Uniform Formulary Beneficiary Advisory Panel

Meeting Summary
March 22, 2007
Washington, D.C.

Panel Members Present:

- John Class, Military Officers Association of America, Chairman
- Kathryn Buchta, Health Net Federal Services
- John Crum, Humana Military Healthcare Services, Inc.
- Deborah Fryar, Military Coalition
- Rance Hutchings, Uniformed Services Family Health Plan
- Jeffrey Lenow, Medical Professional
- 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.

MAJ Watson indicated this meeting of the Panel has been convened to discuss and review the recommendations of the Department of Defense (DOD) Pharmacy and Therapeutic (P&T) Committee meeting held 13-14 February, 2007 in San Antonio, TX.

Agenda

The agenda for this meeting of the Panel is:

- Opening remarks and public comments
- Selection of Chairperson for the term of June, 2007 – March, 2008
- Review and discussion of P&T Committee recommendations for drugs in the following drug classes:
  - Newer Sedative Hypnotics (SED-1s)
  - Narcotic Analgesics
  - Ophthalmic Glaucoma Agents
  - Monamine Oxidase Inhibitor Anti-Depressants (MAOIs)
- Wrap-up comments

Opening Remarks

MAJ Watson stated that Title 10 United States Code (U.S.C.) section 1074g requires the Secretary of Defense to establish a DOD 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 are:

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

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

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

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

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

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

MAJ Watson also announced that for this meeting of the Panel a teleconference feed has been established with the Pharmacoeconomic Center. The PEC members participating in the conference by telephone identified themselves.

MAJ Watson introduced the members of the Beneficiary Advisory Panel present. He then briefly reviewed housekeeping considerations.

Private Citizen Comments

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

Election of New Chairperson

MAJ Watson announced that the Panel would elect a new Chairperson for the coming year at this meeting. The term of the Chair runs from June through March and the new Chair is elected at the meeting before the new term begins. Ground rules for election are: each member votes for one person; election is by simple majority; in case of a tie vote, all ties will be voted again; in the event of a second tie, there will be a tie breaker.

Later in the meeting, MAJ Watson announced that the results of the first ballot were a three-way tie between John Class, Rance Hutchings and Robert Washington. A second vote was then taken and Mr. Robert Washington was elected the Chair for the upcoming June, 2007-March, 2008 term.

Presentation of Drug Class Reviews

Maj Wade Tiller, Deputy Director of the Pharmacoeconomic Center (PEC) began the agenda presentation with introductory remarks.

[Insert Script page 1 through line 2, page 2]

Newer Sedative Hypnotics (SED-1s) Drug Class Review

[Insert script, page 2 line 3 through page 6]

P&T Committee Physician's Perspective

COL Doreen Lounsberry, a member of the P&T Committee, discussed the Committee's recommendations from a physician's perspective. COL Lounsberry agreed with the points made in the clinical effectiveness and cost effectiveness presentations. She said the P&T Committee believed that two agents would be enough given the very little differences in therapeutic effectiveness among the agents in this class. Moreover, the "CR" formulation of Ambien offered very little advantage over Ambien.

Panel Questions and Discussion

Ms. Buchta asked whether providers would be okay with essentially having to jump through two hoops to get Rozerem for patients who are addictive. Since the medical necessity criteria are not listed, she also asked whether these patients would be required to try one of the other agents even though they have a higher addictive potential. Dr. Lounsberry said there are clinical trials for

Rozerem supporting an apparent lack of abuse potential, but there isn't a lot of experience with it yet. She said it's possible that, given Rozerem's lack of effect on sleep duration, the patient population won't want to use it because they won't perceive it as effective. The MHS doesn't really know yet what the demand from the patient population will be. However, she believesd it is quite likely that addiction would be listed as one of the criteria for a medical necessity exception.

Ms. Buchta asked whether the medical necessity criteria have been published yet. The answer given was that they have not. However, while the criteria are somewhat customized for each drug class, they are all based on the same general medical necessity criteria. The P&T Committee usually goes through the five general criteria, decides whether or not they will apply and gives some guidance as to what the medical necessity criteria will look like. In this case, she said she believes all of the standard medical necessity reasons would apply: the formulary drug isn't suitable for that patient, the patient failed to tolerate the adverse effects, the patient was established on therapy and the physician didn't feel the patient could be changed without de-stabilizing them, or there is no suitable drug other than the non-formulary drug.

Ms. Buchta said that she understood the Committee included psychiatrists, who would be the ones most likely to be using Rozerem in that situation. She asked if Dr. Lounsberry would confirm that they didn't perceive the non-formulary status as an undue burden. Dr. Lounsberry said they made no specific comments to the effect that they had to have Rozerem on the formulary. But that could be because they aren't experienced with it yet. The approach to their patient population is conservative.

Ms. Schlaifer asked about the schematic diagram of the "Prior Authorization Process for SED-1 Agents Other Than Zolpidem IR (Ambien)" that was included in the handout on page 6 as "Figure 2." She asked why Lunesta patients will have to go through the Prior Authorization process even though Lunesta is on formulary. Dr. Lounsberry said it has to do with the fact that the medical necessity criteria for obtaining a non-formulary drug at the formulary co-pay price are separate from the Prior Authorization criteria. In this case, there is no reason to allow patients who are just beginning therapy to start off with Lunesta instead of Ambien — Ambien is by far the most cost-effective agent.

Ms. Schlaifer noted that the diagram also shows that when a manual prior authorization is used, the approval period is 12 months. She asked if that 12-month period is standard across all prior authorizations and if there is a reason that the PA is limited to 12 months. Dr. Lounsberry said there are some instances in which the Committee has changed the 12-month time period to an "indefinite" time period. In this case, it was a conscious decision reflecting the fact that this is a new process. The Committee will be looking at the data as it goes along as well as at the appropriate anniversary date.

Mr. Class asked for clarification as to whether the recommended decision would mean that even if a patient is already on Lunesta, they would have to use Ambien or go through this process. He noted that most of the users are located at the retail point of service. When these users go to the pharmacy, they will be forced to switch. Maj Tiller answered that the PA process would only be applied to new SED-1 users. Anyone currently on a sleep agent — anyone who has had a prescription from any of the three points of service in the last 180 days — will not know about the automated prior authorization process. It will be invisible to them. The new automated process will now allow TMA to use novel approaches to moving patients toward a more

preferred product, which is what this particular automated prior authorization is trying to do. The process would have the patient at least try Ambien, which is by far the most commonly used sedative hypnotic currently available. It has the most clinical evidence, providers are comfortable with it, and it will be generically available very soon (April 2007 — well before the implementation date of this class).

Ms. Schlaifer asked if there would be an attempt at some point to get current patients off the non-formulary agents. The answer was "no" and that there should be no need to do that. This drug class has a very high turnover rate and patients don't stay on the drugs very long. The 180-day implementation period should be sufficient to allow those people to remain on therapy. What the program is really trying to do is target new patients — those that have never been on this medication before — and at least have them try the most cost effective agent. If they can't tolerate it or the medicine isn't effective for them, they can go to another agent. If they go to Lunesta, they will be able to receive it at the formulary co-pay. If they opt to go to one of the other agents that are non-formulary, the co-pay will be $22 but they will have the option of going through the "medical necessity" process, which, if approved, would enable them to get it at the formulary co-pay.

Mr. Class said his main concern is at the pharmacy point of service. With the majority of prescriptions being filled at retail, he is concerned with the interaction that will occur when the patient goes to get a prescription filled. He doesn't want the patient to have to go back to providers at that point. Maj Tiller said that the process is new. They will be working closely with Express Scripts to put in some messaging that will facilitate an easy, patient-friendly Prior Authorization process. The technology is available and Express Scripts has experience with using it with both the patient and the pharmacy. There is a lot of work to be done, but the PEC expects to facilitate an easy transfer process. Ms. Trice added that the message will be customized and that pharmacies are very familiar with this process because other plans do it. Most other plans also prefer Ambien, so what TMA is doing will be consistent with the practices of other health care plans. She doesn't think anyone will be surprised by the process.

Mr. Hutchings said he doesn't disagree with the automated PA criteria of 180 days, but he pointed out that the FDA says these agents should be used only for up to 12 weeks of therapy. His experience has been that 95 percent of doctors don't follow this advice. Patients who aren't getting as much sleep as they used to tend to attribute that to a medical condition, so they're on a SED. His organization has been pushing hard to stick with the 12 weeks of therapy and if patients still have problems, look at the depression component and try to identify the medical condition that is causing it. Ms. Trice agreed that very few people should be on these agents long term. Clinical intervention in these cases would be perfectly appropriate, but the PEC didn't see any process by which they could target that behavior. She acknowledged that 180 days is a liberal time allowance.

Dr. Lenow said another question is how long these agents really work. He recalled a recent Panel discussion about the assumed off-label use of certain agents for weight loss. He has a colleague who is a sleep specialist who said that the majority of his patients are on Ambien for much longer than 12 weeks without adverse side effects. But it is a legitimate issue. In cases where there are FDA recommendations and doctors are exceeding them, he asked when, if at all, those get rolled into the P&T Committee's recommendations. Ms. Trice said that those recommendations were in the Ambien labeling when it first came out, but new drugs have come out with slightly different indications. It has to do with marketing. There is now little support

for it being unsafe to use the agents for more than the indicated time as longer-term data has become available. But there is still a question as to whether these agents really remain effective for people after six months. That is very unclear. Dr. Lenow agreed, noting that the subject has been a big marketing differentiator.

