Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS
December 2006

The Uniform Formulary Beneficiary Advisory Panel commented on the recommendations from the DOD Pharmacy & Therapeutics Committee November 2006 meeting.

- For all therapeutic classes, new drugs, and prior authorizations, the Beneficiary Advisory Panel overwhelming supported the recommendations of the Pharmacy & Therapeutics Committee. The Panel commented that much more needs to be done to inform beneficiaries of formulary changes prior to the implementation date.

Director, TMA:

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

William Winkenwerder, Jr., M.D.
Date: 17 January 2007

Uniform Formulary Beneficiary Advisory Panel

Meeting Summary
December 20, 2006
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.
- Lisa Le Gette, Express-Scripts, Inc.
- Jeffrey Lenow, Medical Professional
- Charles Partridge, National Military and Veterans Alliance
- 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 on November 14 and 15, 2006 in San Antonio, TX.

Agenda

The agenda for the December meeting of the Panel is:

- Opening remarks and public comments
- Consideration of Attention-Deficit/Hyperactivity Disorder and Narcolepsy drug class recommendations
- Consideration of Older Sedative Hypnotics (SED-2s) drug class recommendations
- Consideration of Prior Authorization requirement recommendations for Modafinil (Provigil) and fentanyl patches
- Consideration of recommendation s for new drugs in previously reviewed classes
- Review of previous formulary decisions
- 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 introduced the members of the Beneficiary Advisory Panel present, noting that there are no new members for this meeting. He then briefly reviewed housekeeping considerations.

Private Citizen Comments

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

Tribute to Sydney Hickey

MAJ Watson announced the passing of Sydney Hickey, the Panel's first Chair, on December 1, 2006. He and all of the other people who are working on the Uniform Formulary recognize the contributions she made to this committee and to DOD Health Care overall. She was a true champion for DOD beneficiaries who had a passion for what she did.

Opening Remarks by the Chair

The Panel Chairman, Mr. John Class, also stated that the Panel would miss Ms. Hickey and seconded MAJ Travis' remarks.

Presentation on Attention-Deficit / Hyperactivity Disorder and Narcolepsy Agents

Maj Wade Tiller, Deputy Director of the Pharmacoeconomic Center (PEC) opened the drug class review presentation.

[Insert Script pages 1 through fourth paragraph on page 12]

Physician Perspective on P&T Committee Recommendations

Major Roger Brockbank spoke to the P&T Committee recommendations from a physician's perspective. He noted that the P&T Committee agreed unanimously with the clinical and cost effectiveness evaluations. He said there was an initial discussion among the Committee members about the various delivery systems and the nuances of effects of the different medications. In the end, however, the Committee agreed on a few main principles. First, the stimulant medications are similar in efficacy for treatment of ADHD. Second, the response rate is very good for patients on one of these medicines. Those who may not respond to initial therapy can have their medication replaced with a second drug. This approach adequately treats approximately 90 percent of ADHD patients. Third, the Committee thought it was important to have a non-stimulant medication available for patients who can't tolerate stimulants or have unique patient preference issues. Fourth, the Committee agreed that if changes are to be made to the Uniform Formulary, they should affect the least number of patients possible. Based on these principles, the Committee recommended that a variety of shorter- and longer-acting medicines be available on the formulary, such as Concerta, Metadate CD, Ritalin LA, Adderall XR and the non-stimulant Strattera. Focalin and Focalin XR were recommended to be non-formulary because they were clinically equal to the other stimulants, were least cost-effective and were low utilization and would, therefore, impact the fewest number of patients. Because of Daytrana's significant dermatological side effects, which can lead to sensitization to the oral products and

thereby limiting treatment options, it was recommended that this medication also be named non-formulary.

Concerning Provigil and Xyrem, the P&T Committee agreed that these medications had unique indications for the treatment of narcolepsy and should remain on the Uniform Formulary. Provigil use has increased dramatically, especially in the retail sector. Due to concern about non-evidence based uses, the Committee recommended that it be available on the Uniform Formulary but also that there be a Prior Authorization requirement, which will be discussed in more detail later.

Xyrem has very low utilization and prescriptions are strictly regulated by law as well as the manufacturer, so the Committee did not see the need for any further restrictions.

Beneficiary Advisory Panel Questions and Comments on ADHD and Narcolepsy Agents

Dr, Lenow noted that the subject of AHD was of particular interest to him. He said if the data is available it would be interesting to look at the breakdown by age – under-18 and over-18. He suspects that a review of utilization over the last couple of years would show a dramatic increase in the number of adults who are getting this diagnosis. He said he has been doing a review that indicates this. When he hears that Focalin will require pre-authorization and that part of that will be the need for medical necessity, he's curious about how one will establish medical necessity that will be viable and worthy of approval, given that it basically has the same efficacy (as has already been stated). What will "medical necessity" mean in this case?

Dr. Lenow also stated his view that the problem won't be formulary management. The real economic factor at work here is appropriateness of diagnosis. He said if all ADHD diagnoses were subjected to pre-authorization, DOD would find that a significant percentage of them weren't meeting criteria. So the real saving would be in a review of the appropriateness of the diagnosis as opposed to the drug itself.

Major Brockbank acknowledged that this was part of the difficulty of evaluating the class. Even in the medical literature there isn't any consistency in defining ADHD. There have been no head to head trials comparing other stimulants. Other longer acting stimulants will be available and Focalin will also be available through medical necessity. Major Brockbank agrees that the diagnosis is on the rise.

Major Tiller clarified the recommendation by stating that Focalin and Focalin XR are not on prior authorization. They are non-formulary, which provides almost open access to the drug but at a $22 co-pay instead of a $9 co-pay. The other difference is that MTFs will require medical necessity in order to get the medicine there. Criteria for Focalin are still in process, but they will be based on the fundamental criteria in the Uniform Formulary rule.

Mr. Partridge commented that when someone is on one of these drugs and it's working, his impression is that most doctors don't want to change it. In this case, a 90-day period has been recommended. He assumes that patient would have to go off the drug and exhibit something that would indicate a medical necessity. He asked the presenters to discuss that situation – how the change will take place and how adverse effects will be prevented.

Major Brockbank answered that the utilization of Focalin XR is relatively low. The medical necessity criteria usually include an option for the physician to state that there is an unacceptable risk in changing and that the drug may be continued. The reason for making this agent non-formulary was its cost effectiveness.

Major Tiller said the medical necessity criteria for Focalin will be: (1) that use of a formulary agent is contra-indicated; (2) the patient has experienced or is likely to experience significant adverse effects from the formulary alternative; and (3) use of a formulary alternative has resulted in therapeutic failure.

Mr. Class asked what impact making a change has on the cost analysis. He said he has personal experience with having to go in three or four times for appointments after making a change only to end up back where he started. His question concerns what effect things like this have on the cost analysis that is performed. Is it an issue? The answer provided by Dr. Brockbank is that the cost of making the change is included in the cost analysis.

Panel Vote on ADHD & Narcolepsy Drug Class Formulary Recommendations

Mr. Class read the P&T Committee formulary recommendation for this drug class:

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ADHD and narcolepsy agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that mixed amphetamine salts IR (Adderall, generics), mixed amphetamine salts ER (Adderall XR) atomoxetine (Strattera), dexamphetamine IR (Dexedrine, Dextrostat, generics), methamphetamine IR (Desoxyn, generics), methylphenidate 30% IR/70% ER (Metadate CD), methylphenidate IR (Ritalin, generics), methylphenidate OROS (Concerta), methylphenidate SODAS (Ritalin LA), methylphenidate SR (Ritalin SR), modafinil (Provigil), and sodium oxybate (Xyrem) be maintained as formulary on the Uniform Formulary and that dexmethylphenidate IR (Focalin), dexmethylphenidate SODAS (Focalin XR), methylphenidate transdermal system (Daytrana) be classified as non-formulary.

The Beneficiary Advisory Panel voted 8-0 (unanimously) to concur with the recommendation.

Panel Vote on ADHD & Narcolepsy Drug Class Implementation Plan Recommendations

Mr. Class read the implementation plan recommendation:

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

There was no discussion of the recommendation. The Panel voted 8-0 (unanimously) to concur with the recommendation.

BAP Comment

Mr. Class added the comment that the Panel again recommends that affected patients be notified so that they can have the opportunity to consider changing before they go to pick up their medication.

Presentation on Older Sedative Hypnotics (SED-2s) Drug Class

CPT Napier began the presentation on the next drug class — Older Sedative Hypnotics (SED-2s) — by noting that the Committee voted not to make any of these agents on the non-formulary, so the presentation will be a condensed version of the clinical and cost-effectiveness review.

[Insert Script, p.12, paragraph 4 through page 13]

Physician Perspective on Committee Recommendations for the Older Sedative Hypnotics (SED-2s) Drug Class

Major Brockbank said the discussion of this class was fairly straightforward. The medications in this class have been around a long time, are inexpensive and have low utilization. Consequently, the Committee agreed with the PEC's recommendation to keep all of the older sedative hypnotics on the Uniform Formulary.

Beneficiary Advisory Panel Questions and Comments on Older Sedative Hypnotics (SED-2s) Drug Class Recommendations

Dr. Lenow commented that physicians at his organization haven't prescribed Dalmane or Restoril in a very long time. He said he's surprised that there wasn't a lot of feedback from doctors in the field indicating a lack of need, although he recognizes that these drugs may be used more in a military environment.

