may have no response to one SSRI, but will respond to another; and it's difficult to predict which SSRI a patient will respond to. For this reason, clinical practice guidelines for depression support the use of a different SSRI in a patient who has failed treatment with a first SSRI. Clinical practice guidelines tend to reserve SNRIs for use in patients who fail SSRIs. The other antidepressants in this class tend to be used in specific circumstances rather than as general replacements for SSRIs or SNRIs.

Relevance to MHS and Utilization: In FY 2005, $290 million dollars were spent in all three points of service (retail, mail order, and military treatment facilities or MTFs) on the AD1s. Only statins and proton pump inhibitors had higher dollar expenditures.

Let's look at utilization -- please see the graphs starting on page 5 in your handout.

I'll start with Figure 1, which looks at utilization based on subclasses – these graphs are all by number of prescriptions – the SSRIs are the most commonly used type of AD1, followed by the SNRIs and bupropion. The combined line you see for trazodone and nefazodone primarily reflects usage of trazodone, since nefazodone is seldom used (fewer than 1000 prescriptions per month across the entire MHS).

Individual SSRIs are shown in Figure 2. Across the system, sertraline is most commonly used, followed by escitalopram, paroxetine, fluoxetine, and citalopram, with fluvoxamine showing minimal use (fewer than 1000 prescriptions per month across the MHS).

Turning to page 6, Figure 3 shows the SNRIs. Venlafaxine is most the commonly used—and this is primarily as the extended release formulation, Effexor XR—followed by duloxetine. Usage of duloxetine is increasing rapidly.

In the interest of time, I'm not going to go over Figure 4-6, which show the comparative use of those products with special formulations. We'll be talking about each of these special formulations, so you may want to refer back to the handout as we go along.

FDA Indications: Please refer to Table 3, on page 4 in your handout. All but one of the AD1s is approved for major depressive disorder (or MDD). The exception is fluvoxamine, which is only approved for obsessive compulsive disorder (OCD) in the U.S., although it has depression indications in other countries.

Other psychiatric indications include generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), panic disorder (PD), premenstrual dysphoric disorder (PMDD), post-traumatic

stress disorder (PTSD), social anxiety disorder (SAD), and bulimia. Duloxetine is also approved for a non-psychiatric condition, diabetic peripheral neuropathic pain (DPNP).

One thing that Table 3 does not include is the fact that bupropion sustained release is also indicated for smoking cessation in special packaging, under the name of Zyban. Because smoking cessation is not covered by TRICARE, Zyban was not included in the Committee's review.

(Data Source): The AD1 relative clinical effectiveness analysis evaluated information primarily from published meta-analyses, systematic reviews, and head-to-head randomized controlled trials (RCTs) comparing two or more antidepressants. A review of head-to-head trials with newer antidepressants compiled by a group from the University of North Carolina as part of the Oregon Health & Science University Drug Effectiveness Review Project (OHSU-DERP) was particularly useful.

I'm now going to launch straight into the key questions evaluated by the Committee and the conclusions for each question.

Key question #1 is: How do the newer antidepressants compare to each other in terms of safety and tolerability? The Committee came to the following conclusions:

1) Bupropion, mirtazapine, nefazodone, and trazodone appear to have a lower risk of sexual dysfunction compared to SSRIs and SNRIs.
2) Fluvoxamine, fluoxetine, paroxetine and duloxetine have a generally higher potential for drug interactions than citalopram, escitalopram, sertraline, and venlafaxine.
3) Both venlafaxine and duloxetine have been associated with increases in blood pressure. Duloxetine may be less likely to cause blood pressure elevations than venlafaxine, although head-to-head data would be required to draw a definite conclusion. Manufacturers of both products recommend blood pressure monitoring.
4) Discontinuation syndrome refers to characteristic symptoms (for example, dizziness, nausea, muscle pain, anxiety, vivid dreams, and irritability) that can occur when patients abruptly stop taking antidepressants that affect serotonin. Drugs which are cleared from the body more rapidly appear to be associated with a higher risk of discontinuation syndrome. The SSRI with the greatest risk of discontinuation syndrome appears to be fluvoxamine, followed by paroxetine, sertraline, escitalopram, citalopram, and fluoxetine, in that order. Fluoxetine, which remains in the body for a long period of time, is rarely associated with discontinuation syndrome. Venlafaxine is cleared rapidly from the body and may be associated with more discontinuation symptoms than SSRIs. Data are limited with duloxetine, but it may also be associated with discontinuation syndrome. Little information is available for trazodone, nefazodone, or mirtazapine. Bupropion, which alone among the AD1s has little effect on serotonin, does not appear likely to cause discontinuation syndrome.
5) Rare but serious (or potentially serious) adverse effects and issues of particular concern in various patient populations include the following:
    - Nefazodone has a "black box" warning in labeling due to reports of liver damage that severely limits its use.

- Decreases in white blood cell count (which increases the risk of infection) have been reported in clinical trials with mirtazapine.
- Priapism (or prolonged erection), sometimes requiring surgery, has been reported with trazodone.
- Recent evidence suggests that use of paroxetine during pregnancy is associated with about twice the risk of birth defects compared to other SSRIs. Now, at the time of the DoD P&T Committee meeting, all of the AD1s were Pregnancy Category C except for bupropion, which is Pregnancy Category B. (A is the safest.) On 8 December, the manufacturer of paroxetine announced a change to paroxetine labeling, making it Pregnancy Category D.
- Bupropion has been reported to increase seizure risk. For this reason it is not used in patients who have a history of seizure or who are already at an increased risk of seizure for any reason, including those who are abruptly discontinuing use of alcohol or sedatives.
- There have been recent case reports of liver disease in patients taking duloxetine. Labeling for duloxetine recommends not using it in patients with preexisting liver disease, decreases in liver function, or substantial alcohol use. Duloxetine should also be avoided in patients with a particular form of glaucoma.