Mr. Hutchings asked about the time necessary to complete the automated authorization process, specifically if the PEC had any ideas whether it would be more or less than the 90 days called for in the first part of the implementation recommendation. Maj Tiller said the PEC doesn't expect it will be any greater than 90 days. But they want the flexibility to go past the 90 days if that becomes necessary to minimize patient inconvenience. Mr. Hutchings commented that the approach leaves the date nebulous for his organization. Maj Tiller said that the PEC would notify the Uniformed Services Family Health Plan if the period is going to go beyond 90 days. If the don't hear from the PEC, then the period will be 90 days.

Mr. Class also presented questions on behalf of Panel Member Lisa Le Gette, who couldn't attend today's meeting. Question 1: Understanding that only brand new SED-1 users of products other than Ambien will reject with a PA, does PEC have any estimate of how many beneficiaries might be affected by the SED-1 auto PA? MAJ Watson said the approximate number is 12, 500 per quarter.

Question 2: the primary reject mechanism for the auto PA will be "75." Will there be any kind of secondary reject mechanism to the dispensing pharmacy? Maj. Tiller said the answer is "yes."

Question 3: ESI research on SED therapy showed that when SED therapy is implemented, 25-44 percent of the members call in to ESI. Another 9-11 percent call their human resources office or benefits administrator. For this reason, we recommend a member communications program prior to implementation. Given this information, are there any plans to administer a beneficiary communication program prior to implementation? MAJ Watson answered that the usual communication methods would be used. Ms. Legette's follow-on question was whether the beneficiary would find out about the preferred option other than at the point of service? MAJ Watson said it is reasonable to assume that there will have to be some sort of notification.

Ms. Schlaifer said that the Prior Authorization criteria might be more liberal than they need to be. She asked whether there would be any attempt to educate the people who are on Ambien CR to get them off of it. Maj Tiller replied that in the past this hasn't been done. In this case, the tremendous amount of turnover in this drug class should make it unnecessary. Mr. Class added that the increased co-pay should also help with the turnover.

Panel Vote on SED-1 Drug Class Recommendations

Uniform Formulary Recommendations

The Panel Chair, Mr. Class, read the P&T Committee's recommendations for the Newer Sedative Hypnotics (SED-1) drug class:

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the SED-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that: 1) eszopiclone (Lunesta) and zolpidem IR (Ambien) be maintained as formulary on the UF with a

prior authorization requiring a trial of zolpidem IR (Ambien) for new patients and 2) that ramelteon (Rozerem), zaleplon (Sonata), and zolpidem ER (Ambien CR) be classified as non-formulary under the UF with a prior authorization requiring a trial of zolpidem IR (Ambien) for new patients.

The P&T Committee agreed that the following prior authorization criteria should apply to SED-1 agents other than zolpidem IR (Ambien). Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

   The patient has received a prescription for any SED-1 agent (including zolpidem IR [Ambien]) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

2) PA criteria if automated criteria are not met:

   The patient has tried zolpidem IR (Ambien) and had an inadequate response or was unable to tolerate it due to adverse effects.

   Treatment with zolpidem IR (Ambien) is contraindicated.

The P&T Committee noted that in order for a patient to receive a non-formulary SED-1 agent at the formulary cost-share, both the PA and medical necessity criteria must be met. If the PA criteria are met without an approved medical necessity determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved prior authorization for ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) would NOT automatically receive it at the formulary cost share. The P&T Committee also noted that the PA is not intended to apply where there are existing policies and protocols in place for operational/readiness situations and that MTFs should make necessary allowances for such use.

By a vote of 8 for, 0 against the Panel voted to concur with this recommendation.

No comments were added by the Panel.

Implementation Plan Recommendations

Mr. Class next read the P&T Committee's implementation plan recommendations:

The P&T Committee voted to recommend an implementation period of the greater of 1) the first Wednesday following a 90 day implementation period, or 2) the time necessary to complete logistical arrangements to implement the automated prior authorization.

Without further discussion, the Panel voted 8-0 to concur with this recommendation.

Mr. Class asked that the record reflect the Panel's continuing concern with the individual notification process.

Narcotic Analgesics Drug Class Review

Maj Tiller again introduced Shana Trice to present the P&T Committee's clinical effectiveness findings and recommendations on the second drug class reviewed: narcotic analgesics.

[Insert script, pp. 7 -12]

P&T Committee Physician's Perspective on Narcotic Analgesic Recommendations

COL Lounsberry again provided the Panel with a physician's perspective on the recommendations for this drug class. She acknowledged that the drug class is a big group, but said the only place where they saw any possibility of making anything non-formulary was where it was done (Ultram ER). In the high potency category, all of the products have some unique things about them. For the patients who use this category — cancer patients and long-term pain patients — the hassle factor isn't worth what would be achieved by making one of the medications non-formulary. The story is basically the same for the high potency short-acting analgesics. The fentanyl buccal tablets are relatively new, so there isn't enough experience to know how big the use of that will be, but they have an important place in therapy for breakthrough pain. Accordingly, the P&T Committee concurred with the recommendations of the PEC in this drug class.

Panel Questions and Discussion

Dr. Crum asked whether, in the high potency class, it was shown whether oxycodone ER (Oxycontin) has any beneficial advantage and whether there was any consideration of its potential for diversion of use. Ms. Trice replied that the Uniform Formulary process would not be an efficient way to address the diversion issue. There are other avenues for addressing diversion of use and DoD has those programs in place. If that is a major concern, the question should be whether or not to use the drug at all, not what should be the formulary co-pay. So the short answer is that there wasn't any discussion of the subject. There isn't a lot of use of oxycodone and most of that is legitimate. Ms. Trice added that there was discussion of the off label uses of Fentanyl and the issues around that.

Ms. Schlaifer noted that many of the commercial health plans are looking into the inappropriate use of Actiq. The use of it in DoD is small enough that it didn't even make the graph, but she asked if the P&T Committee looked at the question of inappropriate use. Ms. Trice said the main question concerns quantity limits, and TMA does have quantity limits for Actiq and the recommendation includes quantity limits for Fentora that are consistent with those for Actiq. That will be the major approach to the issue.

Mr. Class made a request from Ms. Le Gette for an updated status report on the duragesics PA that was approved in December. MAJ Watson read the following reply from the P&T Committee:

"The patient is likely to be opioid tolerant based on receiving at least one prescription for the following strong opioids: fentanyl patch, morphine, oxycodone (not including the combo products), hydromorphone, methodone or oxymorphone during the last 60 days. The Committee

reached this conclusion after reviewing the estimates of the number and percent of fentanyl patch patients that would be affected by the PA including the number of patients who received fentanyl patch prescriptions during the last 120 days but not within the last 60 days. The P&T Committee concluded that the best tradeoff between ensuring safety and potentially interrupting therapy for established patients would be to allow pharmacists at the retail network pharmacies to override system warnings after determining that the patient could be presumed to be opioid tolerant based on information from the patient or their physician. The retail network pharmacists would also have the option of contacting Express Scripts and have a PA by advising the patient to have their physician contact ESI."

Ms. Trice added that PEC is still in the process of working out the implementation date with ESI. The development of the automated profiler will facilitate the change and also allow the pharmacies to put in an override code to respond to these types of changes. PEC doesn't know about the implementation date yet, but it will be very deliberate.

Mr. Class asked a follow-up question from Ms. Le Gette concerning how many users will be affected by the new quantity level limit for Fentora. Ms. Trice said she did not have an exact number. She said PEC will look at the quantity dispensed and the dates on the prescriptions, which are being written for a maximum of four per day (although there are some exceptions). But there won't be a lot of people affected by the limit because there is not a lot of use of the product yet. If there are circumstances where patients are using two strengths (which isn't supposed to happen with Fentora — the patient should only have one strength on hand) there are well-established procedures for dealing with those. A teleconference participant added that the worst-case scenario would be 121 beneficiaries over 6 months.

Panel Vote on Narcotic Analgesic Drug Class Recommendations

Uniform Formulary Recommendations

The Panel Chair, Mr. Class, read the P&T Committee's Uniform Formulary recommendations for this drug class:

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the narcotic analgesic drug class, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that tramadol extended release tablets (Ultram ER) be designated non-formulary; with all other narcotic analgesic agents designated a formulary on the Uniform Formulary. Additionally, the P&T Committee voted to recommend a quantity limit of 112 tablets/28 days for fentanyl buccal tablets (Fentora), consistent with established quantity limits for fentanyl transmucosal lozenges (Actiq, generics), recommendations in Fentora package labeling, and current DoD prescribing patterns for Fentora buccal tablets."

Panel Vote on Formulary Recommendations

Without further discussion, the Panel voted 8-0 to concur with the P&T Committee's formulary recommendations for the narcotic analgesic drug class.

Implementation Plan Recommendations

Mr. Class next read the P&T Committee's implementation plan recommendations:

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

Panel Vote on Implementation Plan

Without further discussion, the Beneficiary Advisory Panel voted 8-0 to concur with the P&T Committee's recommendations.

Ophthalmic Glaucoma Agents Drug Class Review

Maj Tiller and Shana Trice next presented the P&T Committee's clinical effectiveness findings and recommendations for the ophthalmic glaucoma agents drug class.