Major Brockbank agreed, saying that only three percent of MHS expenditures are in this category.

Dr. Lenow asked if the situation was that there is no point in taking them off formulary when they're not being used a lot. Major Brockbank said that was the case.

Mr. Partridge commented favorably on the recommendations.

Ms. Schlaifer asked if a review of the newer sedatives is scheduled for the near future. MAJ Tiller said they would be reviewed in the very near future — February.

Panel Vote on Older Sedative Hypnotic (SED-2s) Drug Class Formulary Recommendations

Mr. Class read the P&T Committee recommendations for this drug class:

Based on its collective professional judgment, the P&T Committee recommended that Prosom (estazolam), Dalmane (flurazepam), Doral (quazepam), Restoril (temazepam), Halcion (triazolam), Butisol (butabarbital), Seconal (secobarbital), and Notec (chloral hydrate) be maintained as formulary on the Uniform Formulary, and that none of the older sedative hypnotic agents be classified as non-formulary under the UF.

The Panel voted 8-0 (unanimously) to concur with the recommendation.

As no agents were recommended for non-formulary classification, an implementation plan is not needed for this drug class.

There were no formal Panel comments on this drug class recommendation.

MAJ Watson noted that the PEC had used an abbreviated presentation format for this drug class based on the Panel's earlier request for a more expeditious process involving less clinical detail when there are no non-formulary recommendations. He asked then Panel to provide him with feedback on the level of information included in the presentation.

Ms. Buchta said that she is comfortable with the level of detail as long as the supporting information is included in the handout. Mr. Class agreed.

Presentation on Prior Authorization for Modafinil (Provigil)

CPT Napier next presented the P&T Committee recommendations regarding Prior Authorization (PA) for Modafinil (Provigil).

[Insert Script, p. 14 through paragraph 3, page 15].

Physician Comments on Provigil Prior Authorization

Major Brockbank, providing the physician's perspective, said the P&T Committee had done an outstanding job of researching the medical literature to determine the established uses of Provigil beyond FDA indications. The P&T Committee agreed that based on the increased utilization of this medication and the important point that approximately 60 percent of the prescriptions are for non-evidence-based uses, it is necessary to implement a Prior Authorization. It is important not only to ensure the appropriate use of the medication but also to protect DOD beneficiaries.

Beneficiary Advisory Panel Questions and Comments on Modafinil (Provigil) Prior Authorization Recommendations

Ms. LeGette asked how many people are expected to be affected by the Prior Authorization requirement. She noted the handout — figure 3 — suggests about 5,700 patients. Major Brockbank confirmed the figure.

Ms. Buchta commented that the off-label use for appetite suppression is excluded by policy in the occlusion chapter that says only approved weight control procedures are to be used.

Dr. Crum noted that it sounds as though the analysis has already identified the 56 percent of patients on approvable indications. He asked if it would be possible to not make them go through Prior Authorization.

CPT Napier said that it will be necessary to identify the patients as individuals one time, after which they will be covered by their Prior Authorization.

Ms. Buchta asked about the procedure that was used to get the data for the Committee. CPT Napier said they went through the claims database that contains all the clinical contact data for the entire MHS, looked at a 9-month period and specifically identified new users of the drug. They then looked at the diagnoses that these new users had to find appropriate diagnoses associated with the prescription.

Replying to a follow-on question, CPT Napier said it was a representative sample for a 9-month period. It might be possible to help the people in that cohort, but all the rest of the users — a large number — wouldn't be affected by that.

Ms. Buchta also asked whether the review had looked only at the primary diagnosis. She noted that there may be secondary diagnoses, perhaps not written down, that would allow the Prior Authorization. The answer was that all diagnoses were looked at.

Mr. Class asked about progress toward automating the Prior Authorization process. MAJ Tiller said that an automated process will be used for some agents in the next class, but for Provigil the process wouldn't apply because the system doesn't really know who is using what agents for what diagnoses. But they could explore going back through the claims data bases and doing another analysis to identify current users of Provigil and look for codes that would validate appropriate use. But the automated system doesn't lend itself to this class because it's based on diagnosis rather than medication history.

Ms. Schlaifer asked if the 90 days would be enough time to go back and look. The answer was that it would.

Panel Vote on Prior Authorization Requirement Recommendations for Modafinil (Provigil)

Mr. Class read the P&T Committee recommendation:

The Committee recommended that a Prior Authorization be required for modafinil. The Committee recommended that the PA should have an effective date of the first Wednesday

following a 90-day implementation period, consistent with the recommended implementation period for non-formulary medications in the ADHD and narcolepsy agents class. The implementation period will begin immediately following the approval by the Director, TMA.

The Panel voted 7-0 (unanimously) to concur with the recommendation.

Panel Vote on Prior Authorization Criteria Recommendations for Modafinil (Provigil)

Mr. Class read the recommended criteria:

The P&T Committee noted that the PA is not intended to apply to modafinil (Provigil) use in active duty operational/readiness situations based on established protocols; MTFs should make necessary allowances for such use. PA approval would be good for one year. The P&T Committee identified five off-label indications, in addition to the three FDA-approved indications, as supportable based on published clinical evidence or recommendations from nationally recognized expert organizations, based on guidelines from the TRICARE Policy Manual 6010.54 (August 2002) Chapter 1 section 2.1 regarding coverage of unproven drugs, devices, medical treatments and procedures

1) Narcolepsy
2) OSAHS, only after adequate titration of CPAP treatment
3) SWSD, only in patients who work night shifts
4) MS, only after secondary causes of fatigue have been addressed
5) Myotonic dystrophy
6) Depression, only after primary therapy has failed and if the use of other stimulant augmentation is contraindicated
7) Idiopathic hypersomnia diagnosed by a sleep specialist
8) Cocaine dependence when approved by a DoD substance abuse program.

The Panel voted 8-0 (unanimously) to concur with the recommendation.

Presentation on Prior Authorization (PA) Requirement for Fentanyl Patches (Duragesic, Generics)

MAJ Tiller next presented the P&T Committee recommendation regarding Prior Authorization for fentanyl patches.

[Insert script, p.15 paragraph 4 through page 16]

Physician Comments on Prior Authorization for Fentanyl Patches

Major Brockbank said the unanimous Committee action was based on the specific prescription guidelines as well as the safety issues, adverse events and fatalities associated with the appropriate use of this medicine. The Committee also discussed and appreciated the unique automation involvement for Prior Authorization to minimize the impact and "hassle factor" on both patients and providers.

Beneficiary Advisory Panel Questions and Comments on Prior Authorization Recommendations for Fentanyl Patches

Mr. Partridge asked how many people are on this medication now. MAJ Tiller replied that he would have to look into that and get the figure.

Ms. Schlaifer asked if it would be safe to assume that anyone now on this medication would be opioid tolerant so that anyone who is already on it could stay on it. Major Brockbank said that is correct.

Ms. Buchta asked if PEC knows how many patients were inappropriately prescribed fentanyl — whether there is evidence to suggest that is was not being prescribed according to the guidelines. MAJ Tiller said PEC did a retrospective database analysis sometime back looking at this issue by applying the black box warning on the patches to the extent possible. PEC started with the definition of "opioid tolerant." When the definition was applied, nearly 52 percent of the prescriptions dispensed did not meet the definition. When a sensitivity analysis was applied to the definition to weaken it by adding additional substances (such as hydrocodone), more patients met the definition of "opioid tolerant." When PEC develops the criteria for the automated Prior Authorization process, the definition applied will determine how many people will be affected by the PA. He said fentanyl patches are widely used so a significant number of people will be affected by the PA.

Ms. Buchta asked what "look back" period was used in testing the definition. MAJ Tiller answered that PEC went back for a one-year period.

Ms. Schlaifer asked if it is the case that people are being put on the patches without ever first experiencing an even somewhat significant dose. MAJ Tiller replied that the retrospective data review provided evidence to suggest that people are being prescribed fentanyl patches post-op.

CPT Napier added that he had experience with the medical centers in San Antonio that looked at direct patient records for people who were prescribed fentanyl patches. He said the review did find that patients were being given the patches as primary therapy for things like back pain and post-operative pain. However, the black box warning had just come out at the time, so its reasonable to assume that lot of physicians hadn't heard about it yet.

Ms. Buchta asked if consideration has been given to requiring PA's for other products like fentanyl that need to be controlled. MAJ Tiller said the narcotic analgesic class is currently under review and will be taken up at the next Panel meeting. At that time, PEC will do a complete review of the narcotic class, including the Actiq lollipops and the new fentanyl lozenges.

Panel Vote on Prior Authorization Recommendations for Fentanyl Patches (Duragesic, Generics)

Mr. Class read the P&T Committee recommendation:

The P&T Committee recommended that a PA be required for fentanyl patches. The Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible based on availability of the automated PA capability in PDTS. The implementation period will begin immediately following approval by the Director, TMA.

The Committee voted 8-0 (unanimously) to concur with the recommendation.

Panel Vote on Prior Authorization Criteria Recommendations for Fentanyl Patches (Duragesic, Generics)

Mr. Class next read the recommended PA criteria for this drug:

PA Criteria:

1) Automated PA Criteria:
   - Patient is likely to be opioid-tolerant based on the pattern of opioid use in the patient's profile during a defined "look back" period.