Key question #2 concerns comparative effectiveness of the SSRIs: How do the SSRIs compare to each other in efficacy and overall clinical utility for the treatment of MDD? Of particular focus here is whether there is an additional benefit associated with escitalopram (Lexapro) compared to citalopram, and whether there are additional benefits associated with special formulations of paroxetine (Paxil CR) and fluoxetine (Prozac Weekly, Sarafem).

The Committee reviewed 23 head-to-head randomized controlled trials comparing SSRIs to other SSRIs. Only two of these reported any statistically significant differences in efficacy between the SSRIs. Both of these trials reported greater efficacy with escitalopram compared to citalopram; a third trial comparing citalopram and escitalopram showed no significant differences. Results of an unpublished trial comparing escitalopram to sertraline showed no significant differences between these two SSRIs.

The Committee found that fluoxetine has a unique advantage for the treatment of MDD in children, since it is the only one that has demonstrated efficacy in a pediatric population and the only AD1 with a pediatric indication in MDD. Sertraline, fluvoxamine, and fluoxetine have pediatric labeling for the treatment of OCD.

With respect to special formulations of paroxetine and fluoxetine, the Committee noted the following:

- For *paroxetine controlled release (Paxil CR)*, the PEC review found no published data supporting a difference in efficacy compared to paroxetine immediate release or to other SSRIs. The controlled release formulation is intended to decrease nausea and improve tolerability, because it is designed to release medication over 4-5 hours after the medication reaches the small intestine. Both paroxetine immediate release and controlled release are given once daily. Data supporting greater tolerability for paroxetine CR is based on two randomized controlled trials lasting 12 weeks that compared similar doses

of paroxetine CR and IR to placebo. Patients receiving paroxetine CR showed significantly lower rates of nausea in the first week compared to paroxetine IR (14% vs. 23%, $p \leq 0.05$, indicating a statistically significant difference), but not in subsequent weeks, when nausea rates began to decline in both groups. The percentage of patients who stopped therapy because of adverse effects was 6% of those receiving placebo, 10% of those receiving paroxetine CR, and 16% of those receiving paroxetine IR. There was no statistically significant difference between the CR and IR group. The percentages of patients stopping therapy due specifically to nausea were 3% in the CR group, 4% in the IR group, and 0.5% in the placebo group. The PEC review found no published head-to-head trials comparing paroxetine CR to other SSRIs.

- *Fluoxetine 90 mg capsules for weekly dosing (Prozac Weekly)* – Fluoxetine weekly is approved by the FDA only for maintaining response in patients with MDD who have already responded to initial therapy. The weekly dosing is made possible by the fact that fluoxetine is cleared from the body much more slowly than other SSRIs. Weekly dosing may or may not be as effective as daily dosing; the PEC review found no published data directly comparing how well the two regimens maintain response. The potential advantage of weekly dosing is patient convenience and hopefully increased adherence to treatment. Whether or not this advantage exists has not been well established, although one study reported greater compliance with the once-weekly regimen compared to 20 mg given daily during a 3-month maintenance phase. Since compliance during a clinical trial may be very different from compliance in actual practice, it is unclear whether this represents a real advantage for fluoxetine weekly.
- *Fluoxetine in special packaging for PMDD* - Fluoxetine 10 and 20 mg capsules are available in special packaging and with special labeling for the treatment of premenstrual dysphoric disorder (PMDD), under the name of Sarafem. The usual dosing is 20 mg/day; the product does not appear to differ from the other branded fluoxetine product (Prozac), except for differences in the color of the capsules and the packaging. When Sarafem was first introduced, the manufacturer stated the intent was to allow patients with PMDD to avoid the stigma associated with use of antidepressants. The PEC review found no objective data supporting greater compliance or better results based on the special packaging.

Key question #3 concerns comparative effectiveness of the SNRIs**:** How do the SNRIs [duloxetine (Cymbalta) and venlafaxine (Effexor, Effexor XR)] compare to each other in efficacy and overall clinical utility for the treatment of MDD?

The PEC review found no published head-to-head trials comparing venlafaxine and duloxetine for the treatment of depression. A 2005 meta-analysis that included trials comparing venlafaxine or duloxetine to placebo did not show a statistically significant difference between duloxetine and venlafaxine in efficacy, although the efficacy results tended to favor venlafaxine. A summary of results of two unpublished head-to-head RCTs comparing duloxetine and venlafaxine showed no significant differences in efficacy. Overall, there is insufficient evidence to conclude that venlafaxine and duloxetine differ in efficacy for MDD.

Based on laboratory studies, it has been suggested that duloxetine may be a better treatment than other antidepressants for depressed patients presenting with physical symptoms of pain, which is not uncommon in MDD. Support for this argument is limited. Whether a real advantage for

duloxetine exists compared to other antidepressants in depressed patients who complain of painful physical symptoms is unclear; head-to-head trials specifically designed to answer this question are needed.

Key question #4 is: how do the SSRIs compare to the SNRIs in efficacy and overall clinical utility for the treatment of MDD? I'll take this in two parts.

The first part is *Venlafaxine vs. the SSRIs* – The PEC review found a number of head-to-head trials comparing venlafaxine and various SSRIs, including paroxetine, fluoxetine, sertraline, and escitalopram. Few of these trials reported significant differences between venlafaxine and the SSRIs. However, two meta-analyses comparing venlafaxine to fluoxetine have shown a modest efficacy advantage for venlafaxine, although venlafaxine was associated with more adverse effects. This is consistent with the general perception on the part of providers that venlafaxine is slightly more effective but tends to cause more adverse effects than the SSRIs.

Of note, two trials comparing venlafaxine XR to escitalopram showed no differences in efficacy. Significantly more patients receiving venlafaxine XR stopped therapy due to adverse effects compared to those receiving escitalopram in one of these two trials.