[Insert script, pages 13-17]

P&T Committee Physician's Perspective on Ophthalmic Glaucoma Agents Recommendations

COL Lounsberry briefly discussed the Committee's recommendation by sub-classes. Regarding prostaglandins, she said the Committee, with input from other physicians, felt like DoD needed two agents on the formulary so that there would be something to fall back to in case one didn't work. The two prostaglandins being classified as formulary — Xalatan and Lumigan — are the ones most commonly used in DoD. Regarding beta blockers, COL Lounsberry said they are all pretty much efficacious. The recommendations provide for good coverage, including two versions of timolol that are generic and more cist-effective than the branded products recommended for non-formulary status. The Committee is very comfortable with this category. For the carbonic anhydrase inhibitors, the combination drug Cosopt is the most commonly used and the most cost-effective single agent (Trusopt) will also be on the formulary. In the "miscellaneous" category, all of the agents have their place in therapy and there wasn't much discussion of that group.

Panel Questions and Discussion

There were no questions or additional discussion of the P&T Committee's recommendations in the ophthalmic glaucoma agents drug class.

Panel Vote on Ophthalmic Glaucoma Agents Drug Class

Formulary Recommendations

Mr. Class read the P&T Committee's formulary recommendations for this drug class:

The P&T Committee, based upon its collective professional judgment, voted to recommend that latanoprost (Xalatan), bimatoprost (Lumigan), levobunol (Betagan, generics), betaxolol (Betoptic, generics; Betoptic-S), carteleol (Ocupress, generics), metipranolol (Optipranolol, generics), timolol maleate (Timoptic, generics), tomolol maleate gel forming solution (Timoptic XE, generics), brimonidine (generics, Alphagan P), apraclonidine (Iopidine), dorzolamide (Trusopt), dorzolamide/timolol (Cosopt), dipivefrin (Propine), acetylcholine (Miochol-E), carbachol (Isopto Carbachol), pilocarpine (Pilopine HS gel; Pilocar, generics), echothiophate (Phospholine Iodide) be maintained as formulary on the UF and that travoprost (Travatan, Travatan Z). timolol hemihydrate (Betimol), timolol maleate (Istalol) and brinzolamide (Azopt) be classified as non-formulary.

Without further discussion, the Beneficiary Advisory Panel voted 8-0 to concur with the P&T Committee's recommendations.

Panel Vote on Implementation Plan

Mr. Class next read the Committee's implementation recommendations:

The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

The Panel voted 8-0 to concur with the implementation plan.

Mr. Class asked to have a note added regarding beneficiary notification.

Monoamine Oxidase Inhibitor Antidepressants (MAOIs) Drug Class Review

Maj Tiller and Shana Trice also presented the P&T Committee's findings and recommendations for the final drug class to be considered at this meeting — monoamine oxidase inhibitor antidepressants (MAOIs).

[Insert script, p. 18, 3rd paragraph through page 20]

P&T Committee Physician's Perspective on Monoamine Oxidase Inhibitor Antidepressants (MAOIs) Drug Class Recommendations

COL Lounsberry said she didn't have much to add in this class. These are old drugs, not first-line or even second-line agents for depression, and the patch is way more expensive than the other agents without clinical advantage.

Panel Questions and Discussion on Monoamine Oxidase Inhibitor Antidepressants (MAOIs) Drug Class Recommendations

Ms. Schlaifer said she agreed with the Committee regarding the Emsam patch, but noted that there are 158 people on it for some reason. She asked if the reason was because the people were

unable to use anything else or whether there is another reason. She said it isn't going to be easy for these people when they go the pharmacy and there isn't something that the pharmacist can just recommend they be converted to. She said she normally is wary about things going beyond 90 days because of the increased utilization that comes with it. But in this case, she would like to see if some way can be found to notify the 158 people, since it's such a small number. Since the drug is for major depression she doesn't want them to show up at the pharmacy and find out they can't get their prescription for the amount they're now paying. MAJ Watson said the amount of the co-pay is the key point, because the particular product would be available through mail and retail, although the cost will be $13 more. At the MTF, the situation is different, but there are no beneficiaries getting the drug at MTFs.

Dr. Lenow expressed the opinion that the users of this drug may be old timers who have been on the drug for a while and their physicians have switched them to a safer patch. Ms. Schlaifer agreed that if that is the case they can just go back to what they were on before.

Panel Vote on Monoamine Oxidase Inhibitor Antidepressants (MAOIs) Drug Class Recommendations

Formulary Recommendations

The Panel Chair read the P&T Committee's formulary recommendations for the MAOI drug class:

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MAOIs, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that phenelzine (Nardil), tranylcypromine (Parnate, generics) and isocarboxazid (Marplan) be maintained as formulary on the UF and that transdermal selegiline (Emsam) be classified as non-formulary.

Without further discussion or comment, the Panel voted 8-0 to concur with the P&T Committee's formulary recommendations.

Implementation Plan

Mr. Class next read the implementation plan recommendations:

Because of the small number of unique utilizers affected (135 patients per quarter at all three POS), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

Again with no further discussion, the Panel voted 8-0 to concur with the implementation plan.

Mr. Class asked to have his comment regarding beneficiary notification included with the Panel's action.

Wrap Up and Adjournment

MAJ Watson announced that Mr. Robert Washington would assume the duties of Panel Chairperson beginning with the next meeting.

The next meeting is scheduled for June 21, 2007.

The meeting was adjourned at 10:45.

Appendix 1

3/22/07 Meeting Minutes

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.

- BAK — Benzalkonium chloride (a preservative used in ophthalmic drugs)
- BAP — Uniform Formulary Beneficiary Advisory Panel (the "Panel" referred to above)
- BCF — Basic Core Formulary
- BIA — Budget Impact Analysis
- CEA — Cost-effectiveness analysis
- C.F.R — Code of Federal Regulations
- CMA — Cost-Minimization Analysis
- CR — Controlled Release (a drug formulation)
- DEA — U.S. Drug Enforcement Administration
- DFO — Designated Federal Officer
- DOD — Department of Defense
- ECF – Extended Core Formulary
- ER — Extended Release (a drug formulation)
- ESI — Express-Scripts, Inc.
- FACA — Federal Advisory Committee Act
- FDA — U.S. Food and Drug Administration
- HMO — Health Maintenance Organization
- IOP — Intraocular pressure
- IR — Immediate Release (a drug formulation)
- MAOIs — Monoamine Oxidase Inhibitor Antidepressants (a drug class)
- MHS — Military Health System
- MTF — Military Treatment Facility
- NNH — Number Needed to Harm
- NNT — Number Needed to Treat
- OTC — Over the counter
- PA — Prior Authorization
- P&T Committee — DOD Pharmacy and Therapeutics Committee
- PDTS — Pharmacy Data Transaction Service
- PEC — DOD Pharmacoeconomic Center
- POS — Point of Service
- RCTs — Randomized Control Trials
- SED-1 — Newer Sedative Hypnotics (a drug class)
- 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

22 March 2007 BAP Meeting Script

(Maj Tiller) Good Morning,

I'm Major Wade Tiller, Deputy Director of the PEC. Joining me today from the PEC Clinical Operations staff are Shana Trice, a PEC pharmacist, and CAPT Richerson, the PEC Director. Our P&T Committee physician who is with us today is Col Doreen Lounsbery. She will provide the physician perspective for the recommendations made by the Committee. Also joining us today from TMA are RADM McGinnis, the Director of Pharmaceutical Operations, CAPT Blanche, Director of Pharmacy Programs and CAPT Patricia Buss, Chairman of the DoD P&T 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 and I are here to present an overview of the analyses presented to the DoD P&T Committee. 32 Code of Federal Regulation (C.F.R.) establishes procedures for inclusion of pharmaceutical agents on the Uniform Formulary based upon both 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 Newer Sedative Hypnotics, Narcotic Analgesics, Glaucoma Agents, and MAOI Antidepressants.
4) The DoD P&T Committee's recommendation as to the effective date of the agents being changed from formulary tier to the non-formulary tier of the Uniform Formulary. Based on 32 C.F.R. 199.21, such change will not be longer than 180 days from the final decision date but may be less.

We've given you a handout which includes the Uniform Formulary recommendations for all the drugs discussed today; this is found on pages two-four. There are tables and utilization figures for all the drug classes. We'll be using trade names as much as possible, so you can refer to your handout throughout the presentation. However, especially in the narcotic analgesic drug class, we may use generic names for some older drugs that have been generically available for a long time or which are available under multiple brand names.

Shana Trice will now present the Newer Sedative Hypnotics agents, or SED-1s, relative clinical effectiveness evaluation.

NEWER SEDATIVE HYPNOTICS CLINICAL EFFECTIVENESS

(Shana): Background – The relative clinical effectiveness evaluation was conducted by CPT Josh Napier, an Army internal medicine physician stationed at the PEC, and by me. The SED-1 agents are listed in Table 1. All but one are classified as benzodiazepine receptor agonists, meaning that they work at the same receptor site in the brain as the older benzodiazepine drugs, but at a different binding site. These agents are Ambien, Ambien CR, Lunesta, and Sonata. Rozerem acts by a different mechanism of action; it works at melatonin receptors in the area of the brain responsible for regulation of the 24-hour sleep-wake cycle (circadian rhythm). Ambien CR is a controlled release version of Ambien that has an immediate release phase followed by a prolonged release phase intended to maintain higher blood levels 3 to 6 hours after the dose, thus providing a longer duration of action than Ambien.

About 4 million SED-1 prescriptions per month are filled for DoD beneficiaries. Expenditures in this class have doubled in the last two years (from $54 million in FY04 to $111 million in FY06). All of the SED-1 agents are currently brand-only; Ambien is expected to become generically available in April 2007. (Keeping in mind that predicting generic availability is difficult and subject to change depending on the outcomes of litigation.)