2) PA Criteria if automated criteria are not met:
   - Patient is likely to be opioid-tolerant based on prior opioid use not captured by PDTS (e.g., medications started on an inpatient basis or prescriptions filled outside the DoD pharmacy benefit) AND
   - Patient requires a fentanyl patch for treatment of persistent, moderate to severe chronic pain requiring continuous, around-the-clock administration for an extended period of time that cannot be managed by other means and NOT for management of acute pain or short periods of opioid analgesia, post-op pain (including outpatient/day surgeries), mild pain or intermittent pain.

The Panel voted 8-0 (unanimously) to concur with the recommendation.

Presentation on Drugs from Previously Reviewed Classes

MAJ Watson said the next group of presentations involve considering new drugs in therapeutic classes previously reviewed by the P&T Committee. MAJ Watson said this is an indication that the Uniform Formulary process is maturing.

Review of Contraceptive Agents (Seasonique and Loestrin 24 FE)

CPT Napier began the presentation.

[Insert script, pages 17 and 18]

Physician Comments on P&T Committee Recommendations

Major Brockbank discussed the P&T Committee's recommendations. He said that an Air Force OB-GYN had supported the recommendations at the P&T Committee meeting. There was discussion of the fact that the new oral contraceptive agents had no clinical advantage over the current formulary options. Based on that discussion and the cost-effectiveness analysis, the P&T Committee agreed that the new agents should be classified in the non-formulary category.

Panel Questions and Comments on New Oral Contraceptive Agents

Dr. Lenow asked if the Committee had any rationale — either from the manufacturers, from the literature or from studies — as to why there is an urgent need to reduce the withdrawal phase from seven days to three days. He said his first training was as an OB-GYN and he's having difficulty trying to understand the scientific rationale or therapeutic basis for this. He asked if there are any solid studies.

Major Brockbank answered that the manufacturer thinks there might be decreased migraines with estrogen withdrawal. There are no studies to support this yet, however.

Beneficiary Advisory Panel Vote on New Contraceptive Agents Formulary Recommendation

The Panel Chair, Mr. Class, read the recommendation:

The P&T Committee, based upon it collective professional judgment voted to recommend that Seasonique and Loestrin 24 Fe be classified as non-formulary.

The Panel voted 8-0 (unanimously) to concur with the recommendation.

Beneficiary Advisory Panel Vote on New Contraceptive Agents Implementation Plan

Before reading the recommendation, Mr. Class read an e-mail from an absent Panel member (Mr. Hutchings) recommending that the implementation period should be at least 90 or 120 days because he feels that a shortened timeframe as proposed would discourage current Seasonale patients from going to Seasonique just to end up with a $20 co-pay further down the road.

MAJ Tiller said the P&T Committee had raised and discussed this concern. Their view was that the shorter implementation period would mean that fewer people would be affected by the decision.

Ms. Schlaifer agreed with Committee, noting that if right now we have 100 people who will be affected by a non-formulary decision, 90 days from now there will be 400 people affected by it.

MAJ Watson noted that the implementation date for the oral contraceptives previously reviewed is January 24, 2007.

Mr. Class read the recommendation:

The P&T Committee discussed the prospect for coordinating implementation of non-formulary status for Seasonique and Loestrin 24 Fe with the already established effective date for Seasonale non-formulary status (24 Jan 07). The Committee recommended a short implementation period because it would avoid patient disruption as utilization of new products increases. If a coordinated implementation cannot be achieved due to timing constraints of the UF process, the P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

The Panel voted 8-0 (unanimously) to concur with the recommendation.

Review of New Antiemetic Agent (Cesamet)

CPT Napier next presented the results of the review of a new antiemetic agent — Cesamet.

[Insert script, page 19]

Physician Perspective on Cesamet

Major Brockbank discussed the Committee's recommendations from a physician's perspective. He said the Committee agreed that Cesamet was similar to the already-approved Marinol both clinically and as to cost and that therefore it was logical to recommend that the medicine be on the Uniform Formulary.

Panel Questions and Comments on Cesmaet Recommendation

Mr. Partridge asked if the decision was based primarily on cost and the fact that there isn't a significant cost differential. The answer was that the rationale took into account that both the clinical effectives and cost of Cesamet is similar to Marinol.

Panel Vote on New Antiemetic Agent Cesamet

Mr. Class read the P&T Committee recommendation:

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon it collective professional judgment, voted to recommend that nabilone (Cesamet) be maintained on the Uniform Formulary.

The Panel voted 8-0 (unanimously) to concur with the recommendation.

Since the agent was not recommended for non-formulary status, no implementation plan is required.

Review of New Topical Antifungal Agent, Vusion

CPT Napier began the presentation on the review of the new topical antifungal agent Vusion.

[Insert script, page 20 through third full paragraph on page 21]

Physicians Comments on Review of Vusion

Major Brockbank said the P&T Committee had heard from pediatricians during the course of its discussion of the agent. It agreed unanimously to recommend non-formulary status for Vusion based on its lack of a meaningful clinical advantage over the topical antifungals already on the UF. Additionally, Vusion was the least cost effective by a significant margin.

Panel Questions and Comments on Vusion Recommendations of the P&T Committee

Dr. Crum commented that, based on the apparent shortcomings of the drug, and that it would be used only for short-term treatment of a rather trivial illness, he believes a shorter implementation time could be used without disrupting patient care.

Panel Vote on Vusion Formulary Recommendation

Mr. Class read the P&T Committee recommendation:

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted to recommend that Vusion be classified as non-formulary.

The BAP voted 8-0 (unanimously) to concur with the P&T Committee recommendation.

Panel Vote on Vusion Implementation Plan Recommendation

Mr. Class read the P&T Committee implementation plan recommendation for Vusion:

The P&T Committee recommended an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

The BAP Panel vote was 7 concurring and 1 not concurring with the recommendation.

The non-concurring member, Dr. Crum, added the comment that there would be no adverse effect of having a shorter implementation period.

Presentation on Review of Previous Formulary Decisions

MAJ Watson introduced Mr. Dave Bretzke of the Pharmacoeconomic Center to present overview information on the status and results of previous decisions concerning the DOD Uniform Formulary. MAJ Watson said TMA plans to present this type of information to both the P&T Committee and the BAP annually.

Mr. Bretzke said today's presentation, which is much briefer than last year's, would be based on the slide handout. The first slide shows timelines of the implemented classes.

[Insert slide 1]

The dates along the bottom indicate when the P&T Committee performed their evaluation of the drug classes indicated by the corresponding dots. The classes indicated in light blue color (BCs, H2s, TZDs, LIP1s, SED2s and ADHDs) have yet to be implemented and so were not included in the scope of this evaluation.

The slide shows mainly that TMA has been busy evaluating lots of classes and there is a lot of overlap between new classes being addressed and old classes being implemented. The pace of the work has been rather high.

Slide number two, titled "Non-Formulary 3rd Tier Prescriptions for MTFs" displays changes in the use of various drug classes at Military Treatment Facilities (MTFs) after formulary changes were implemented.

[Insert slide 2]

This data is normalized on a 30-day equivalent prescription, which is a normalizing technique PEC uses so it can compare a standard prescription across all three points of service. The data do not indicate actual prescription count, but, rather, a normalized 30-day supply. The lines show dramatic decreases for the relevant drug classes and their implementation periods. He said it is worth noting that now, several months after implementing all these classes, there is very little use of third tier drugs in all classes at MTFs. The calcium channel blocker (CCB) line (at the top) shows a particularly dramatic decrease. The overall pattern is that of a consistent decrease.

The next slide shows similar data for the retail point of service (TRRx) for all of the implemented classes to date, including classes that have been implemented within a 30-day or 60-day time period.

[Insert slide 3]

What was somewhat surprising was that on all drug classes across-the-board in the retail network, where TMA has little ability to manage utilization, all classes except GABAs have had a flattening of third tier agents. The most obvious decrease has been in the proton pump inhibitor (PPI) class (the third line from the top). At the implementation date of July 2005 there was a significant decrease.

Ms. Schlaifer asked if there is any way to show how many people were using the retail point of service before the formulary change and how many people from the MTF switched to retail. Mr. Bretzke said he doesn't think there is any evidence of MTF people moving to the retail network. If there were, the number would be going up, not down.

Slide number four is titled "Non-Formulary 3rd Tier 30d Rxs, Mail Order." It shows corresponding data for the TRICARE Mail Order Pharmacy (TMOP).

[Insert slide 4]

For this point of service, there has been an increase in nearly all classes of agents. However, the increase has not been of the same extent as the decreases in either the combined or the MTFs alone. This means there is no direct evidence that all of the prescriptions are being shifted wholesale from one point of service to another. But there is some shifting going on. PEC is currently analyzing whether the increase is a result of retail shifting to mail order or MTFs shifting to mail order. The analysis is being conducted in two different places — the PEC and by a post-graduate program at a university. However, it is clear that the Mail Order Pharmacy is becoming a "catch all" for third tier use. From an economic point of view, it makes sense for

patients to come in to mail order from retail — $22 instead of $66 for a 90 day supply. Even though DOD in general doesn't like to use third tier drugs, but the TMOP does have Federal pricing, which makes them significantly less expensive than retail. In many cases the third tier agents are less expensive from Mail Order than second tier agents at retail. The PEC has been told that MTFs are advising patients who do not want to switch to get their third tier drug from the Mail Order Pharmacy. And the numbers indicate that some of that is happening. At the same time it should be noted that the vast majority of MTF patients are switching to an alternative drug rather than switching points of service.