The second part is *Duloxetine vs. the SSRIs* – The PEC review found no published head-to-head trials designed to compare duloxetine with other AD1s, although some of the duloxetine trials did randomize patients to fluoxetine or paroxetine as active controls. However, these trials were not designed to directly compare duloxetine with fluoxetine or paroxetine. In addition, dosing for duloxetine ranged from 40-120 mg/d, while dosing of paroxetine and fluoxetine was limited to 20 mg per day. Comparative efficacy, safety, and tolerability of duloxetine compared to the SSRIs remains unclear. Duloxetine 60 mg/d appeared generally comparable to escitalopram 10 mg/d based on results of an unpublished randomized placebo-controlled trial.

Key question #5 – concerns other antidepressants compared to SSRIs and SNRIs: What place in therapy is filled by the other antidepressants included in this review (bupropion, mirtazapine, nefazodone, and trazodone), and how do they compare to the SSRIs and SNRIs in efficacy and overall clinical utility for the treatment of MDD? Of particular focus here is whether there is an additional benefit associated with the once-daily formulation of bupropion (Wellbutrin XL) compared to the twice-daily sustained release formulation.

We'll start with *Bupropion* – Bupropion appears similar in efficacy to SSRIs (fluoxetine, paroxetine, sertraline). The primary place in therapy for bupropion appears to be for patients who have experienced or who are concerned about sexual dysfunction with SSRIs or SNRIs.

With respect to bupropion extended release (Wellbutrin XL), the PEC review found no published data supporting greater efficacy compared to the immediate or sustained release formulations of bupropion or to other SSRIs. The main advantage offered by the extended release bupropion product compared to sustained release bupropion is once-daily vs. twice-daily administration. This is not regarded as an overwhelming advantage for medications in most disease states, although there is some evidence that patients have poorer compliance to twice daily vs. once daily regimens and that patients with depression are in general less likely to be compliant with medication than non-depressed patients. In the case of bupropion sustained release, package labeling advises separating doses by 8 hours in order to decrease the risk of seizure. Since patients are usually advised not to take bupropion late in the day since it may interfere with sleep, bupropion sustained release is likely to be dosed in the morning and early afternoon. This

might be harder for a patient to remember than typical twice-daily regimens. Bupropion extended release may be taken as a single dose in the morning.

Switching to the other antidepressants - Based on data from head-to-head trials, mirtazapine, nefazodone, and trazodone appear similar in efficacy to SSRIs for the treatment of MDD. Trazodone is seldom used by itself for the treatment of depression; because of its sedating effect, its major role appears to be as an add-on medication for the treatment of insomnia in patients receiving other antidepressants. Nefazodone is rarely used because of the potential for liver toxicity and the presence of a black box warning in product labeling. Mirtazapine tends to be sedating and to cause weight gain, limiting its use except in patients in whom these side effects are beneficial. An example of this might be cancer patients or elderly patients who need to gain weight.

Key question #6 concerns use in conditions other than MDD: How do the newer antidepressants compare with respect to efficacy and overall clinical utility in psychiatric conditions other than MDD and in non-psychiatric conditions?

Results of the few head-to-head trials performed in psychiatric conditions other than MDD did not indicate a substantial advantage for a specific AD1 in any condition. Based on FDA-approved indications and clinical data, sertraline and paroxetine appear to be the most broadly useful AD1s. Fluoxetine may have a unique niche as the only AD1 approved for bulimia.

Turning to a non-psychiatric condition, I'd now like to talk about diabetic peripheral neuropathic pain (DPNP). DPNP refers to the pain associated with nerve damage that can occur over time in diabetic patients. Duloxetine is FDA-approved for the treatment of DPNP and appears to be safe and effective. Although venlafaxine is not FDA-approved for DPNP, doses of 150 to 225 mg per day appear to be safe and effective, based on one RCT. The PEC review found no published head-to-head data comparing duloxetine to venlafaxine in treating DPNP.

In addition to duloxetine, a number of medications are currently used to treat DPNP, including tricyclic antidepressants (TCAs) and anticonvulsants (e.g., gabapentin). The use of SNRIs such as duloxetine have not yet been incorporated into clinical practice guidelines, such as those released by the American Diabetes Association. Overall, there is insufficient evidence to determine the relative effectiveness of TCAS, SNRIs, or anticonvulsants for the treatment of DPNP or for non-diabetic neuropathic pain.

The Committee did not attempt to review all non-psychiatric conditions in which one or more of the AD1s may have a beneficial effect. The Committee noted the following:

- Duloxetine is approved for the treatment of stress urinary incontinence (SUI) in Europe, but the manufacturer has withdrawn its application for approval in the U.S. It is unclear whether this is because clinical evidence was felt to be insufficient or whether the FDA is further investigating reports of suicide attempts and suicidal ideation occurring during clinical trials of duloxetine for SUI. Increases in suicidality have not been reported in trials of duloxetine for depression or DPNP, and there is insufficient evidence to link any specific antidepressant with a higher risk of suicidality.
- There are several clinical trials assessing use of AD1s for the treatment of hot flashes in postmenopausal women, but insufficient data to support greater efficacy for any specific AD1.

- Duloxetine was shown to be safe and effective for the treatment of fibromyalgia in a 10-week trial comparing duloxetine to placebo in female patients with or without MDD.

Provider Opinion

The Committee reviewed results of a survey sent to Army, Navy, and Air Force internal medicine, family practice, and psychiatry providers.

Of 42 responses, 21 were from psychiatrists and 21 from primary care providers. Overall, providers agreed that SSRIs as a class were more useful than SNRIs, followed by bupropion, trazodone, and mirtazapine, in that order. Among the SSRIs, providers found sertraline to be most useful, followed by escitalopram, fluoxetine, citalopram, paroxetine, and fluvoxamine, in that order. Providers were also asked the "desert island" question – if they were on a desert island and had to treat the inhabitants with only three different antidepressants, which would they chose, and why? When these results were tallied, the most votes went to bupropion, sertraline, and citalopram, in that order. Most providers selected at least one SSRI to take to the desert island, with bupropion as an almost universal second choice for patients experiencing sexual adverse effects. Overall, about half of the responders perceived escitalopram to offer an efficacy or tolerability advantage over citalopram; the other half saw little or no difference.