If you'll look at Figure 1 on page 5 in your handout, it compares the different agents across the MHS. Zolpidem IR (Ambien) continues to be the most commonly prescribed SED-1, followed by Ambien CR and Lunesta. Use of Sonata is low but steady, while use of the most recently approved agent, Rozerem, is low but increasing. This graph also includes Restoril (and its generic equivalents), which is by far the most commonly used older sedative hypnotic, as a comparator – as you can see, there is a steady amount of continuous use of Restoril, but use of the newer agents is much greater.

Efficacy measures used in clinical trials commonly address two of the most common insomnia complaints—getting to sleep and staying asleep. The most common measure of sleep onset is decreases in sleep latency, or how long it takes to fall asleep (in minutes). Increases in sleep duration are typically measured as increases in total sleep time, or awake time after sleep onset (or the amount of time spent awake after initially falling asleep). Measurements can be either objective (based on monitoring performed in a sleep lab) or subjective (based on patient reports).

The most relevant difference between the agents is half-life, which refers to how long it takes for the medication to be eliminated from the body and is associated with duration of action. The SED-1 agent with the longest half-life is Lunesta, with a half-life of 6 hours (up to 9 hours in elderly patients); followed by Ambien and Ambien CR, which have half-lives of about 2.5 hours (although remember that Ambien CR has a longer duration of action because of its controlled release component); then by Rozerem, with a half-life of 1 to 2.6 hours; and Sonata, with a half-life of 1 hour.

Clinical Conclusion – I'm not going to read the full clinical conclusion, just summarize the points that compare SED-1 agents to each other.

With respect to efficacy:

- Based on placebo-controlled trials, all SED-1 agents decrease sleep latency to a similar degree. Data supporting the effect of Rozerem on sleep latency appears to be the least robust,

both in terms of the number of published studies and the amount of improvement demonstrated versus placebo. Ambien and Lunesta have evidence indicating consistent and similar increases in sleep duration. Sonata and Rozerem do not appear to consistently increase sleep duration.

- Based on three comparative trials, Sonata appears to decrease sleep latency more than Ambien, but Ambien appears to increase total sleep time more than Sonata. In one comparative trial, very similar results were reported for Lunesta vs. Ambien with respect to measures of sleep latency and sleep duration.
- Note that I have not mentioned Ambien CR. Data with Ambien CR is limited. Certainly, one would expect that Ambien CR would have similar effects on sleep latency compared to Ambien. However, it is unclear whether Ambien CR is associated with a clinically significant increase in sleep duration compared to Ambien, as comparative trial data are not available and reported effects on sleep duration with Ambien CR do not appear markedly different from those reported for Ambien.

With respect to safety and tolerability:

- The SED-1 agents appear to have similar adverse effect profiles and to result in similar rates of discontinuation due to adverse events in clinical trials. Lunesta is associated with an unpleasant taste. There do not appear to be any major disadvantages for any one agent with respect to drug-drug interactions. Rozerem may be less effective in smokers.
- Daytime sleepiness, impairments in psychomotor function and cognitive function, adverse effects on driving safety, and increased risk for falls may occur with any of the benzodiazepine receptor agonists; there is little or no data for the melatonin receptor agonist Rozerem. Agents with longer half-lives tend to pose a greater risk for these effects. Lower starting doses of all SED-1 agents except Rozerem are recommended in elderly patients.
- Driving safety studies have reported impaired performance and increased risk of accidents with a 7.5 mg dose of zopiclone (the drug from which Lunesta is derived), but applicability to Lunesta is unclear due to lower dosing. There was no reported difference between Lunesta and Ambien on subjective measures of next day effects based on results of an unpublished trial reported in the FDA statistical review of Lunesta.
- Because of its very short half-life, Sonata may be taken in the middle of the night after a patient has had difficulty falling asleep without demonstrating adverse effects on driving performance the next morning. It may have an advantage in elderly patients, since risk of falls and hip fracture tends overall to increase with increasing half-life (although the relationship between falls and half-life is not straightforward and prescribers must take into account patient activity patterns).
- No specific SED-1 agent appears preferable in other special patient populations (hepatic or renal dysfunction, pregnancy, pediatrics); there is some concern about use of Rozerem in pediatric patients due to possible endocrine effects.
- Rebound insomnia has been reported in clinical trials with all SED-1 agents except Rozerem; more rebound insomnia was noted with Ambien than with Sonata during comparative trials.
- All SED-1 agents, with the exception of Rozerem, probably have a small but significant potential for abuse. Rozerem appears to lack significant abuse potential and may be

preferable in patients at high risk for substance abuse. It is the only SED-1 agent that is not a DEA scheduled substance.

Overall Relative Clinical Effectiveness Conclusion –The major difference between the SED-1 agents lies in their effects on sleep duration. Ambien and Lunesta have evidence indicating consistent and similar increases in sleep duration, while the shorter half-life agents Sonata and Rozerem do not appear to consistently increase sleep duration. It is unclear whether Ambien CR has a clinically significant increase in sleep duration compared to Ambien. With respect to sleep latency, all SED-1 agents have been shown in clinical trials to decrease sleep latency, although limited data are available for Rozerem and Ambien CR. Sonata may decrease sleep latency more than Ambien based on three comparative trials. The SED-1 agents appear similar with respect to adverse effect profiles, discontinuation rates due to adverse events, and overall drug interaction potential. Other differences include Lunesta's long duration of action, which may cause safety concerns in some patients; it is also associated with an unpleasant taste. Sonata, with a very short duration of action, may be dosed more flexibly than the other SED-1 agents and causes less rebound insomnia than Ambien; however, it does not appear to increase sleep duration and is not widely used in DoD. Rozerem is mechanistically different from the other agents, does not require dose adjustment in elderly patients, appears to lack significant abuse potential, and is not a controlled substance.

Overall, based on clinical issues alone, there is no compelling reason to classify any of the SED-1 agents as non-formulary under the Uniform Formulary.

This concludes the Newer Sedative Hypnotics clinical effectiveness discussion. Maj Tiller will discuss the cost-effectiveness section next.

NEWER SEDATIVE HYPNOTICS COST-EFFECTIVENESS

(Maj Tiller) The relative cost-effectiveness evaluation for this class was conducted by Eugene Moore, Pharm D. Given the overall clinical conclusion that the agents within the SED-1 class have similar relative clinical effectiveness, a cost-minimization analysis (CMA) was employed to assess the relative cost-effectiveness of the agents within this therapeutic class. The agents were evaluated on their weighted average cost per day of therapy across all three points of service.

Relative Cost Effectiveness Conclusion: Based on the results of the CMA and other clinical and cost considerations, the P&T Committee concluded that:

1) Lunesta was the most cost-effective agent until Ambien becomes generically available with competitive pricing.
2) Rozerem, Sonata, and Ambien CR were more costly than Lunesta and provided no meaningful clinical therapeutic advantage compared to Lunesta or Ambien.
3) The UF scenario utilizing a prior authorization requiring a trial of zolpidem IR (Ambien) by new SED-1 patients was more cost-effective relative to UF scenarios not requiring a trial of zolpidem IR by new SED-1 patients.

COMMITTEE ACTION: UF RECOMMENDATION – Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the SED-1 agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (13 for, 1 opposed, 2 abstained, 1 absent) to recommend that: 1) eszopiclone (Lunesta) and zolpidem IR (Ambien) be maintained as formulary on the UF with a prior authorization requiring a trial of zolpidem IR for new patients, and 2) that ramelteon (Rozerem), zaleplon (Sonata), and zolpidem ER (Ambien CR) be classified as non-formulary under the UF with a prior authorization requiring a trial of zolpidem IR for new patients.

The Committee agreed that the following prior authorization criteria should apply to SED-1 agents other than zolpidem IR (Ambien). Coverage would be approved if a patient met any of the following criteria:

1) Automated PA criteria:

   The patient has received a prescription for any SED-1 agent (including zolpidem IR [Ambien]) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during this previous 180 days.

2) PA criteria if automated criteria are not met:

   The patient has tried zolpidem IR (Ambien) and had an inadequate response or was unable to tolerate it due to adverse effects.

   Treatment with zolpidem IR (Ambien) is contraindicated.

In order for a patient to receive a non-formulary SED-1 agent at the formulary cost-share, both the PA and medical necessity criteria must be met. If the PA criteria are met without an approved medical necessity determination, the patient cost-share will be at the non-formulary level. In other words, patients obtaining an approved prior authorization for ramelteon (Rozerem), zaleplon (Sonata), or zolpidem ER (Ambien CR) would NOT automatically receive it at the formulary cost share.

The P&T Committee also noted that the PA is not intended to apply where there are existing policies or protocols in place for operational/readiness situations and that MTFs should make necessary allowances for such use.

NF Justification:

The P&T Committee recommended that Rozerem, Sonata, and Ambien CR be classified as non-formulary under the UF. The Committee's recommendation was based on:

1) The clinical effectiveness review did not suggest a compelling therapeutic advantage for Rozerem, Sonata or Ambien CR, compared to the UF candidates Ambien IR and Lunesta. Although Rozerem may have benefits over the other SED-1s in a subset of patients due to its apparent lack of abuse potential and non-scheduled status, the medical necessity process should adequately allow for such use.
2) Both Ambien and Lunesta have consistent evidence supporting effects on both sleep latency and sleep duration, while Sonata and Rozerem lack evidence of effects on sleep duration. Ambien CR lacks data supporting any clinically significant increase in sleep duration compared to Ambien.