Mr. Class asked if there is any comparison of how this data looks in industry, i.e. is the use of the same drugs also going down or up in industry. Mr. Bretzke said the PEC doesn't have commercial information. And the industry is made up of many little managed organizations with their own formulary policies, so there is no way to get a direct comparison. Mr. Bretzke added that PEC's regular numbers also do not reflect commercial practices because of the general increase in the use of the retail network over the last several years, particularly with the introduction of the TRICARE For Life benefit. DOD's trends of drug use have been going up at a much higher rate than traditional commercial plans due to the expansion of the benefit. But the decrease in the use of third tier agents compares extremely well to commercial plans. Studies indicate a $1 per percent decrease in third tier use. In the DOD system there is a $13 difference between the $9 co-pay and the $22 co-pay, which would suggest a 13-15 percent decrease. DOD sees about double that amount, indicating it is performing at a much higher level, at least for now. It is also expected that increasing the spread between second tier and third tier co-pay amounts will also decrease the use of non-formulary medications. However, the mail order and retail points of service do not perform at the same level as a managed point of service like an MTF.

The next slide, titled "NF/3rd Tier 30d RXs By POS, All Implemented UF Classes" shows aggregated data for all classes and compares the three points of service.

[Insert slide 5]

This slide again shows the dramatic decrease in the number of third tier prescriptions in the MTFs compared to the decrease in the retail network and the increase in the Mail Order at a rate higher than the rate prior to the change.

The next slide shows the change data expressed as a percentage of total.

[Insert slide 6]

The graph shows that for all implemented classes there has been a 30 percent decrease in the number of third tier prescriptions (normalized by 30-day equivalent), which include drug classes that were implemented only recently and may have only 1-3 months worth of data. For classes that have been implemented for six months or more, the overall decrease rises to 40 percent. This means there is a further decrease in non-formulary agent use over time following implementation. By point of service, the percentages are: an 89 percent decrease at MTFs, a 6 percent increase in Mail Order and an 11 percent decrease in Retail. The corresponding figures for classes implemented for six months or more are: a 93 percent decrease in MTFs, a 1 percent increase in Mail Order and a 21 percent decrease in Retail.

Mr. Bretzke said one of the goals of the program, beside promoting the most cost effective medication and being more efficient is using fewer taxpayer dollars. The next slide is a graphical representation of the cost per day by Point of Service (POS).

[Insert slide 7]

The aggregated data shows there has been an overall decrease of five percent in the cost per day for all points of service combined. For classes implemented for at least 6 months, the decrease is seven percent. The largest driver is the MTF where the switching has resulted in an overall 23 percent decrease in the cost per day for all classes combined (30 percent for agents implemented for more than six months). This means that average cost of therapy per day in DOD MTFs has decreased by a third, which is a great show of efficiency.

Mr. Partridge asked if the figures show a real dollar decrease or if they have been adjusted for inflation and for the increased cost of drugs. Mr. Bretzke said the figures have been normalized for the cost per day of therapy, which doesn't indicate the changes in the number of patients that are new or have been added to therapy, so the average cost decreases even though the total amount spent might have increased due to the number of patients being treated.

The other points of service have shown only marginal decreases in the cost per day of treatment. Until the classes that were implemented after the August meeting (statins and TZDs) there has been no ability to garner any price concessions in the retail network. So the decreases so far have been modest (two percent for retail (four percent for classes implemented more than six months) and five percent for Mail Order (also five percent for classes implemented more than six months). These decreases are due both the increased co-pay (which means DOD pays less) and the switching between points of service.

The final slide summarizes the key results to date.

[Insert slide 8]

It shows that:

- MTFs are exceeding the original expectations that 80 percent of patients would switch off non-formulary drugs with about 90 percent of patients switching.
- In the Retail Pharmacy, there has been zero or negative growth in third tier agents in all but one class.
- The Mail Order seems to be the catch-all for non-formulary use in that it is increasing, unlike the other points of service. This is a good thing for DOD as a whole.
- There have been small but consistent cost-per-day decreases across MHS.
- PEC is continuing to monitor the LIP1 class closely.

Administrative Announcements

MAJ Watson, noting that previous meetings have discussed having the DOD formulary published with ePocrates or some other electronic publication medium, informed the Panel that the Program Office has issued a Request for Information (RFI) that has now been out for about a month asking industry to submit their ideas and requirements. So information is being gathered looking toward the possible development of a formal proposal for some sort of electronic formulary publication.

Mr. Class expressed appreciation for the reduction in the amount of material presented verbally for classes where there is no recommendation to move agents to non-formulary status. He also asked the Office to consider the amount of on devoted to medications that are staying in the formulary. He said the paperwork should continue provide the level of information that the Panel has been receiving but questioned whether it is necessary for the Panel to hear all of it presented as opposed to zeroing in on the information and justification behind the recommendations to move agents to non-formulary. He said it seems to him as though 70 percent of the discussion concerns matters that the Panel isn't expected to deal with. MAJ Watson asked if the comment pertains to all new classes or just classes that have previously been reviewed. Mr. Class said the comment is intended to apply in general. He said he thinks it would save a lot of time and effort that is now spent discussing agents that are to remain on formulary. But the material should still be included in the read ahead. Ms. Buchta said if the discussion is relevant to a new drug, then it should be included.

Mr. Class also asked whether the BAP could be informed of the rationale and issues behind dissenting votes on the P&T Committee, when those occur (although there were none in today's items). He said that background would add to the discussion. MAJ Watson said that bringing in the physician member to comment was intended to clarify what issues were being debated. Mr. Class said he thinks it would be helpful to know about instances in which P&T Committee members had specific disagreements.

Mr. Class identified some future topics of discussion for consideration. One concerns the handling of new medications that come to market. He wants to make sure that the process being used is the best way to handle those. Different plans handle these in different ways and he wants to make sure everybody is comfortable with the process. Ms. Schlaifer said the case of Seasonique, discussed earlier, is an example. She said she isn't familiar with the legal requirements, but would like to know if there is any way to consider new drugs coming out before they are released. MAJ Watson said there is no way to make a new drug non-formulary without going through the review process. Everything is presumed to be formulary until it has been reviewed by the Committee and been put through the process. Dr. Crum suggested that an alternative might be to require Prior Authorization for new drugs until they have been reviewed by the Committee. MAJ Watson said he would have to take that idea under consideration. Mr. Bretzke added that before a cost effectiveness review can be made, Federal pricing has to be in place. It takes at least six months for this to happen. It would be unfair to ding somebody when we know Federal pricing is coming but it has happened yet. The PEC general rule is that once a drug hits the market, if it is in a class and has Federal pricing, it's on the agenda.

Mr. Class said another matter that still requires further discussion is the issue of communication. Also, since the Panel has been in business for a year and a half, it might now be time to look at

whether this is the best way to operate the BAP. MAJ Watson agreed that he and Mr. Class should discuss the matter.

Dr. Lenow said that he has consistently had a problem with staying overnight. The hotels want to see a Federal ID in order to honor the rate quoted and have been reluctant to accept travel orders or other forms of identification. He asked if someone could look into this and come up with something to validate the status. MAJ Watson agreed to take on this item.

Mr. Class announced that the next meeting of the Beneficiary Advisory Panel will be March 22 at the same location in Washington, D.C.

MAJ Watson thanked the Panel members for their hard work and continued service.

The meeting was adjourned at 11:05.

Appendix 1

12/20/06 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.

- 5-HT3 — 5 Hydroxytryptamine3 (a drug sub-class)
- ACE — Angiotensin converting enzyme inhibitors (a drug class).
- AD1 — Antidepressant I (a drug class)
- ADHD — Attention Deficit Hyperactivity Disorder
- AF-DERMS — Topical anti-fungals (a drug class)
- ARBs — Angiotensin Recptor Blockers (a drug class)
- BAP — Uniform Formulary Beneficiary Advisory Panel (the "Panel" referred to above)
- BCF — Basic Core Formulary
- BIA — Budget Impact Analysis
- BPH — Benign Prostatic Hyperplasia
- CCB — Calcium channel blockers (a drug class)
- CEA — Cost-effectiveness analysis
- C.F.R — Code of Federal Regulations
- CMA — Cost-Minimization Analysis
- CNS — Central Nervous System
- CPAP — Continuous Positive Airway Pressure
- 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
- GABA — Gamma-aminobutyric acid
- HMO — Health Maintenance Organization
- LIP-1 — Antilipidemic (a drug class)
- MHS — Military Health System
- M/ks — Macrolide/Ketolide (a drug class)
- MS-DMD — Multiple Sclerosis Disease Modifying Drugs (a drug class)
- MTF — Military Treatment Facility
- NCSs — Nasal Corticosteroids for Allergic Rhinitis (a drug class)
- NNH — Number Needed to Harm
- NNT — Number Needed to Treat
- OABs — Overactive Bladder drug (a drug class)
- OTC — Over the counter

- PA — Prior Authorization
- P&T Committee — DOD Pharmacy and Therapeutics Committee
- PDE-5 — Phosphodiesterase Type 5 Inhibitors (a drug class)
- PDTS — Pharmacy Data Transaction Service
- PEC — DOD Pharmacoeconomic Center
- PPI — Protein pump inhibitors (a drug class)
- RCTs — Randomized Control Trials
- TMA — TRICARE Management Activity
- TMOP — TRICARE Mail Order Pharmacy
- TRRx — TRICARE Retail Pharmacy Program
- TZD — Thiazolidinedione (a drug class)
- UF — DOD Uniform Formulary
- U.S.C. — United States Code
- VA — U.S. Department of Veterans Affairs

20 December 2006 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 CPT. Joshua Napier, who is our Army physician representative, and David Bretzke, a PEC pharmacist. Our P&T Committee physician who is with us today is Maj Roger Brockbank. He will provide the physician perspective for the recommendations made by the Committee. Also joining us today is CAPT Richerson the PEC Director, 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).