Provider comments indicated definite places in therapy for sertraline (commenting that it has many indications and a lower risk of adverse effects and drug interactions); fluoxetine (because it can be used in children and is activating); venlafaxine (because it may be more effective than SSRIs, but also has more adverse effects); bupropion (because of a low risk of sexual adverse effects, because can be used to treat sexual adverse effects from SSRIs; and because it may be useful in smokers and patients with attention deficit hyperactivity disorder [ADHD]); trazodone (for treatment of sleep symptoms); and mirtazapine (because it may be useful to stimulate weight gain in elderly or oncology patients or in HIV wasting and is sedating).

B.) Antidepressants-1 (AD1) Uniform Formulary Relative Cost Effectiveness: The P&T Committee evaluated the relative cost-effectiveness of the agents within AD1 therapeutic class in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e) (2).

The P&T Committee determined that AD1s differed in regards to efficacy, safety, and tolerability and clinical outcomes in the treatment of Major Depressive Disorder (MDD) and other psychiatric conditions. To account for the difference in relative clinical effectiveness, two cost-effectiveness analyses (CEA) were performed, a CEA based on the results obtained via a Multi-attribute Utility Theory Analysis (MAUT) and a CEA based on the findings reported in Drug Class Review on Second Generation Antidepressants by the Oregon Health & Science University's Drug Effectiveness Review Project (OHSU-DERP). A summary analysis was then conducted on the results of the two CEAs. The summary analysis focused on comparisons either between the most cost-effective agent and the more costly agents within a sub-class or between a generic agent and its branded product extension.

The results of the analyses for the SSRI sub-class showed that fluoxetine branded product extensions - fluoxetine in special packaging for Premenstrual Dysphoric Disorder (PMDD) and fluoxetine weekly were > 7-fold more costly and had similar relative clinical effectiveness compared to fluoxetine. Sertraline was shown to have similar relative clinical effectiveness in the treatment of MDD but slightly greater overall relative clinical effectiveness but was significantly more costly compared to fluoxetine. Escitalopram was shown to have lower overall relative clinical effectiveness compared to fluoxetine but potentially greater relative clinical effectiveness in the treatment of MDD compared to citalopram at a significantly greater cost. Paroxetine CR was shown to have similar relative clinical effectiveness but was significantly more costly compared to paroxetine IR. In regards to the SNRI sub-class, venlafaxine was shown to have greater overall relative clinical effectiveness and greater relative clinical effectiveness in the treatment of MDD compared to duloxetine for a similar cost. Finally, bupropion XL was shown to have greater overall relative clinical effectiveness but similar relative clinical effectiveness in the treatment of MDD compared to bupropion SR at a significantly greater cost.

The results of the CEA analyses were incorporated into a budget impact analysis (BIA). The goal of the BIA was to assist the Committee in determining which group of AD1s best met the majority of the clinical needs of the DoD population at the lowest cost to the MHS. Based on the BIA results and other clinical considerations, such as the need to make a broad array of antidipressants available to meet the clinical coverage needs of the DoD Population, the Committee agreed that a group of AD1s that included: bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine IR, sertraline, trazodone, and venlafaxine best achieved this goal when compared to other combination groups of AD1s, and thus were determined to be more cost-effective relative to other combination groups.

There was lengthy discussion among the DoD P&T Committee members (the longest discussion to date) regarding potential non-formulary designation for bupropion XL, duloxetine, escitalopram, and paroxetine CR given the agents' current utilization and the characteristics of the psychiatric and non-psychiatric conditions they are used to treat. In the discussion, the DoD P&T Committee re-examined the evidence supporting the relative

clinical effectiveness of the agents, the relative cost-effectiveness of the agents, current utilization and the number of beneficiaries affected by a potential decision to designate one or more agents as non-formulary, and MHS provider opinion. The Committee readily agreed that fluoxetine weekly and fluoxetine in special packaging for PMDD offered no additional benefit at a substantially increased cost to the MHS and should be designated as non-formulary.

In consideration of bupropion XL, the Committee evaluated bupropion XL's dosing convenience (once-a-day dosing) at an increased cost relative to bupropion SR, which is dosed twice-a-day. At the end of the discussion, the DoD P&T Committee did not value once-daily dosing of bupropion XL enough to compensate for the significantly increased cost compared to bupropion SR.

In regards to duloxetine, the DoD P&T Committee agreed with the PEC's relative cost-effectiveness analyses showing venlafaxine to be a more cost-effective treatment for Major Depressive Disorder and other psychiatric conditions compared to duloxetine. However, some members of the committee were concerned that non-formulary status for duloxetine would create an unnecessary barrier for patients using the drug for its other FDA approved indication, diabetic peripheral neuropathic pain. Other committee members voiced concerns that the manufacturer's marketing of duloxetine for the "painful symptoms of depression" could result in its uncontrolled use regardless of adverse effects and cost concerns and the absence of head-to-head data establishing an advantage over other antidepressants in treating somatic symptoms of depression. Considerable discussion then ensued to address these concerns. Ultimately, the DoD P&T Committee determined that there was currently insufficient evidence comparing duloxetine to other established agents used in the treatment of neuropathic pain to warrant placement on the Uniform Formulary solely for this indication.

The Committee next deliberated escitalopram's value focusing on the evidence of relative clinical effectiveness presented in the clinical review, the agent's high current utilization, and provider opinion. In general, the Committee recognized the evidence supporting escitalopram's potential increased relative clinical effectiveness compared to citalopram, but ultimately agreed with polled MHS providers that any potential increased relative clinical effectiveness was not worth the significant additional cost (greater than 3-fold). The Committee expressed some concern about potentially disrupting therapy for the high number of beneficiaries currently receiving escitalopram (over 112,000), but recognized that there is an inherently high self-discontinuation rate in this drug class (up to 30% reported in clinical trials) and that in majority of these patients, another SSRI could be used without detrimental results. The Committee did state that use of the medical necessity process would ensure that those patients who truly need escitalopram would be able to receive it at the lower co-pay.