3) A survey of MTF providers suggested that the majority of DoD patients could be successfully treated with two formulary agents.

4) The cost-effectiveness analysis showed that the UF scenario that employed an automated prior authorization to be more cost-effective relative to other UF scenarios considered. Automated PA criteria requiring an initial trial of Ambien in patients newly starting SED-1 therapy is both clinically rational and cost-effective. Impending generic availability of Ambien will result in cost-savings to DoD without compromising patient care.

COMMITTEE ACTION: IMPLEMENTATION PERIOD – The P&T Committee voted (14 for, 0 opposed, 2 abstained, 1 absent) to recommend an effective date of the greater of 1) the first Wednesday following a 90 day implementation period, or 2) the time necessary to complete logistical arrangements to implement the automated prior authorization. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have Ambien CR, Sonata, or Rozerem on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider and 2) medical necessity is established. MTFs may (but are not required) to fill a prescription for non-formulary SED-1 agents written by a non-MTF provider to whom the patient was referred, as long as medical necessity was established. In addition, MTFs will be able to fill prescriptions for Ambien CR, Sonata, Rozerem or Lunesta for patients newly starting SED-1 therapy only if the patient has tried and failed, been unable to tolerate, or has contraindications to treatment with zolpidem IR (Ambien).

COL Lounsbery will now present the DoD P&T Committee's perspective on the UF recommendation for the SED-1 class.

(COL Lounsbery): ... That concludes the SED-1 therapeutic class presentation, the PEC staff and I will now gladly answer any questions you may have.

(Maj Tiller) Shana will now continue with the Narcotic Analgesics clinical effectiveness review.

NARCOTIC ANALGESICS CLINICAL EFFECTIVENESS

(Shana): Background – The relative clinical effectiveness evaluation was conducted by LCDR Joe Lawrence, a PEC clinical pharmacist; LtCol Jim McCrary, an Air Force internal medicine physician stationed at the PEC; and me. The drugs in this class comprise all narcotic analgesics (also referred to as opioids or opiate agonists) used for the treatment of pain on an outpatient basis, including combinations with acetaminophen (APAP), aspirin (ASA), and other non-opioids. This is a very large class and a very commonly used class. The narcotic analgesics accounted for approximately $153 million dollars in MHS expenditures in FY 2006, which would make them the #8 class. Approximately 437,000 DoD beneficiaries received one or more prescriptions for a narcotic analgesic during FY 2006.

For review purposes, the narcotic analgesics were divided into the categories outlined on pages 2 and 3 of your handout, based on their controlled drug status (which in general reflects their potency), and whether or not they are combined with a non-opioid analgesic. Most of the narcotic analgesics are now generically available.

- The first category is the high-potency, single analgesic ingredient agents. This category is further subdivided into the long-acting agents (dosing every 12 hours or longer), which are generally used for long-term treatment of chronic pain, and the short-acting agents, which may be used alone for acute pain or with a long-acting agent for treatment of breakthrough pain.
    - The most commonly used high potency long-acting agents are fentanyl transdermal patches (Duragesic and generics); morphine, which is available in both a 12- and 24-hour formulations; and oxycodone (Oxycontin). The oxymorphone products (Opana ER and Opana) are new to the market and are not widely used.
    - The high potency short-acting agents most often used for breakthrough pain are morphine, oxycodone, and fentanyl. There are two short-acting fentanyl products, the transmucosal lozenges or "lollipops" (Actiq), and the buccal tablets (Fentora), which are inserted between the cheek and gum. The other short-acting agents listed in the table are less commonly used or have specific clinical niches (or both). For example, codeine, hydromorphone, levorphanol, meperidine, and methadone all have clinical characteristics that limit their usefulness as first-line choices for chronic pain. The oldest products—opium tincture and opium / belladonna suppositories—occupy very specific clinical niches. I would also like to note that codeine is listed in the high-potency category only because it is classified by the Drug Enforcement Administration (DEA) as a C-II controlled substance; pharmacologically it is a relatively weak opioid.
- The high-potency combination agents are limited to combinations of oxycodone with acetaminophen or aspirin, with the acetaminophen combinations being by far the most commonly used. Multiple combination products containing various strengths of oxycodone and acetaminophen are available; some brand names include Tylox and Percocet. All of the combination products are short-acting; they are usually given every 4-6 hours.

- The low potency single analgesic ingredient agents are not very commonly used, with the exception of tramadol (Ultram). Tramadol is the only narcotic analgesic with a dual mechanism of action; in addition to acting on opioid receptors, it also has some effects on serotonin and norepinephrine receptors similar to some antidepressants. It is not a controlled substance. It is available in both a short-acting and a long-acting formulation (Ultram ER). Also notable in this category is the nasal spray formulation of butorphanol (Stadol nasal spray), which achieved some notoriety and was moved from a non-controlled to a controlled status by the DEA following reports of abuse in patients taking it for migraine. I should also point out that there is a typo on the handout—the brand name for the injectable form of buprenorphine should be Buprenex, not Subutex.
- The low potency combination agents account for the majority of narcotic analgesic prescriptions. By far the most commonly used products are combinations of acetaminophen with hydrocodone (e.g., Vicodin, Lortab, Lorcet), codeine (e.g., Tylenol #3), propoxyphene (e.g., Darvocet N-100), and tramadol (Ultracet). Figure 3 on page 7 of your handout focuses on the tramadol products, but you can also see the relative usage of the most commonly used products, most of which are combinations. Both the high- and low-potency combinations are most commonly used for acute pain (for example, after surgery, dental procedures, or injuries). They are not as suitable for long-term use as the single analgesic ingredient agents because of the potential toxicity of acetaminophen or aspirin at high doses or after prolonged use.

The clinical efficacy review was divided into two major areas: chronic pain (cancer, non-cancer, or neuropathic) and acute pain (post-operative or non-specific). Because ample information is available for most of these agents, the review focused primarily on published meta-analyses, systematic reviews, and well-accepted tertiary literature sources, including clinical practice guidelines. A more detailed review of the literature was performed for specific issues affecting potential formulary decisions.

Clinical Conclusion – Again, I'm going to summarize only the points that compare the narcotic analgesics to each other, since you have the full text in your background materials.

With respect to efficacy:

- There is insufficient evidence to support efficacy differences between narcotic analgesics, including high potency long-acting agents for the treatment of chronic cancer or non-cancer pain, high potency immediate release agents for the treatment of breakthrough pain, or narcotic analgesics in general for the treatment of neuropathic pain.
- There is no evidence suggesting efficacy differences between long-acting and short-acting formulations of the same agents; however, long-acting products offer greater convenience and may be associated with fewer episodes of breakthrough pain.
- There is insufficient evidence to support efficacy differences between 12-hour (e.g., MS Contin and generics) and 24-hour ER morphine products (Avinza, Kadian), or between the two 24-hour products (Avinza vs. Kadian). Avinza is restricted to a maximum dose of 1600 mg daily and cannot be taken with alcohol (including alcohol-containing medications). Kadian has a much longer time to achieve maximum serum levels (~9.5 hours) compared to Avinza (~0.5 hour) or to 12-hour

ER morphine (2-3 hours). Both Avinza and Kadian capsules can be opened and sprinkled on food; the contents of Kadian capsules can be given via gastrostomy tube.

- There is insufficient evidence to support efficacy differences between immediate release agents for the treatment of breakthrough pain in patients with chronic cancer or non-cancer pain, including the newer immediate release fentanyl products (oral transmucosal lozenges [Actiq, generic] and buccal tablets [Fentora])). Buccal fentanyl (Fentora) is more bioavailable and may offer more consistent dosing; it is also sugar-free.
- Narcotic analgesics are rarely considered first line agents for the treatment of neuropathic pain. There is insufficient evidence to support efficacy differences between agents. Evidence of efficacy in various types of neuropathic pain exists for morphine, oxycodone, tramadol, and methadone.
- There is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics for treatment of acute pain. Dosing of combination agents is limited by their non-opioid ingredient, most commonly acetaminophen.

With respect to safety and tolerability:

- Narcotic analgesics are associated with multiple adverse effects, including nausea, vomiting, constipation, mood changes, somnolence, urinary retention, pruritis, and oral/dental problems. Respiratory depression is uncommon but potentially serious; the risk is generally small when narcotic analgesics are appropriately titrated, as tolerance rapidly develops.
- A decrease in seizure threshold occurs with the use of all narcotics, but is of particular concern with meperidine (Demerol), propoxyphene (e.g., Darvon, Darvocet), and tramadol (e.g., Ultram, Ultram ER, Ultracet). Both meperidine and propoxyphene have neurotoxic metabolites. Tramadol is associated with an increased risk of seizure at higher than recommended doses or in patients who are taking other medications or who have conditions that increase seizure risk.
- Propoxyphene is not considered appropriate in elderly patients due to adverse effects affecting the central nervous system, including sedation, confusion, and increased likelihood of falls and fall-related fractures. A consumer watchdog group has petitioned the FDA to phase out propoxyphene from the U.S. market due to the association of excessive doses of propoxyphene with drug-related deaths. Many DoD providers surveyed cited concerns for safety with the use of meperidine and propoxyphene, although others pointed out that they were useful and could be used safely if limited to short-term use in the correct patients.
- While there are clearly differences among narcotic analgesics with regard to likelihood for abuse (e.g., onset of action and potency), there are no data supporting differences in potential for abuse among like medications (e.g., high potency, long-acting agents) that the P&T Committee considered useful for formulary decision-making.