CPT Napier, Dave Bretzke and I are here to present an overview of the analyses presented to the DoD P&T Committee. 32 Code of Federal Regulation (C.F.R.) establishes procedures for inclusion of pharmaceutical agents on 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 Attention Deficit Hyperactivity Disorder (or ADHD) and narcolepsy drugs, the older sedative hypnotic agents, and four new drugs in classes previously reviewed for UF status.
4) The DoD P&T Committee's recommendation as to the effective date of the agents being changed from formulary tier to the non-formulary tier of the Uniform Formulary. Based on 32 C.F.R. 199.21, such change will not be longer than 180 days from the final decision date but may be less.

We've given you a handout which includes the Uniform Formulary recommendations for all the drugs discussed today; this is found on page two. There are tables and utilization figures for all the drug classes. We'll be using trade names, so you can refer to your handout throughout the presentation.

(*MAJ Tiller*) CPT Napier will now present the Attention Deficit Hyperactivity Disorder and narcolepsy agents drug class review. The relative clinical effectiveness section will be discussed first.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND NARCOLEPSY DRUGS CLINICAL EFFECTIVENESS

(CPT Napier) **Members in the class:** The Attention Deficit Disorder, or ADHD drugs, and narcolepsy agents were reviewed for placement on the DoD Uniform Formulary. The ADHD drugs are used to treat both children and adults with impulsivity, hyperactivity and inattention difficulties, while the narcolepsy drugs are used to treat patients with excessive sleepiness that interferes with activities of daily living. The ADHD and narcolepsy agents were evaluated together in one drug class, as some of the agents have indications for both conditions. This class accounted for approximately $84.5 million dollars in Fiscal Year 2006, and is ranked number 16 in terms of total expenditures for the Military Health System, or MHS.

Please refer to Table One on Page Two of your handout. We will discuss the ADHD drugs first, and then address the narcolepsy agents. There are six parent compounds in the ADHD class. We have one product that is not a stimulant, atomoxetine, or Strattera. There are five stimulants in the class, methylphenidate, mixed amphetamine salts, dextroamphetamine, methamphetamine, and dexmethylphenidate. There are two drugs for narcolepsy, modafinil, or Provigil, and sodium oxybate, or Xyrem.

Relevance to MHS and Utilization: If you go back to the handout on page 5, Figure 2, the utilization of the ADHD drugs is shown. Concerta is the highest utilized ADHD drug in the MHS, at approximately 40,000 thirty-day equivalent prescriptions dispensed monthly. This is followed by Adderall XR, at approximately 30,000 thirty-day equivalent prescriptions dispensed monthly. The non-stimulant product Strattera is in third place at about 10,000 thirty-day equivalent prescriptions dispensed monthly, closely followed by the narcolepsy drug Provigil. Adderall, which is the immediate release form of mixed amphetamine salts, and Focalin, the immediate release form of dexmethylphenidate, are near the bottom of the graph. The narcolepsy drug Xyrem is hovering around the zero point.

Conclusion: We will give the clinical effectiveness conclusion first, and then discuss the data further. The relative clinical effectiveness conclusion for the ADHD and narcolepsy agents is as follows:

1) For ADHD, interpretation of the clinical data is difficult due to the limited number of comparator trials, varying rating scales used, small number of patients enrolled, and short study duration.
2) There is no evidence to suggest a difference in efficacy between immediate release formulations of Ritalin (methylphenidate), Dexedrine (dextroamphetamine), Focalin (dexmethylphenidate), and Adderall (mixed amphetamine salts).

3) The overall efficacy of the once daily methylphenidate formulations appears similar based on a few small studies, but differences exist in reported outcomes at specific times of the day, due to the individual release mechanisms of the products. Metadate CD and Ritalin LA are eight- to nine-hour products, while Concerta, Focalin XR and the Daytrana patch are 12-hour products.

4) Adderall XR appears to have similar efficacy to Concerta, based on one small study.

5) The efficacy of Strattera appears to be inferior to the stimulants, but it is the only non-stimulant available in the ADHD class.

6) Between 40% and 80% of patients who do not respond to one type of stimulant may respond to the other.

7) The adverse events and warnings of the stimulants are well-recognized and are similar between products.

8) The Daytrana patch can cause significant dermatological adverse events, which can lead to sensitization to oral products.

9) Strattera remains the only alternative for patients who cannot tolerate stimulants, despite its association with an increased risk of hepatotoxicity and suicidal ideation.

10) Several products can be sprinkled on food for patients with swallowing difficulties.

11) MTF providers requested availability of Concerta, an immediate release methylphenidate product (Ritalin), Adderall XR and Strattera, to cover the clinical needs of their patients.

12) The narcolepsy drug Provigil provides a unique niche in therapy as a drug to promote wakefulness.

13) The narcolepsy drug Xyrem has a high incidence of adverse events, but serves a unique niche in therapy for cataplexy. The manufacturer's restricted distribution program limits use to appropriate patients.

14) Based on clinical issues alone, there are no reasons to designate any of the ADHD drugs or narcolepsy drugs as non-formulary under the UF.

Dosing Frequency: The five stimulant drugs are available in several different formulations that allow for the dosing period to be extended from three or four times daily, to only once or twice daily. Since ADHD primarily affects school-aged children and adolescents, a product that can be given in the morning, and that does not have to be dosed at school is desirable.

Several different products have the same parent compound, but will have different release mechanisms, duration and onset of action, and different trade names. Back on Table 1 on page two of your handout, we've further divided the stimulants into once daily use products and multiple use products. There are six products that can be dosed once daily, and these include the mixed amphetamine salts extended release, under the trade name of Adderall XR;

dexmethylphenidate, which is called Focalin XR; and four different methylphenidate products, Concerta, Metadate CD, Ritalin LA and the Daytrana patch. The Daytrana patch is the only non-oral dosage formulation in the class.

The multiple daily use products include sustained release products, which can be dosed two to three times a day, or immediate release products, which require three to four times daily dosing. The multiple daily use products include methylphenidate sustained release, or Ritalin SR and methylphenidate immediate release, or Ritalin. There are also immediate release formulations of mixed amphetamine salts, Adderall and generics; dextroamphetamine, or Dexedrine and generics; and methamphetamine, or Desoxyn and generics.

Strattera is the only product that is not a stimulant. It is dosed once daily.

Efficacy: Next we will move on to efficacy. The stimulants are the mainstay of ADHD treatment. Approximately 60 to 80% of patients respond to therapy. When we evaluated the studies, it was difficult to directly compare the ADHD drugs, since many of the trials had short treatment durations, only enrolled low numbers of patients, and used several different rating scales.

Immediate Release vs. Immediate Release The state of Oregon Evidence Based Practice Center conducted a systematic review that evaluated trials comparing the immediate release formulations of the ADHD drugs. The conclusion was that there was no difference in efficacy between immediate release Dexedrine (dextroamphetamine), Ritalin (methylphenidate), Adderall (mixed amphetamine salts), and Focalin (dexmethylphenidate).

Release Mechanisms: Let's briefly discuss the release mechanisms of the once daily use products, as this will help with understanding the next section of the clinical efficacy review. For the once daily use products, some of the drug is released immediately, and the remainder of the dose is slowly released over several hours. Patients with a heavy school or college workload early in the morning may require a product where the majority of the dose is released early in the day. However, patients who have problems concentrating on homework in the afternoon and evening may require a longer acting agent.

Concerta is available in a tablet that has about 20% of the drug released immediately, with the remainder released slowly over a 12 hour period. For the other once daily methylphenidate products, Metadate CD is available in a capsule containing coated beads, where 30% of the drug is released immediately, and 70% is released over 8 to 9 hours. Ritalin LA has about 50% of the dose released immediately, with the remainder released over 8 to 9 hours. The Daytrana patch has slow, steady release of the drug over 9 hours, however the duration of action is 12 hours. The only products that are true 12 hours products for methylphenidate are Concerta, and the Daytrana patch. Dexmethylphenidate is available in a 12 hour product, Focalin XR, which also uses the same technology as the Ritalin LA.

Immediate release vs. once daily use products: Let's focus back on the clinical trial data. When the immediate release products were compared to the once daily use products, three studies were available that compared Ritalin immediate release with Concerta. In short-term studies, once daily Concerta was preferred over Ritalin immediate release. However in the longer term trial, there was no difference in efficacy reported between the two drugs.