In consideration of paroxetine CR, the Committee evaluated Paroxetine CR's beneficial tolerability profile at an increased cost relative to paroxetine IR. Ultimately, the DoD P&T Committee did not value the evidence suggesting lower rates of nausea in the first week of treatment with paroxetine CR compared to paroxetine IR enough to overcome the agent's significant increased cost compared to paroxetine IR.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 1 abstention, 1 absent) to accept the AD1 cost-analysis presented by the

PEC. The P&T Committee concluded that: fluoxetine in special packaging for PMDD (Sarafem®), fluoxetine weekly (Prozac Weekly®), escitalopram, and paroxetine CR were not cost-effective relative to the other agents within the SSRI sub-class; duloxetine was not cost-effective compared to venlafaxine; and that bupropion XL was not cost-effective compared to bupropion SR. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the AD1s, and other relevant factors, the P&T Committee recommended Uniform Formulary status for the AD1s.

COMMITTEE ACTION: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 1 abstention, 1 absent) to recommend that fluoxetine in special packaging for PMDD (Sarafem®), fluoxetine weekly (Prozac Weekly®), escitalopram, paroxetine CR, duloxetine, and bupropion XL be classified as non-formulary under the UF, with bupropion (IR, SR), citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine IR, sertraline, trazodone, and venlafaxine remaining on the UF. In addition, the P&T Committee recommended that existing quantity limits for fluoxetine 90-mg delayed release capsules (Prozac Weekly) of 4 capsules per 30 days, 12 capsules per 90 days be continued.

Implementation Plan: Due to the large number of beneficiaries potentially affected by this decision (183,000; 24% of all AD1 users), the DoD P&T Committee proposed an effective date of no later than the 1st Wednesday following a 180-day transition period for implementation of a decision by the Director, TMA, to classify the agents as non-formulary on the Uniform Formulary.

Committee Action: The P&T Committee voted to recommend an effective date no later than the first Wednesday following a 180 day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Macrolide / Ketolide Relative Clinical Effectiveness

Background: The relative clinical effectiveness of the macrolide / ketolide drug class takes into consideration their efficacy (likelihood to work), relative safety (likelihood to do no harm), and tolerability (likelihood to be taken). Although only the macrolides/ketolides were evaluated for this drug review, the P&T Committee was aware and took in consideration that there are a number of other formulary antibiotics available that will treat the same infections as macrolides/ketolide.

There are 6 antibiotics that we will be discussing in this class; five macrolides, and one ketolide (See table 5 on page 8 in your handout). Azithromycin, clarithromycin immediate release, and erythromycin are available generically. The announcement of azithromycin generic availability occurred on the same day the committee was deliberating its UF status during the November DoD P&T meeting. Erythromycin is available in several different formulations, however, for our review, we will not discuss these different products, and just refer to "erythromycin". The two non-generic macrolides are clarithromycin extended release (Biaxin XL), which is dosed once a day, and Zmax which is a new 2 gram suspension formulation of azithromycin. With Zmax, patients only need to swallow one dose, and that is their entire course of therapy.

The 6th product is telithromycin (Ketek), which is the only ketolide on the market; it is not available in a generic. The P&T Committee evaluated the macrolides and the ketolide together, since they generally cover the same microorganisms and treat the same infections.

Azithromycin, clarithromycin and erythromycin are available in suspensions and are indicated for use in pediatric patients.

Generic Name	Brand Name	Available in Pediatric Suspension
Azithromycin	Zithromax, generics	Yes
Azithromycin extend release suspension	Zmax	No
Clarithromycin IR	Biaxin, generics	Yes
Clarithromycin ER	Biaxin XL	No
Erythromycin	Generics	Yes
Telithromycin	Ketek	No

Relevance to Military Health System (MHS) and Utilization: The macrolides/ketolide currently rank #31 in terms of MHS drug class expenditures. (Look at figure 7 on page 8 in your handout). In fiscal year (FY) 2004, $40.7 million dollars was spent in all three points of service (military treatment facility (MTF), TRICARE Retail Pharmacy (TRRx) program, and TRICARE Mail Order Pharmacy (TMOP)). Azithromycin is the most popular agent in this drug class in the MHS; it is ranked #1 in utilization (number of prescriptions) at all three points of service (MTF, TRRx, TMOP).

Indications: The macrolides/ketolides are used to treat a number of infections (Refer to table 6 on page 9 in your handout, we'll go in the order that these are listed in the table). The macrolides/ketolides were evaluated for the treatment of the following infections: community

acquired pneumonia, acute bacterial exacerbation of chronic bronchitis (ABECB) (bronchitis), acute bacterial sinusitis (sinus infection), acute pharyngitis (strep throat), acute otitis media (ear infections), *Helicobacter pylori* infections (infection of the stomach and upper small intestines), and *Mycobacterium avium* complex (MAC) (infection that can occur in patients with weakened immune systems, like HIV patients).