- In general, drug interactions are relatively similar for all of the drugs in this class and it does not appear that any particular medication offers a substantially higher potential for drug interactions.
- There are differences among narcotic analgesics with regard to clinical evidence, extent of clinical experience, and labeling for use in special patient populations (including pediatric and elderly patients, patients who are pregnant or breast-feeding, and patients with renal or hepatic dysfunction). However, the P&T Committee overall did not find sufficient evidence of a unique advantage or disadvantage for specific products that it considered useful for formulary decision-making.
- Patients with swallowing difficulties may require liquid formulations or products that can be sprinkled on food or administered via a non-oral route. The available narcotic analgesics offer various formulations that meet these needs.

With respect to other factors:

- Providers surveyed in general emphasized that they require a broad array of narcotic analgesics in their practice to treat their patients and that excessive formulary restrictions would be detrimental to their ability to adequately treat various clinical presentations. They favored extended release narcotic analgesics, including the fentanyl transdermal patch, as well as a broad array of strengths of opioid / acetaminophen combination products.
- Clinical coverage considerations support a broad array of formulary agents and formulations.

Overall Relative Clinical Effectiveness Conclusion – There is insufficient evidence to support efficacy differences between narcotic analgesics, including high potency long-acting agents for the treatment of chronic pain, high potency immediate release agents for the treatment of breakthrough pain, and narcotic analgesics in general for the treatment of neuropathic pain. Long-acting products may be associated with fewer episodes of breakthrough pain. There is insufficient evidence to support efficacy differences between 12-hour and 24-hour ER morphine products, or between the two 24-hour products (Avinza vs. Kadian). There are minor pharmacological differences between Avinza and Kadian that do not consistently favor either product. There is insufficient evidence to support efficacy differences between immediate release agents for the treatment of breakthrough pain, including the two immediate release fentanyl formulations (Actiq and Fentora). There are minor pharmacological differences between these two products that may favor the buccal tablets (Fentora). With respect to acute pain, there is insufficient direct evidence to draw definitive conclusions regarding the relative efficacy of narcotic analgesics (typically the combination agents).

All narcotic analgesics can be associated with serious adverse effects. The risk of respiratory depression is generally small if narcotic analgesics are properly titrated, as tolerance rapidly develops. Narcotic analgesics that may offer particular safety or tolerability concerns include meperidine and propoxyphene. Other narcotic analgesics may be infrequently used and/or limited to specific clinical niches by toxicity concerns. Based on clinical issues alone, the Committee agreed that there is no compelling reason to classify any of the narcotic analgesics as non-formulary under the Uniform Formulary.

This concludes the Narcotic Analgesics clinical effectiveness discussion. Maj Tiller will discuss the cost effectiveness section next.

NARCOTIC ANALGESICS COST EFFECTIVENESS

(Maj Tiller) The relative cost-effectiveness evaluation for this class was conducted by Eugene Moore, Pharm D. Several cost-minimization analyses (CMAs) were performed to determine the relative cost-effectiveness of the agents within each subclass. The CMAs compared the agents based on their weighted average cost per equianalgesic dose.

Cost Effectiveness Conclusion

1) *High potency long-acting single analgesic agents* – Although the 24-hour ER products (Kadian and Avinza); fentanyl transdermal patch (Duragesic, generics), oxycodone extended release (Oxycontin), and oxymorphone (Opana ER) were considerably more costly relative to the 12-hour morphine sulfate ER product (MS Contin and generics), they have unique clinical advantages and should be maintained on the UF in order to sufficiently meet the clinical needs of the DoD population.
2) *High potency short-acting single analgesic agents* – Even though fentanyl citrate buccal tablets (Fentora) and fentanyl citrate transmucosal lozenges (Actiq, generics) were more than 40-fold the cost of the two most cost-effective agents, morphine sulfate IR and oxycodone IR, the fentanyl citrate products provide an additional therapeutic alternative for breakthrough pain with novel routes of administration. There was no substantial difference in cost effectiveness between the two fentanyl citrate products.
3) *Low potency single analgesic agents* – Tramadol extended release (Ultram ER) was not cost-effective relative to other formulations of tramadol (tramadol; tramadol/APAP), which are generically available. All other products in this subclass were cost-effective.
4) *Combination agents* – The products within this generic-dominated subclass were all determined to be cost-effective relative to their comparators.

UF Recommendations

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and the relative cost effectiveness determinations for the narcotic analgesic drug class, and other relevant factors, the P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) that tramadol extended release tablets (Ultram ER) be designated non-formulary under the UF; with all other narcotic analgesic agents designated as formulary on the Uniform Formulary. Additionally, the P&T Committee voted to recommend (14 for, 0 opposed, 1 absent, 1 abstain) a quantity limit of 112 tablets/ 28 days for fentanyl buccal tablets (Fentora), consistent with established quantity limits for fentanyl transmucosal lozenges (Actiq, generics),

recommendations in Fentora package labeling, and current DoD prescribing patterns for Fentora buccal tablets.

NF Justification:

The P&T Committee recommended that tramadol ER (Ultram ER) be classified as non-formulary under the UF. The Committee's recommendation was based on:

1) The clinical effectiveness review concluded that the primary difference between Ultram ER and the immediate release products Ultram and Ultracet was the reduced dosing frequency and not enhancements in clinical efficacy or safety. While Ultram ER may offer another option in patients with neuropathic pain, narcotic analgesics in general, and tramadol specifically, are rarely considered to be first-line treatments for neuropathic pain.
2) The results of the cost-effectiveness analysis showed that Ultram ER was not cost-effective relative to other formulations of tramadol, which are generically available.
3) The proposed UF candidates provide a wide selection of formulary narcotic analgesics to meet the needs of DoD beneficiaries.

UF Implementation Period

Because of the small number of unique utilizers affected (approximately 1000 patients [~0.2%] out of approximately 437,000 unique utilizers at all three POS). The P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have Ultram ER on their local formularies. MTFs will be able to fill non-formulary requests for this medication only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) medical necessity is established. MTFs may (but are not required to) fill a prescription for a non-formulary narcotic analgesic 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 (13 for, 0 opposed, 1 abstained, 3 absent) an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following the approval by the Director, TMA.

COL Lounsbery will now present the DoD P&T Committee's perspective on the UF recommendation for the Narcotic Analgesic class.

(COL Lounsbery): ... That concludes the Narcotic Analgesic therapeutic class presentation, the PEC staff and I will now gladly answer any questions you may have.

(Maj Tiller) Shana will now present the Glaucoma Agents clinical effectiveness review.

GLAUCOMA AGENTS CLINICAL EFFECTIVENESS

(Shana): Members in the class: The clinical effectiveness review for the glaucoma agents was conducted by CAPT Don Nichols, a Navy family medicine physician stationed at the PEC, along with Julie Liss, Harsha Mistry, and Angela Allerman, who are all PEC clinical pharmacists. If you will refer to Table 1 on page 3 of your handout, you will see the seven categories that the Glaucoma Agents were divided into, based on their chemical structure and mechanism of action. These categories are prostaglandin analogs; beta blockers; carbonic anhydrase inhibitors; alpha 2 adrenergics; adrenergics; cholinergics; and cholinesterase inhibitors. All of the agents in this class are given as eye drops. Combination therapy is common in this class, more than one agent from different subclasses frequently used. For the purpose of the clinical effectiveness evaluation, drugs within each subclass were compared to each other with regards to efficacy, safety and tolerability, clinical outcomes, and other factors.

Relevance to MHS and Utilization: Glaucoma agents accounted for $51.1 million in MHS expenditures in Fiscal Year 2006, making this drug class #34 in terms of total expenditures during that time period. Figure 4 on page 7 in your handout shows the breakdown in utilization among the seven categories. The prostaglandin analogs have the highest utilization, at about 40,000 prescriptions dispensed monthly in the MHS, followed by beta blockers, with about 15,000 prescriptions dispensed monthly. The remaining categories have less than 10,000 prescriptions dispensed monthly.

Mechanism of Action: In glaucoma, pressure in the eye (referred to as intraocular pressure or IOP) is elevated, which can lead to loss of vision over time. All of the agents in this class reduce elevated intraocular pressure. Prostaglandins in general are more effective at reducing IOP than agents in other categories; they reduce IOP by 25-35%, compared to less than 30% for agents in other categories.

Preservative: Preservatives are used in most ophthalmic drugs to maintain stability of the product. The most commonly used preservative is benzalkonium chloride, or BAK. BAK has been associated with local ocular effects, including burning and stinging, so many newer products are formulated with preservatives different from BAK. I'll specifically mention differences in preservatives when it's important.

Conclusion: I'll first give you some background and the relative clinical effectiveness conclusion for each of the various categories, and then I'll provide the overall relative clinical effectiveness conclusion. Let's start with the prostaglandin analogs.

Clinical Effectiveness Conclusion

1) *Prostaglandin analogs* – None of the three prostaglandin analogs are available in generic formulations. If you turn to Figure 5 on page 8 of your handout, you can see that in the MHS, Xalatan is by far the most prescribed prostaglandin analog, at about 25,000 prescriptions per month. Travatan and Travatan Z (which has a non-BAK preservative) are least often prescribed, at about 5,000 prescriptions per month. Lumigan is in 2nd place, at a little more than 5,000 prescriptions per month.