Once daily use products vs. once daily use products: I'd like to concentrate for a few minutes on the clinical trial data with the products that can be dosed once daily compared to each other, since these are most commonly used in DoD. As we just discussed, the different release mechanisms will influence the timing of effect for the ADHD drugs. In one study that compared Metadate CD with Concerta in a classroom setting, Metadate CD was superior to Concerta in the morning, since Metadate CD has 30% of the dose released immediately, vs. only 20% with Concerta. By noon, there were no differences in the efficacy between the two drugs. In the evening Concerta was superior to Metadate CD, reflecting the long duration of action of the Concerta release mechanism. Similar results were seen in another trial when Concerta was compared with Ritalin LA, which is a 50-50 mixture of methylphenidate immediate release and extended release.

We have one trial comparing different parent compounds for the once daily products. Concerta was evaluated with Adderall XR and placebo in an assessment of driving skills and aggressive behavior in 35 adolescents. Concerta was not directly compared to Adderall XR, so it is difficult to make a definitive conclusion about differences in efficacy between the two drugs. However, Concerta compared more favorably to placebo than Adderall XR.

Focalin XR and Daytrana patch: Focalin XR and the Daytrana patch are the two remaining once daily products. There are no published trials comparing efficacy of Focalin XR and Daytrana to other once daily stimulants. Both products were found to be more efficacious than placebo. The pharmacokinetic profiles of these two drugs do reflect a 12 hour duration of action.

Non-stimulant: Now we are going to discuss the efficacy of the only non-stimulant in the ADHD class, Strattera, or atomoxetine. The Oregon review concluded that Strattera was superior to placebo, but Adderall XR and Concerta were superior to Strattera.

Non-responders: Clinically, we need to address treatment options for patients who do not respond to one drug. This is important to discuss, because data shows that among first-time treatment recipients of the stimulants, 60-70% will show a response to treatment. There is one study that compared Ritalin immediate release (methylphenidate) with Dexedrine immediate release (dextroamphetamine) in terms of treatment response. The study found that 40 to 80% of initial non-responders would respond to the second drug. With this cross-over response, approximately 90% of patients are adequately treated.

Safety: The safety profile of the ADHD drugs will be discussed next.

Black box warning: All of the stimulants (methylphenidate, dextroamphetamine, dexmethylphenidate, mixed amphetamine salts, and methamphetamine) carry a black box warning for dependence, tolerance and abuse potential. The amphetamines also carry a black

box warning for sudden cardiac death, however, most of the deaths reported to the FDA occurred in patients with pre-existing structural heart defects.

Strattera, which has a mechanism of action similar to the antidepressants, carries a blackbox warning of increased thoughts of suicide, or suicidal ideation.

Other safety issues: The stimulants have been associated with a reduction in growth velocity, however, treated patients do appear to catch up in height to non-treated peers. The most common adverse events with the stimulants are decreased appetite, delayed onset of sleep, headache and weight loss. Additionally, the five stimulants are controlled schedule II drugs, meaning they have the potential for abuse. Adderall and Adderall XR in particular have a high percentage of patients who experience irritability and insomnia.

The Daytrana patch has been associated with dermatological reactions, which can lead to an intense local reaction with redness (erythema) and skin eruptions. After a reaction to the patch, there is a concern that up to 13% of patients will also experience a similar reaction when oral methylphenidate products are administered. This could be an issue in the clinical setting in that patients will have limited treatment options available to them.

For Strattera, the major safety issues include hepatotoxocity (liver toxicity), although this is a rare occurrence. Other adverse effects with Strattera include somnolence, nausea, and vomiting, particularly if dosages are titrated up to maximum doses quickly. Decreased appetite is less of a concern with Strattera than with the stimulants. Also, Strattera is not a controlled substance, and does not have the abuse potential that the stimulants have. Patients who cannot tolerate the adverse effects of the stimulants are frequently changed to Strattera.

Both the stimulants and Strattera can cause slight elevations in blood pressure (by about 2-4 mm mercury) and heart rate (by about 3-6 beats per minute). Overall, about 1-7% of patients receiving a drug for ADHD will discontinue therapy due to adverse effects, most commonly irritability, headache, anorexia, nervousness and agitation.

Other factors:
Special Populations: We will briefly discuss some other factors with the ADHD drugs. All the drugs in the class are approved for use in children down to the age of six. Dexedrine immediate release is a dextroamphetamine product that can be used in patients as young as three years of age.

Dosage formulations: Since the ADHD drugs are frequently used in children, it's necessary to have several different dosing formulations available for patients who have difficulty swallowing tablets and capsules. The Daytrana patch is the only non-oral formulation in the class. For the once daily preparations, Metadate CD, Ritalin LA, Focalin XR, and Adderall XR are bead-filled capsules, which can be opened up and sprinkled on food. Immediate release methylphenidate is available in a tablet, chewable tablet, and oral syrup for patients.

Abuse potential: The stimulants have the potential to be misused and diverted. Two surveys of college students found that patients often increased their dose, or crushed and snorted the drugs

for euphoric effects. Adderall and Adderall XR were the most frequently abused products. The stimulants were also used for weight loss and to increase concentration for studying.

MTF provider opinion: Over 200 MTF providers responded to a survey asking for their opinions on this class. All the respondents requested availability of a once daily methylphenidate product, in particular Concerta when initiating therapy. Providers also requested availability of both Adderall XR and Strattera as alternatives for patients unable to tolerate or not responding to Concerta. An immediate release methylphenidate product (Ritalin) was also requested. MTF providers were not familiar with and had not prescribed the Daytrana patch, Focalin, Focalin XR and immediate release methamphetamine (Desoxyn).

(CPT Napier) **Narcolepsy**

Relevance to MHS and utilization: Next we are going to focus on the two narcolepsy drugs, modafinil (Provigil) and sodium oxybate, or Xyrem (spelled with an X). Provigil has experienced a sharp increase in use in the MHS over the past year. As noted on page five of your handout, Figure 2, the number of MHS prescriptions for Provigil increased approximately 33% in the one-year period between September 2005 and August 2006. Although not shown in the figure, most of the increase in utilization has been at the retail point of service, with the other two points of service (MTF and mail order) remaining generally stable. With this increase in utilization, there has also been an increase in expenditures. During the one-year time period ending in July of 2006, MHS expenditures for Provigil accounted for approximately $24 million dollars.

Efficacy: Provigil is a stimulant medication which is approved by the FDA for three specific indications: treatment of excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder. For the treatment of narcolepsy, the FDA approved Provigil based on four randomized, double blind, placebo-controlled trials. The American Academy of Sleep Disorders considers Provigil as a standard treatment for narcolepsy.

When Provigil is used for the treatment of sleep apnea, it should only be used as an adjunct to, or along with, continuous positive airway pressure, or CPAP treatment. In sleep apnea, the patient's upper airway essentially collapses on itself, which leads to the patient unconsciously having to labor harder to get a good breath, and when that is not successful, this leads to a decrease in the level of oxygen in the blood, or apnea. As the body struggles to maintain the airway, the result is multiple (sometimes hundreds) of short awakenings throughout the night, and severely disrupted sleep. CPAP is a machine with a face mask that is worn at night which forces the airways to remain open, which decreases the number of episodes of apnea and improves sleep and daytime wakefulness. In some cases, in spite of maximal increase of CPAP air pressure, patients still remain sleepy during the day. It is in these cases that Provigil is approved for use. The FDA approved Provigil for sleep apnea based on three trials.

Provigil is also approved for treating excessive sleepiness associated with shift work sleep disorder. This condition can occur in people who work the night shift and have difficulty adapting, and maintaining wakefulness during the waking hours. The rationale for approval of Provigil was maintaining wakefulness to the extent that the individuals were at less risk for

sleepiness-related accidents, or impaired performance and functioning. Two clinical trials were used to gain FDA approval for this indication.

In addition to the FDA approved indications, there are several off-label uses for Provigil. These off-label uses can be divided into uses supported by the literature, and those not supported by the literature. We will discuss this issue in more detail in the section on the Provigil Prior Authorization.

Safety: In regard to safety and tolerability, the most commonly reported adverse events are headache, nausea, nervousness, insomnia and anxiety. In the clinical trials used to gain FDA approval, 8 % of Provigil recipients withdrew due to an adverse experience, compared to 3% of placebo patients.

Efficacy and safety of Provigil has not been established in adults over the age of 65 or in children under the age of 16. Unlike other stimulants, Provigil has not been associated with a clinically significant increase in heart rate or blood pressure. The drug has not shown the propensity to produce withdrawal or tolerance, and as such is listed as a schedule IV drug.

The manufacturer of Provigil was pursuing an indication for ADHD treatment in children, but the application was denied by the FDA due to safety concerns. Three children in the ADHD clinical trials and five adults in post-marketing experience developed severe rashes, including Stevens-Johnson syndrome or erythema multiforme. Because of the issues with rash, the manufacturer has abandoned further pursuit of an ADHD indication for Provigil.

Xyrem

MHS Utilization: Now let's move on to the last drug in the class, sodium oxybate or Xyrem. MHS expenditures in Fiscal Year 2006 for Xyrem were approximately $725,000 dollars. If you look back on Figure two on page five of your handout, you'll see that the utilization of Xyrem is very low. Although it is difficult to see on the graph, for the period between Sept 05 and Aug 06, there were only about 100 thirty-day equivalent prescriptions for Xyrem dispensed monthly. In that same one-year period, there were a total of 233 Xyrem unique utilizers.