We're going to summarize the results first. Based on the relative clinical effectiveness review, the DoD P&T Committee concluded the following points:

1) Clinical trials show all macrolides have similar benefits in respiratory infections, except erythromycin has less benefit against the *influenzae* (a bacterium that can cause a variety of infections).
2) Although telithromycin has greater effectiveness against resistant pneumococcus bacteria in test tubes, it is equivalent in studies with live, actual patients.
3) Azithromycin, Zmax, clarithromycin, erythromycin, and telithromycin have similar relative (relative meaning in comparison of a macrolide/ketolide to a macrolide or another antibiotic) clinical effectiveness for treating four of the seven infections we evaluated: community acquired pneumonia, acute exacerbation of chronic bronchitis, strep throat (accept Zmax which has not been studied), and sinus infections.
4) For the treatment ear infections (acute otitis media), cure rates with azithromycin, clarithromycin IR, and erythromycin are similar. Zmax, clarithromycin ER, and telithromycin have not been studied for treating ear infections.
5) Clarithromycin shows the best evidence for treating *Helicobacter pylori* infection (a common infection of the stomach and upper small intestines that is often seen in people with stomach ulcers.)
6) Either azithromycin or clarithromycin can be used to prevent *Mycobacterium avium* complex (MAC) infections (this is a type of infection that people with weakened immune systems are susceptible to). Clarithromycin is preferred over azithromycin for treating (MAC) infections.
7) Azithromycin is preferred over the other macrolides and telithromycin in terms of safety and tolerability (taking in to account all the factors which include adverse drug reactions, risk in pregnancy, use in children, or drug interactions)
8) There were minor differences among the agents in terms of dosing frequency and palatability of suspension.
9) Provider opinion preferred azithromycin.
10) When asked to give a choice, providers chose Zmax and telithromycin most often for non-formulary status.
11) Overall the DoD P&T Committee concluded azithromycin has increased overall clinical effectiveness relative to Zmax, clarithromycin, erythromycin, and telithromycin.

(Data Source): Data sources used to address the key questions for this class review included medication package inserts, clinical trials, meta-analyses, treatment guidelines/recommendations, and provider opinion (which were used to produce the macrolide/ketolide class review). The FDA website was monitored as well for new indications and safety for all macrolides and telithromycin.

Key question #1: What is the spectrum of activity among the agents, and does *in-vitro* resistance (antibiotics shown to be resistant to bacteria in a test tube) equate to clinical failure (the antibiotic does not kill bacteria in a patient, or the patient does not improve or is cured)?

Erythromycin is frequently not effective against a bacterium called *Haemophilus influenzae*; we refer to this as resistance. However, the other macrolides and telithromycin remain active against this bacterium. Because of this resistance, erythromycin may have a limited role in the treatment of many common respiratory tract infections.

Telithromycin is the only antibiotic reviewed in this drug class that remains active against macrolide and penicillin resistant *Streptococcus* (a common bacteria found in a variety of respiratory tract infections) *in-vitro* (in the test tube). However, there is no conclusive evidence that resistance in a test tube equates to clinical failure in a patient (e.g. patient's infection is not cured, or the bacteria is not killed). Additionally, telithromycin has not been shown to be superior to other antibiotics at curing patients' infections or eradicating bacteria.

Conclusion: The DoD P&T Committee agreed that while telithromycin can overcome multi-drug resistant *Streptococcus pneumonia*, this has not translated into superior clinical cure or bacteria eradication rates in actual patients. Erythromycin may have a limited role in treating many common types of respiratory tract infections due to inactivity against *Haemophilus influenzae*.

Key question #2: Are there significant differences in clinical effectiveness for the treatment of community acquired pneumonia, acute exacerbation of chronic bronchitis, sinus infections, strep throat, ear infections, *Helicobacter pylori* infection, and *Mycobacterium avium* complex among the agents (refer to table 6 on page 9 in your handout)?

Efficacy:
We will be discussing the 7 most common infections here. There are other infections that the macrolides/ketolides treat, however the 7 infections in table 6 are most commonly seen in the DoD population. The Committee agreed, based on clinical evidence that looked at clinical cure rates or bacterial eradication rates, that all macrolides/ketolides appear equally effective at treating community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis and sinus infections. For treating strep throat (acute pharyngitis), all macrolides/ketolides (except Zmax which has not been studied) appear equally effective.

Clarithromycin, azithromycin, and erythromycin immediate release appear equally effective when treating ear infections (otitis media), as there is no difference in clinical cure rates/bacterial eradication rates between the products. Zmax, clarithromycin ER, and telithromycin have not been evaluated for ear infections.

For the treatment of *Helicobacter pylori* infections, clarithromycin immediate release appears superior over azithromycin, based on head-to-head trials.

Both azithromycin and clarithromycin are effective at **preventing** *Mycobacterium avium* complex infections in patients with Human Immunodeficiency Virus. However, when **treating** *Mycobacterium avium* complex infections, clarithromycin is preferred over azithromycin.

Zmax, Clarithromycin ER, erythromycin and telithromycin have not been evaluated for *Helicobacter pylori* or *Mycobacterium avium* complex infections.

Guidelines/recommendations:
Guidelines and recommendations from national infectious disease professional organizations were also taken in consideration when evaluating this drug class. Telithromycin has been on the market about one year, so none of the national guidelines have yet addressed this antibiotic. For the treatment of community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, sinus infections, and ear infections, the guidelines recommend that either clarithromycin or azithromycin can be used, but don't prefer one over the other. The guidelines are unanimous in not recommending erythromycin because of its poor tolerability and lack of activity (or 'resistance') against *Haemophilus influenzae.*

For strep throat, erythromycin is preferred over all the other macrolides/ketolides due to its narrow spectrum of action. Clarithromycin is preferred for *Helicobacter pylori* infections. Either azithromycin or clarithromycin is preferred for prevention of *Mycobacterium avium* infections whereas clarithromycin is preferred over azithromycin for treatment of this infection. Overall, the P&T Committee conclusions closely mirror the national guideline recommendations.

Conclusions: The DoD P&T Committee agreed that there is no evidence that any one macrolide/ketolide is more efficacious than any other for treating community acquired pneumonia, acute exacerbation of chronic bronchitis, sinus infections, strep throat and ear infections. Clarithromycin is preferred for treating *Helicobacter pylori* infections. Clarithromycin or azithromycin is preferred for preventing *Mycobacterium avium* complex infection; however clarithromycin is preferred for treating this infection.

Key question #3: Are there significant differences in the safety and tolerability among the agents (refer to table 6 on page 9 in your handout)?

Adverse effects:
The safety and tolerability factors that the Committee assessed included differences in adverse drug reaction profiles, risk in pregnancy, use in children, and drug interaction profiles.