   The P&T Committee concluded that in terms of efficacy, Lumigan, Xalatan, and Travatan (including Travatan Z) all decrease intraocular pressure from baseline by 28% to 33%. Meta-analyses and head-to-head clinical trials have shown no difference in efficacy. In

regards to adverse effects, Xalatan has the most favorable ocular adverse event profile of the three prostaglandin analogs.

2) *Beta blockers* – Several of the ophthalmic beta blockers are available in generic formulations. If you'll notice on the table, there are several different timolol formulations. Timolol is available as the maleate salt as a regular opthalmic solution and as a solution that turns into a gel upon administration. The timolol maleate solutions are Timoptic (which has generic equivalents) and the brand-only product Istalol. The timolol maleate gel-forming solution is Timoptic XE, which has generic equivalents. Timolol is also available as the hemihydrate salt – this brand-only product is called Betimol. The other ophthalmic beta blockers are levobunolol (Betagan, generics), metipranolol (Optipranolol, generics) carteolol (Ocupress, generics), and betaxolol (Betoptic, Betoptic-S).

   If you look on page 8 at Figure 6, you can see that the beta blockers have much lower utilization than the prostaglandins. The Timoptic XE gel forming solution is the number one ophthalmic beta blocker in the MHS, at about 2,000 prescriptions per month. Utilization of the branded timolol hemihydrate or Betimol product is holding steady at about 1,000 prescriptions per month. The branded timolol maleate or Istalol formulation is holding steady at about 500 prescriptions per month

   For efficacy, the intraocular pressure-lowering effects of Timoptic, Timoptic XE, Istalol, Betimol, Betagan, Optipranolol, and Ocupress appear similar, based on several head-to-head studies. Both the Timoptic solution and Timoptic XE gel-forming solution reduce intraocular pressure by 20-35%. The Timoptic XE gel-forming solution has the advantage of once daily dosing, but is associated with transient blurred vision due to the thick consistency of the gel. Betoptic and Betoptic-S may decrease intraocular pressure to a lesser extent than Timoptic, but may have an advantage in patients with cardiac or pulmonary co-morbidities, since they may be less likely to cause systemic adverse effects in this population than the other ophthalmic beta blockers.

   The P&T Committee concluded that there is no evidence that the timolol maleate product Istalol or the timolol hemihydrate product Betimol have additional clinical benefits over other timolol maleate products in intra-ocular pressure lowering or safety profiles. Betimol—the timolol hemihydrate product— was formulated to have enhanced ocular availability; however, no difference in efficacy was found in two head-to-head trials with the timolol maleate product Timoptic. The timolol maleate solution Istalol is formulated with an extra ingredient, potassium sorbate, which theoretically enhances ocular penetration, however, one head-to-head trial showed no difference in efficacy compared to the other timolol maleate solution, Timoptic.

3) *Carbonic anhydrase inhibitors* – There are only three carbonic anhydrase inhibitors: brinzolamide (Azopt), dorzolamide (Trusopt), and the combination of dorzolamide with timolol maleate, which is called Cosopt. On page 9 of your handout, Figure 7 shows utilization of these drugs. The Cosopt combination has about 8,000 prescriptions dispensed per month, while Azopt and Trusopt both have about 2,000 prescriptions dispensed per month.

   The P&T Committee concluded that the intraocular pressure lowering effects of Azopt and Trusopt appear similar. Cosopt is the only combination product marketed, and offers a dosing convenience to patients. Trusopt causes more local ocular irritation than Azopt;

however, burning and stinging upon instillation last less than 10 seconds, diminish over time, and have not translated into a higher discontinuation rate due to adverse events.

4) *Alpha 2 adrenergics* – For the alpha 2 adrenergics, there are two parent compounds, apraclonidine (brand name Iopidine) and brimonidine, which is available in several difference formulations. Brimonidine is available in a 2% concentration with the BAK preservative; this product is only available as a generic. Brimonidine with a purite preservative is available in a 0.15% and 0.10% solution, both under the brand name of Alphagan P; there are no generics available for these two drugs. Although not shown in the handout, the Alphagan P 0.15% solution is the alpha 2 adrenergic most utilized in the MHS, at about 8,000 prescriptions per month.

   The P&T Committee concluded that Iopidine and brimonidine lower intraocular pressure to a similar extent. For brimonidine, changing the BAK preservative to a purite preservative (as found in Alphagan P) and reducing the concentration from 0.2% to 0.15% or 0.1% does not appear to affect efficacy. There is conflicting data as to whether brimonidine with the purite preservative in a 0.15% concentration (Alphagan P) causes less ocular irritation than brimonidine 0.2% generic with the BAK preservative. Brimonidine purite 0.1% (Alphagan P) may have an improved safety and tolerability profile compared to brimonidine BAK 0.2% (generic), but the one supportive study has not been published in a peer-reviewed journal.

5) *Adrenergics, cholinergics, and cholinesterase inhibitors* – The last three categories are the cholinergics, adrenergics, and cholinesterase inhibitors. The drugs in these subclasses have been marketed for several decades, and have largely been replaced by the newer products discussed previously, primarily due to adverse effect profiles. There are three cholinergic agents, pilocarpine (Pilocar, or Pilopine HS-gel), acetylcholine (Miochol-E) and carbachol (Isopto Carbachol). There is one adrenergic agent, dipivefrin (Propine), and one cholinesterase inhibitor echothiophate (Phospholine Iodide).

   Pilocarpine has the highest utilization among these older agents, at about 1,000 prescriptions per month in the MHS. It is used for acute angle closure glaucoma, which is considered an emergency situation and requires surgery; it is also used as a miotic agent during ocular surgery to dilate the pupil. Although not routinely used today, Propine, Miochol-E, Isopto Carbachol and Phospholine Iodide serve unique niches in therapy. In the MHS, these three drugs have less than 200 prescriptions dispensed monthly in the MHS (the figure is not shown).

Overall Relative Clinical Effectiveness Conclusion: Clinically significant differences in intraocular pressure were not found when agents were compared within each of the seven categories (prostaglandin analogs, beta blockers, carbonic anhydrase inhibitors, alpha 2 adrenergics, and the older drugs, adrenergics, cholinergics, and cholinesterase inhibitors). There are minor differences in local adverse event profiles, but these differences have not resulted in differences in discontinuations due to adverse events. Overall, based on clinical issues alone, the P&T Committee concluded that there is no compelling reason to classify any of the Glaucoma Agents as non-formulary under the Uniform Formulary.

Major Tiller will now discuss cost-effectiveness for the Glaucoma Agents.

GLAUCOMA AGENTS COST-EFFECTIVENESS

(Maj Tiller) Several cost-minimization analyses (CMAs) were performed to determine the relative cost-effectiveness of the agents within each subclass. The cost-effectiveness determinations were completed by Maj Josh Devine, PhD. The CMAs compared the weighted average cost per day of treatment for each drug product.

In regard to the relative cost-effectiveness of the agents within the Glaucoma Agent therapeutic class, the P&T Committee concluded:

1) The CMAs compared the weighted average cost per day of treatment for each drug product. For the prostaglandin analogs, a) travoprost (Travatan, Travatan Z) was most cost-effective under a scenario where it was the sole agent on the uniform formulary; b) latanoprost (Xalatan) and bimatoprost (Lumigan) were most cost-effective under a scenario where only two prostaglandin products were placed in the Uniform Formulary; and c) an all-on scenario (i.e., all three prostaglandin products were included on the Uniform Formulary) was less cost-effective than a scenario where at least one prostaglandin was designated non formulary.
2) For the other ophthalmic glaucoma agents, only two products were identified as not cost-effective in the beta-blocker subclass. Timolol hemihydrate (Betimol) and timolol maleate (Istalol) were both shown to be significantly more costly and no more effective than other agents in the subclass.
3) Similarly, a comparison of the topical carbonic anhydrase inhibitors showed that brinzolamide (Azopt) was not cost-effective compared to dorzolamide (Trusopt). All other medications in the remaining subclasses were determined to be cost-effective relative to their comparators.

COMMITTEE ACTION: In view of the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations of the ophthalmic glaucoma agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, and 1 absent) to recommend that Xalatan (latanoprost), Lumigan (bimatoprost), Betagan (levobunolol), Betoptic and Betoptic-S (betaxolol), Ocupress (carteolol), Optipranolol (metipranolol), Timoptic and Timoptic XE gel forming solution (timolol maleate), Alphagan P (brimonidine and generics), Iopidine (apraclonidine), Trusopt (dorzolamide), Cosopt (dorzolamide/timolol), Propine (dipivefrin), Miochol-E (acetylcholine), carbachol (Isopto Carbachol), Pilopine HS gel and Pilocar (pilocarpine), and Phospholine Iodide (echothiophate) be maintained as formulary on the UF and that the prostaglandins Travatan and Travatan Z (travoprost), the beta blockers Betimol (timolol hemihydrate), and Istalol (timolol maleate), and the carbonic anhydrase inhibitor Azopt (brinzolamide) be classified as non-formulary under the UF.

NF Justification:

For the prostaglandins, Travatan and Travatan Z were recommended to be classified as NF on the UF. The Committee's recommendation was based on:

1) The results of the cost-effectiveness analysis for the 2 of 3 UF condition set, which competed the agents within the sub-class under a scenario where only two prostaglandin products were placed on the Uniform Formulary. The analysis showed that latanoprost (Xalatan) and bimatoprost (Lumigan) were the most cost-effective agents under this condition set. Moreover, the condition set that allowed all three prostaglandin products

to be included on the Uniform Formulary was less cost-effective than a scenario where at least one prostaglandin was designated non formulary.