FDA-Indications: Xyrem is FDA-approved for the treatment of excessive daytime sleepiness associated with narcolepsy. It is also approved for the treatment of cataplexy associated with narcolepsy. Cataplexy is a condition that approximately 2/3rds of patients with narcolepsy will suffer. It involves the sudden and uncontrollable loss of muscular strength, resulting in loss of the ability to move or remain standing or sitting. It is brought on usually by emotional stimulus such as laughter, excitement, or anxiety.

Efficacy: There have been five double-blinded, randomized, placebo controlled clinical trials performed to establish the effectiveness and safety of Xyrem. For narcolepsy, the evidence showed that when Xyrem was taken prior to sleep, it caused a significant improvement in measures of daytime sleepiness, levels of alertness, and ability to concentrate. The results for improvement of cataplexy were also significant; treatment with Xyrem resulted in a 50-90%

reduction in the number of cataplexy attacks. When the study was extended out to one year, Xyrem was still effective, as the cataplexy attacks were reduced by 80-90%.

History: Xyrem has an unusual history. It is known chemically as gamma-hydroxybutyrate which you may have heard referred to in the past as the "date rape drug". This drug was available over the counter in health food stores until about 1992 to aid in fat reduction, but became popular as a drug of abuse in the late 1980s for its sedative and hypnotic properties. After the drug became illegal, sale on the streets from underground make-shift laboratories became common. Due to the therapeutic benefit of Xyrem for the treatment of narcolepsy, particularly for those who suffer cataplexy, the US Congress modified the "Date Rape Prohibition Act" of 2002 allowing gamma-hydroxybutyrate to be renamed as "Sodium Oxybate" and sold legally for therapeutic purposes with a prescription.

As part of this action, a restricted distribution program was designed by the manufacturer, which includes a mandatory registration of both the physician and the patient, as well as mandatory educational materials for both, controlled distribution exclusively through a single centralized pharmacy, and a tracked method of shipping. In the DoD, we are not exempt from these restrictions, and all MHS prescriptions are processed through this same system.

Safety and Tolerability: In regard to safety, there is a "black box warning" on the FDA product label warning that the medication is a CNS depressant with abuse potential, and that it should not be used with alcohol or other CNS depressants, such as narcotic drugs. In the clinical trials performed to gain FDA approval, 10% of participants withdrew due to an adverse event, compared to 1% with placebo. The most common adverse events were headache, nausea, and dizziness. Safety, effectiveness, and tolerability have not been established in patients over the age of 65 or under the age of 16.

There were two deaths that occurred during the trials due to drug overdoses, but they occurred in the setting of intentional multiple drug ingestions. Illicit gamma hydroxybutyrate use has resulted in several deaths, but these were also cases of intentional abuse.

Other Factors: For clinical coverage, the P&T Committee determined that, given its important role in the small number of patients who have narcolepsy, particularly those with cataplexy, that Xyrem has a unique therapeutic niche. Xyrem would likely only be prescribed by specialists who treat narcoleptic patients. Although serious safety concerns exist, mainly in the form of abuse and diversion potential, the drug is carefully regulated by law through the restricted distribution program, and there would be no benefit from further limitations placed on it by the DoD.

Overall Relative Clinical Effectiveness Conclusion: Now, for our overall relative clinical effectiveness conclusion, the committee concluded the following: There is little difference in efficacy between the immediate release stimulant products for ADHD. Differences in efficacy between the once daily methylphenidate products Concerta, Metadate CD, Ritalin LA, and the Daytrana patch are determined by their delivery mechanism. Patients who do not respond to one stimulant product have a high likelihood of responding to another stimulant. Strattera was less efficacious than the once daily stimulant products. The adverse events and warnings of the drugs

in this class are well recognized and similar between the stimulants. The Daytrana patch can cause significant skin irritation problems which can lead to sensitization. This sensitization can preclude the use of oral methylphenidate products. Despite the increased risk of liver injury and thoughts of suicide, Strattera remains the only alternative for patients who cannot tolerate stimulants. There are several dosage forms of stimulants available for patients who cannot swallow tablets or capsules. Providers identified Concerta, Adderall XR, Strattera, and an immediate release form of methylphenidate, as products needed to provide the best clinical coverage for ADHD patients. For the narcolepsy drugs, both Provigil and Xyrem provide unique niches in therapy as treatment options.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstention, and 1 absent) to accept the ADHD and narcolepsy agents relative clinical-effectiveness analysis as presented by the PEC.

This concludes the ADHD and narcolepsy agents clinical effectiveness discussion. Maj Tiller will discuss the cost effectiveness next.

(MAJ Tiller) ATTENTION DEFICIT HYPERACTIVITY DISORDER AND NARCOLEPSY DRUGS COST EFFECTIVENESS

(MAJ Tiller) The P&T Committee evaluated the relative cost-effectiveness of the ADHD and narcolepsy agents in relation to efficacy, safety, tolerability, and clinical outcomes of the other agents in the class.

The cost-effectiveness review evaluated the ADHD and narcolepsy agents by subclass. The subclasses were defined based on each drug's indication for treatment (ADHD or narcolepsy). The ADHD drugs were then furthered classified by their duration of action resulting in three subclasses, a once-daily use subclass for ADHD, a multiple daily use subclass for ADHD, and a subclass of drug products indicated for the treatment of narcolepsy. A cost-effectiveness analysis was conducted for each category.

1) For the once-daily use subclass, a cost-utility analysis compared the costs per quality-adjusted life year for each drug product. The results showed that Concerta was the most cost-effective option in this group. Adderall XR and Metadate CD also performed well, with similar cost-effectiveness ratios. Strattera was cost-effective under a scenario assuming greater patient preference for a non-stimulant drug product. Focalin XR and Daytrana were the least cost-effective drug products in this subclass.
2) The multiple daily use subclass was evaluated with a cost-minimization analysis that compared the weighted average cost per day of treatment across all three points of service for each drug. The results revealed that most products within this subclass were cost-effective, with Ritalin immediate release being the most cost-effective. Focalin was less cost-effective than other agents in this subclass. Furthermore, the absence of a compelling clinical rationale for inclusion on the UF suggested that Focalin should be evaluated for non-formulary status.

3) Drug products in the narcolepsy class also were evaluated using a cost-minimization analysis. The results showed that Ritalin immediate release was the most cost-effective agent in the treatment of narcolepsy, followed closely by Dexedrine and Adderall. Xyrem and Provigil, although more costly per day of treatment, possessed unique clinical advantages justifying their inclusion on the Uniform Formulary. Provigil possessed a unique niche in wakefulness promotion for a variety of other disorders (which will be described later in the Provigil Prior Authorization section), and Xyrem had proven efficacy for narcolepsy complicated by cataplexy.

Now, let's go on to discuss the budget impact model. This analysis considered various formulary scenarios and was designed to estimate the influence of other factors associated with a UF decision (i.e., market share migration, switch costs, non-formulary cost shares). The goal of the budget impact analysis was to aid the Committee in determining which group of ADHD/narcolepsy drugs best met the majority of the clinical needs of the DoD population at the lowest expected cost to the MHS.

Conclusion: The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstention, and 1 absent) to accept the ADHD and narcolepsy drugs relative cost-effectiveness analysis as presented by the PEC. The P&T Committee concluded that the Uniform Formulary scenario that included all of the ADHD and narcolepsy drugs with the exception of the Daytrana patch, Focalin (dexmethylphenidate immediate release) and Focalin XR (dexmethylphenidate extended release) on the UF best met the majority of the clinical needs of the DoD population, and was the most cost-effective UF scenario.

Committee Action: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations of the ADHD and narcolepsy agents, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstention, and 2 absent) to recommend that Strattera (atomoxetine), Concerta (methylphenidate extended release), Metadate CD (methylphenidate extended release), Ritalin LA (methylphenidate extended release), Adderall XR (mixed amphetamine salts extended release), Ritalin SR (methylphenidate sustained release, generics), Ritalin (methylphenidate immediate release, generics), Adderall (mixed amphetamine salts immediate release, generics), Dexderine, Dextrostat (dextroamphetamine immediate release, generics), Desoxyn (methamphetamine immediate release, generics), Provigil (modafinil) and Xyrem (sodium oxybate) be maintained as formulary on the UF, and that Daytrana patch (methylphenidate transdermal system), Focalin (dexmethylphenidate immediate release), and Focalin XR (dexmethylphenidate extended release) be classified as non-formulary under the UF. Immediately following this recommendation, a vote was taken to recommend Prior Authorization for Provigil, which will be discussed later.

Implementation Plan: The P&T Committee recommended an effective date no later than the first Wednesday following a 90-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

MTFs will not be allowed to have the Daytrana patch (methylphenidate transdermal system), Focalin (dexmethylphenidate immediate release), or Focalin XR (dexmethylphenidate extended release) 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 ADHD and narcolepsy agents written by a non-MTF provider to whom the patient was referred, as long as medical necessity was established.

Committee Action: The P&T Committee recommended (15 for, 0 opposed, 0 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 the approval by the Director, TMA.

Now, for the P&T Committee physician member comments on the ADHD and narcolepsy agents, Major Brockbank will give his perspective on the recommendation.