Adverse drug reactions:
Some of the rare but serious side effects that have been associated with **all** the macrolides/ketolides include pseudomembranous colitis (an extremely severe diarrhea), liver toxicity, and cardiac rhythm problems (prolonged QTc interval). No one macrolide/ketolide is more likely to cause these three problems than another. Erythromycin and telithromycin may worsen myasthenia gravis (an autoimmune disorder characterized by weakness of skeletal muscles) and should be used with caution in these patients.

Other adverse effects associated with all macrolides/ketolides include, taste perversion or abnormal taste, dizziness, rash, headache, and transient hearing loss. Telithromycin is the only one in the class that has been associated with visual disturbances, such as double vision or blurred vision. Azithromycin and clarithromycin are associated with the lowest incidence of gastrointestinal side effects (nausea, vomiting, upset stomach and diarrhea), followed by Zmax and telithromycin. Erythromycin appears to have the highest incidence of gastrointestinal adverse effects.

Pregnancy risk and pediatric use:
Azithromycin, Zmax and erythromycin are considered safer in pregnancy compared to clarithromycin and telithromycin. Azithromycin, clarithromycin, and erythromycin are the only agents that have been evaluated in pediatric patients.

Drug interactions:
Azithromycin and Zmax are associated with significantly fewer drug interactions compared to clarithromycin, erythromycin, and telithromycin.

Conclusion: The DoD P&T Committee agreed azithromycin has the most favorable safety and tolerability profile; followed by Zmax; then clarithromycin and telithromycin. Erythromycin has the least favorable safety and tolerability profile, primarily due to its high incidence of nausea and vomiting.

Key Question #4: Are there significant differences in other factors such as dosing, suspension palatability, and provider opinion among the agents?

Conclusions: Dosing/Duration of therapy**:** All of the macrolides/ketolides are primarily used to treat acute infections, thus they are not used chronically. With antibiotics, it is important to look at dosing frequency and duration of therapy to ensure that patients will be compliant with therapy. The duration of therapy will vary depending on the infection being treated. The Committee agreed that Zmax has the greatest advantage in terms of dosing frequency and duration of therapy, since it is given as a one-time dose. Azithromycin, telithromycin, and clarithromycin extended release (Biaxin XL) are dosed once daily, so they are preferred over clarithromycin immediate release and erythromycin which require dosing 2-4 times daily.

Palatability: Pediatric patients prefer the taste of azithromycin over clarithromycin and erythromycin. Erythromycin is notorious for tasting horrible to children.

Provider opinion: Primary care, pulmonary, and infectious disease providers at the MTFs were asked to answer questions and provide feedback concerning this drug class. Most providers felt azithromycin had the greatest clinical benefit in this drug class. A majority of providers felt Zmax and telithromycin did not confer a significant clinical advantage compared to azithromycin, clarithromycin and erythromycin. When given a choice as to which of the macrolides should be non-formulary, Zmax and telithromycin were chosen most frequently.

Overall Clinical Conclusion: Overall the DoD P&T Committee concluded that azithromycin has increased clinical effectiveness relative to Zmax, clarithromycin, erythromycin and telithromycin, based on the factors addressed in the key questions.

I'm now going to move on to the **Macrolide/ketolide Uniform Formulary Cost Effectiveness evaluation:**

The DoD P&T Committee evaluated the relative cost-effectiveness of the agents within the macrolide/ketolide antibiotic class in relation to safety, tolerability, effectiveness, and clinical outcomes of the other agents in the class. Information considered by the P&T Committee included but was not limited to sources of information listed in 32 C.F.R. 199.21(e)(2). The agents included in this review are listed in Table 5 of the BAP handout.

The macrolide cost-effectiveness review was conducted as two discreet analyses: The first analysis considered only the different forms of erythromycin, while the second analysis compared the newer macrolides [azithromycin, Zmax (brand), clarithromycin and telithromycin]. The first step for each evaluation was to calculate the total weighted average cost per course of therapy for the different antibiotics. The second step was to conduct the appropriate pharmacoeconomic analysis taking into account the conclusions of the clinical review. Because the clinical review suggested minimal differences in clinical effectiveness (efficacy, safety and tolerability) between the erythromycin formulations, the appropriate pharmacoeconomic analysis for these agents was determined to be cost-minimization. However, a cost-effectiveness analysis (CEA) was used to evaluate Zmax, azithromycin, clarithromycin and telithromycin because the clinical review suggested differences in clinical effectiveness (efficacy, safety and tolerability) between these agents. A summary of some of the clinical differences between these agents is provided in Table 6 on page 9 of the BAP handout. Effectiveness differences between the agents were quantified through the use of a Multi-Attribute Utility Table (MAUT).

Although the results of the cost analysis for the different formulations of erythromycin determined erythromycin base to have the lowest total weighted average cost per course of therapy across all points of service (MTF, Retail, Mail), the cost-effectiveness profiles for all the erythromycin formulations were considered favorable.

The cost-analysis evaluation between azithromycin, Zmax, clarithromycin and telithromycin determined azithromycin to have the lowest total weighted average cost per course of therapy across all points of service, followed by Zmax, clarithromycin and telithromycin. The CEA produced results with the same rank order: azithromycin being the most cost-effective followed by Zmax, clarithromycin and telithromycin.

The results of the above analyses were then incorporated into a Budget Impact Analysis (BIA), which accounted for other factors and costs associated with a potential decision regarding formulary status of macrolide antibiotics within the UF. These factors included market share migration (due to changing provider prescribing practices), cost reduction associated with non-formulary status, and medical necessity processing fees. Switch costs were not included because the macrolides were assumed to be used acutely rather than on a chronic basis. The results of the budget impact analysis confirmed the results of the preliminary analyses. Erythromycin and azithromycin (other than the Z-max formulation) were found to be the most cost-effective macrolide antibiotics overall. A sensitivity analysis conducted around the uncertainty of azithromycin prices due to its generic availability suggested: 1) as the price of generic

azithromycin falls, azithromycin becomes even more cost effective compared to other newer macrolides; and 2) as the price of generic azithromycin falls, scenarios placing the branded Z-max formulation into the non-formulary tier become increasingly more cost beneficial to DoD.