2) Based on the clinical needs of our population in DoD, providers should be able to adequately treat patients with two prostaglandins, Xalatan and Lumigan. There is no data to suggest that the efficacy or safety profiles of Travatan or Travatan Z offer a clinical advantage over Xalatan and Lumigan.

For the ophthalmic beta blockers, the timolol maleate product Istalol and the timolol hemihydrate products were recommended to be classified as NF on the UF. The Committee's recommendation was based on:

1) The results of the relative cost-effectiveness analysis for the beta-blocker subclass revealed that timolol hemihydrate (Betimol) and timolol maleate (Istalol) were significantly more costly relative to the other agents within the subclass.

2) The results of the relative clinical effectiveness evaluation determined that timolol hemihydrate (Betimol) and timolol maleate (Istalol) provide no clinically meaningful therapeutic advantage relative to the other more cost-effective agents within the subclass. Istalol is similar to other timolol maleate products, such as Timoptic, except that it has an added ingredient, potassium sorbate and is dosed once daily (as is Timoptic XE gel forming solution). The addition of potassium sorbate has not been shown to enhance efficacy or safety. Likewise, the timolol hemihydrate product Betimol has a different salt than the maleate product Timoptic. The active ingredient is still timolol. Betimol is dosed twice daily, as is Timoptic, and has not been shown to have a clinical advantage over Timoptic. The beta blockers remaining on the Uniform Formulary, including Timoptic and Timoptic XE gel forming solution, are more than sufficient to meet the needs of the DoD population.

3) For the carbonic anhydrase inhibitors, Azopt (brinzolamide) was recommended to be classified as NF on the UF. The Committee's recommendation was based on the results of the relative cost-effectiveness analysis for the carbonic anhydrase inhibitors subclass, which showed that brinzolamide (Azopt) was not cost-effective compared to dorzolamide (Trusopt), and the relative clinical effectiveness determination that brinzolamide (Azopt) provides no clinically meaningful therapeutic advantage relative to dorzolamide (Trusopt).

Implementation Plan: The P&T Committee recommended (14 for, 0 opposed, 1 abstained, 2 absent) 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.

MTFs will not be allowed to have Travatan, Travatan Z, Istalol, Betimol or Azopt on their local formularies. MTFs will be able to fill non-formulary requests for these agents only if both of the following conditions are met: 1) the prescription must be written by a MTF provider, and 2) medical necessity is established. MTFs may (but are not required) to fill a prescription for non-formulary glaucoma agents written by a non-MTF provider to whom the patient was referred, as long as medical necessity was established.

COL Lounsbery will now present the DoD P&T Committee's perspective on the UF recommendation for the Glaucoma Agent class.

(COL Lounsbery): ... that concludes the Glaucoma Agent therapeutic class presentation, the PEC staff and I will now gladly answer any questions you may have.

(Maj Tiller) Shana will now move on to the MAOI Antidepressant drug class clinical effectiveness review.

MAOI ANTIDEPRESSANTS CLINICAL EFFECTIVENESS

(Shana) Members in the class: The clinical effectiveness review for the monoamine oxidase inhibitor, or MAOI, Antidepressants was completed by Harsha Mistry, PharmD, a PEC clinical pharmacist. Please turn to Table 1 on page 4 of your handout for a list of these medications. The drugs in this class include three oral MAOI antidepressants—isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate, which is the only one that has generics)—and one transdermal patch, selegiline (Emsam). The oral formulation of selegiline (Eldepryl) is not included in this class because it is indicated for Parkinson's disease, not for depression. The three oral MAOI antidepressants were first marketed in the early 1960s, while the Emsam patch was launched in 2006.

Relevance to MHS and Utilization: I would now like to refer you to Figure 8 on page 9 of your handout, which shows the utilization of the MAOI Antidepressants. Overall, the utilization of this drug class is quite small; however, increasing utilization of the Emsam patch and the desire to finish reviewing the antidepressant medications prompted the UF review. For the oral MAOI antidepressants, Nardil and Parnate have the highest utilization: about 45 to 60 prescriptions per month in the MHS. Since its introduction to the market in April 2006, the Emsam patch has averaged about 80 to 100 prescriptions per month.

The MAOI antidepressants accounted for approximately $283,000 dollars spent in FY 06, which amounts to less than 1% of total MHS expenditures for all antidepressants. Expenditures for the Antidepressant I class reviewed in November 2005, which included the selective serotonin reuptake inhibitors (SSRIs) and other commonly used antidepressants, accounted for $290 million in expenditures in FY05.

Conclusion: In general, the P&T Committee concluded that:

- The oral MAOI antidepressants Marplan, Nardil, and Parnate have been marketed for several decades, but have been largely replaced by newer antidepressants (including the SSRIs), which have more favorable adverse event profiles.
- The Emsam patch is the newest MAOI antidepressant marketed. This non-oral formulation may reduce the risk of a food-drug interaction seen with oral MAOI agents. Patients consuming a diet high in a substance called tyramine (which is found in smoked meats and aged cheese) who take MAOIs are at risk of developing increased blood pressure, including hypertensive crisis. Since the patch bypasses the gastrointestinal tract, theoretically, the risk of hypertensive crisis should be lower with the patch than with oral MAOIs.

With regards to efficacy:

- There do not appear to be major differences in efficacy between the three oral MAOI antidepressants when used for depression, based on the results of one meta-analysis showing response rates ranging between 53% to 61%, and one inpatient clinical trial.

- Response rates ranging from 27% to 30% were reported with the Emsam patch in three placebo-controlled trials. There are no clinical trials directly comparing the oral MAOI antidepressants with the Emsam patch and no data to suggest that treatment with the Emsam patch would result in improved response rates compared to the oral MAOI antidepressants.

With regards to safety:

- Only the lowest dose of the Emsam patch (6 mg/24 hr) is labeled for use without dietary tyramine restrictions. Like oral MAOI antidepressants, the 9 mg/24 hour and 12 mg/24 hour dosages of the Emsam patch continue to require dietary restrictions. The higher doses are likely to be required to treat depression.
- The MAOI antidepressants have a well-established safety profile, in the sense that most clinicians using these medications are likely to be familiar with the extensive list of possible drug-drug and drug-food interactions. Drug interaction concerns with the oral MAOI antidepressants also apply to the Emsam patch. Local application site reactions are common with the Emsam patch.

With regards to other factors:

- Off-label usage of the Emsam patch may be seen in patients with Parkinson's disease, despite a lack of evidence with the patch formulation in this condition, since oral selegiline (Eldepryl) is approved for treating Parkinson's disease.
- The primary advantage of the Emsam patch is for patients unable to swallow oral medications.
- There is insufficient evidence to support a therapeutic advantage of the Emsam patch over the oral MAOI antidepressants.

Overall Relative Clinical Effectiveness Conclusion: Based on clinical issues alone, there are no reasons to designate any of the MAOI antidepressants—Marplan, Nardil, Parnate or the Emsam patch—as non-formulary under the Uniform Formulary.

(Shana): This concludes the MAOI Antidepressants relative clinical effectiveness section. Maj Tiller will now present the cost effectiveness section for the MOAI antidepressants.

MAOI ANTIDEPRESSANTS COST-EFFECTIVENESS

(Maj Tiller): The cost effectiveness review was conducted by Eugene Moore, PEC clinical pharmacist. Given the overall clinical conclusion that the agents within the MAOI class have similar relative clinical effectiveness, a cost-minimization analysis (CMA) was employed to assess the relative cost-effectiveness of the agents within this therapeutic class. The agents were evaluated on their weighted average cost per day of therapy across all three points of service.

Results of the cost minimization analysis for the MAOI class showed that:

1) Among the oral agents, Nardil was the most cost-effective agent, followed closely by Parnate and Marplan.
2) The Emsam patch was the least cost-effective MAOI for the treatment of depression. The weighted average cost per day of treatment with the Emsam patch was 4-fold higher than the most costly oral MAOI, Marplan.

COMMITTEE ACTION: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the MAOI antidepressants, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (14 for, 0 opposed, 1 abstained, 2 absent) to recommend that phenelzine (Nardil), tranylcypromine (Parnate, generics) and isocarboxazid (Marplan) be maintained as formulary on the UF, and that transdermal selegiline (Emsam) be classified as non-formulary under the UF.

NF Justification:

For the MAOI Antidepressants, the Emsam patch was chosen as non-formulary under the Uniform Formulary. The Committee's recommendation was based on the following:

1) Transdermal selegiline (Emsam) is not cost-effective relative to the other agents in the class in the treatment of depression, and provides no clinically meaningful therapeutic advantage to justify the increased cost. There are no trials comparing the Emsam patch with any other antidepressant.

2) The Emsam patch was formulated to help ease dietary restrictions required with the oral MAOIs. However, dietary tyramine restrictions are still required with the two highest doses of the patch, the 9 mg/24 hour and 12 mg/24 hour, which are likely to be required to treat depression.

Implementation Plan: Because of the small number of unique utilizers affected (approximately 135 patients per quarter at all three points of service), the P&T Committee recommended an effective date of the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

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

COL Lounsbery will now present the DoD P&T Committee's perspective on the UF recommendation for the MAOI Antidepressant class.

(COL Lounsbery): ... That concludes the MAOI Antidepressant therapeutic class presentation, the PEC staff and I will now gladly answer any questions you may have.