The primary discussion in this class centered on determining the UF formulary status for two agents: telithromycin and Zmax. Although the clinical review suggested some minor coverage benefits over other macrolides with telithromycin in terms of resistance, the committee noted that agents in other antibiotic classes were available to address these needs. The committee did not feel that the minor coverage benefits of telithromycin with resistance were enough to compensate for the significantly increased cost of telithromycin compared to the other available macrolides.

The macrolide/ketolide clinical review suggested that Zmax offered no additional antimicrobial coverage benefits than the other available forms of azithromycin. The clinical review determined that the primary advantage of Zmax was its ability to deliver an entire course of therapy in one dose. The committee recognized that in rare instances, a 'one-dose' course of therapy could be beneficial, however it was noted that in the majority of DoD cases, patients could easily manage the steps necessary to complete a course of therapy with the azithromycin tablets which are given once a day for 3 to 7 days. The committee also noted that any increase in azithromycin market share by Zmax would reduce the ability of the DoD to take advantage of lower prices generated by generic azithromycin competition. This was of special concern in the retail market where the DoD has limited ability to manage factors influencing market penetration of one product over another. Because of these reasons the Committee agreed that the 'one dose' course of therapy of Zmax was not enough benefit to compensate for the potential of increased cost it would generate over the long term.

Conclusion: The P&T Committee agreed (17 for, 0 against, 1 abstained, 1 absent) with the relative-cost effectiveness analyses presented for the macrolide antibiotics. Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the macrolide antibiotics, the P&T Committee recommended that the status of telithromycin and the Zmax formulation of azithromycin be changed from formulary to non-formulary on the Uniform Formulary, with erythromycin, clarithromycin immediate, clarithromycin extended release and non-Zmax formulations of azithromycin maintaining formulary status on the Uniform Formulary with the formulary cost share.

Committee Action: The P&T Committee, based upon its collective professional judgment, voted (17 for, 0 opposed, 1 abstained, 1 absent) to recommend non-formulary status on the Uniform Formulary for telithromycin and the Zmax formulation of azithromycin, with erythromycin salts and base, all forms of clarithromycin and non-Zmax formulations of azithromycin maintaining formulary status on the Uniform Formulary at the formulary cost share.

Macrolide/ketolide Implementation: Because of the low utilization of Zmax and telithromycin at the military treatment facilities (MTFs), and the fact that these agents, for the most part, are not used chronically, the Committee recommended an effective date no later than the first Wednesday following a 60-day implementation.

Committee Action: The DoD P&T Committee voted (16 for, 1 opposed, 1 abstained, 1 absent) to recommend an implementation period of 60 days.

PRIOR AUTHORIZATION REQUIREMENTS FOR MECASERMIN (INCRELEX)

Background: Mecasermin (marketed as Increlex) is an injectable medication containing human insulin-like growth factor-1 (IGF-1), which is a naturally occurring hormone. IGF-1 is one of the main hormones necessary for normal increases in height in children; it must be present in order for children's bones, cartilage and organs to grow normally. It is not the same as growth hormone.

Mecasermin is approved for use in patients with severe primary IGF-1 deficiency. Children diagnosed with severe primary IGF-1 deficiency have height and serum IGF-1 levels that are more than three standard deviations below normal. In other words, they are not producing normal levels of IGF-1. These children have normal or above normal levels of growth hormone, but they are resistant to its effects. Therefore, it does not make sense to treat these children with growth hormone.

Mecasermin is also approved in children with growth hormone gene deletion (meaning they are not producing growth hormone) **if** they have developed neutralizing antibodies to treatment with growth hormone.

Unlike growth hormone, mecasermin is not indicated for use in adult patients.

Mecasermin can lower blood glucose levels. In some cases it can cause severe hypoglycemia (dangerously low blood glucose levels) which can result in seizures or loss of consciousness. Testing of blood glucose levels before meals is suggested when mecasermin therapy is started or changed, and this testing should continue if frequent symptoms of hypoglycemia or severe hypoglycemia occur. What is particularly important to realize is that these children are not necessarily diabetic and they and their families may very well have had no previous exposure to blood glucose monitoring or recognizing when their blood glucoses are low.

Mecasermin is generally well tolerated. However, some potentially serious adverse effects can occur and must be monitored for. These include enlarged tonsils (sometimes causing sleep apnea), increased pressure in the brain (intracranial hypertension), and skeletal effects.

The dosage of mecasermin is individualized for each patient. It is given by an injection just below the skin within 20 minutes of a meal or snack, twice daily. Unlike growth hormone, Mecasermin is available only in vials and not in a pen or other dosing device. Patients must be educated on dosing and administration of mecasermin injection and blood glucose monitoring.

Patient Selection Requirements

Mecasermin is not intended for every child with growth deficiencies – there are specific requirements for selecting appropriate patients in product labeling. Technically, mecasermin should only be used by patients with height standard deviation scores $\leq$ -3 **and** basal IGF-1 standard deviation score $\leq$ -3 **and** normal or elevated growth hormone levels. Patients using mecasermin must understand how to monitor their blood glucose, must be able to recognize when their blood glucose levels are low, and must routinely follow up with their provider.

PA Criteria

Refer to page 38 of your background document (not the handout) that lists the actual prior authorization criteria. The major concern of the DOD P&T Committee was to ensure appropriate patient selection and that patients receiving mecasermin would be able to safely

manage the dosing, administration, and monitoring requirements, and that they would benefit from its use.

Recommendations

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

The implementation period will begin immediately following the approval by the Director, TMA.

Committee Action: The DoD P&T Committee voted (17 for, 0 against, 1 abstained, 1 absent) that a prior authorization be required for mecasermin, with an effective date no later than the first Wednesday following a 30-day implementation period.