(Major Brockbank) (Comments). This concludes the ADHD and narcolepsy drugs section. MAJ Tiller will now present the clinical and cost effectiveness review for the older sedative hypnotic agents.

OLDER SEDATIVE HYPNOTIC DRUGS CLINICAL EFFECTIVENESS

***(MAJ Tiller)*:** I'll now present the data for our second drug class, the older sedative hypnotics. Please turn to Page 2, Table One of your handout. The class is comprised of five hypnotic benzodiazepines, Prosom (estazolam,), Dalmane (flurazepam), Doral (quazepam), Restoril (temazepam,) and Halcion (triazolam); two barbiturate hypnotics, Butisol (butabarbital), and Seconal (secobarbital); the last member in the class is Noctec (chloral hydrate). These drugs have all been on the market for several years, even decades.

MHS Utilization: For utilization, please refer to your handout on page five, Figure 1. Restoril is the highest utilized drug in the class, at over 16,000 prescriptions dispensed monthly in the MHS. The older sedative hypnotic drug class accounted for approximately $2.5 million in MHS expenditures for the period from Aug 05 to Jul 06, and ranks #165 in terms of total expenditures.

Relative Clinical Effectiveness Conclusion: For the relative clinical effectiveness conclusion, the Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) The five hypnotic benzodiazepines, Prosom, Dalmane, Doral, Restoril, and Halcion are widely considered interchangeable for the treatment of short-term insomnia when used in equipotent doses, despite differences in onset and duration of action.
2) Restoril is the most desirable benzodiazepine in the older sedative hypnotic drug class, based on clinical factors, including duration of action, tolerance to therapeutic effects, and adverse effect profile.
3) The hypnotic barbiturates, Seconal and Butisol, have fallen out of favor compared to newer therapies, primarily due to safety concerns, and are infrequently utilized at any MHS point of service.
4) Noctec appears to have a unique niche in the setting of outpatient pediatric sedation.

5) There are no clinical reasons to justify designating any of the older sedative hypnotics as non-formulary under the UF.

OLDER SEDATIVE HYPNOTIC DRUGS COST EFFECTIVENESS

(MAJ Tiller) **Relative Cost Effectiveness Conclusion**: In regards to the relative cost effectiveness conclusion, based on the results of the cost minimization analysis (CMA) and other clinical and cost considerations, the P&T Committee voted (15 for, 0 opposed, 0 abstained, 2 absent) that:

1) Seconal, Noctec, Dalmane, Restoril 15 and 30 mg, Prosom, and Halcion have similar relative cost-effectiveness.
2) Butisol, Doral, and Restoril 7.5 and 22.5 mg are more costly relative to the other agents in the class, but placing these agents in the non-formulary tier of the UF would achieve little savings due to current and projected low utilization.

Committee Action: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for the older sedative hypnotics, and other relevant factors, the P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 2 absent) to recommend that Prosom (estazolam), Dalmane (flurazepam), Doral (quazepam), Restoril (temazepam), Halcion (triazolam), Butisol (butabarbital), Seconal (secobarbital), and Noctec (chloral hydrate) be maintained as formulary on the UF, and that none of the older sedative hypnotics be classified as non-formulary under the UF.

Implementation Plan: In regards to the implementation plan, since no older sedative hypnotic agents were recommended for non-formulary status under the UF, nr the establishment of an implementation period is not applicable.

Now, for the P&T Committee physician member comments on the older sedative hypnotic agents, Major Brockbank will give his perspective on the recommendation.

(Major Brockbank): (Comments). This concludes the older sedative hypnotics clinical and cost effectiveness discussion. CPT Napier will discuss the prior authorization recommendation for Provigil.

(CPT Napier) **MODAFINIL (PROVIGIL) PRIOR AUTHORIZATION**

(CPT Napier **Background:** Now let's discuss Provigil in more detail. Recall that earlier we discussed the three FDA-approved indications for Provigil, which are shown on Page Six, Table Three of your handout. These are narcolepsy, sleep apnea, and shift worker sleep disorder. There is a very low prevalence of narcolepsy and shift work sleep disorder in the general population, and specifically among DoD beneficiaries. Given the low prevalence of these two conditions, and given Provigil's role as a second-line treatment for sleep apnea, a database analysis was undertaken to evaluate exactly how the medication was being used across the MHS.

To perform this analysis, the M2 claims database was used to identify new users of Provigil over a 9 month period between 1 November 2005 and 31 July 2006. For those new users, ICD-9 diagnosis codes were collected and analyzed to determine the conditions for which Provigil was likely being prescribed. With this data it was determined that the majority of Provigil use in the MHS was for non-FDA approved uses. In fact, only 33% of prescriptions written during this time period for new users of the drug were for FDA approved uses.

Because of this fact, a thorough search of the published medical literature was performed to determine the level of scientific evidence available to support use of Provigil for conditions not approved by the FDA. The standard used to evaluate the evidence was the TRICARE policy manual 6010.54 from August 2002, specifically chapter 2 section 2.1 entitled "Unproven drugs, devices, and medical procedures". In that section, there are criteria to assist in determining whether a drug has moved from the status of unproven to the position of nationally accepted medical practice, based on a hierarchy of reliable evidence. That hierarchy includes well-controlled studies of clinically meaningful endpoints, studies published in refereed medical literature, published formal technology assessments, published reports of national professional medical associations, published national medical policy organization positions, and published reports of national expert opinion organizations.

As a result of this search, an additional five conditions were identified that had the support of sufficient scientific evidence based on good-quality published research, or published guidelines from nationally recognized expert organizations. Refer back to Table Three on Page Six of your handout for these supportable uses of Provigil. The non-FDA approved uses that were supported by sufficient medical evidence are the following: augmentation of existing pharmacologic therapy for depression, treatment of fatigue associated with multiple sclerosis, augmentation of cognitive-behavioral therapy in acute cocaine abuse rehabilitation, treatment of fatigue associated with myotonic dystrophy, and treatment of idiopathic hypersomnia.

Now look at Figure Three on Page Six. Using the TRICARE policy criteria, among the new prescriptions identified in the 9 month study period, 56% of the MHS prescriptions were for supportable uses, and 44% were for uses where treatment with Provigil has not been established by the scientific medical literature, on the grounds of efficacy, safety and tolerability.

Based on the increasing utilization and increasing expenditures, particularly in conditions where treatment with Provigil has not been established in the medical literature in regard to efficacy, safety and tolerability, the P&T Committee recommended that a PA be required for Provigil (15 for, 0 against, 0 abstained, 2 absent).

PA Criteria: For the PA criteria, the Committee agreed (15 for, 0 against, 0 abstention, 2 absent) that Prior Authorization would be met for the three FDA-approved indications (narcolepsy, obstructive sleep apnea only after adequate titration of CPAP treatment, and shift-work sleep disorder only in patients who work night shifts.). Prior Authorization would also be met in the five non-FDA approved conditions where there is sufficient published medical evidence supporting its safe and efficacious use. These conditions include augmentation of medical treatment for depression only after primary treatment has failed, and use of other stimulant medications are contraindicated; treatment of fatigue associated with multiple sclerosis after secondary causes of fatigue have been addressed; use in treatment of fatigue associated with myotonic dystrophy; treatment of idiopathic hypersomnia when diagnosed by a sleep specialist; and augmentation of cognitive-behavioral therapy for the acute rehabilitation of cocaine abuse when such treatment is conducted in an approved outpatient rehabilitation program, such as the Army Substance Abuse Program. The Committee did note that the PA would not apply to use of Provigil in Active duty operational or readiness situations based on established protocols.

Implementation: The Committee recommended (15 for, 0 against, 0 abstention, 2 absent) that the PA should have an effective date of the first Wednesday following a 90-day implementation period, consistent with the recommended implementation period for the non-formulary medications in the ADHD and narcolepsy agents class. The implementation period will begin immediately following the approval of the Director, TMA.

Dr. Brockbank will once again give his comments on the Provigil PA, as a physician member of the P&T Committee

(Major Brockbank): (Comments). This concludes the Provigil Prior Authorization discussion. MAJ Tiller will now present the fentanyl patch prior authorization.

***(MAJ Tiller)*: FENTANYL PATCH PRIOR AUTHORIZATION REQUIREMENT**

***(MAJ Tiller)*: Background**: Fentanyl is a strong opioid narcotic. It can cause respiratory depression in patients who have not built up a tolerance to this adverse effect, primarily in patients who have not been receiving opioid narcotics at large doses for a sufficient period of time. The product labeling for fentanyl patches (which include brand name Duragesic and generics) was strengthened in July 2005 following reports of serious adverse events and fatalities.

The revised labeling has very specific guidelines for the use of fentanyl patches, and should only be used in the following situations: for the management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock administration for an extended period of time; for pain that cannot be managed by other means; and ONLY for patients who are already receiving opioids, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl 25 mcg/hr. Fentanyl patches should not be used for management of acute pain or short periods of treatment; for post-operative pain, including outpatient surgeries; for mild pain; or for intermittent pain.

Many organizations, including the DoD Patient Safety Center, the FDA, and the Institute of Safe Medication Practices, have issued warnings about safe use of fentanyl patches. The Air Force has established a policy restricting use to pain specialists and other authorized providers, and requires drug utilization review by each facility. Air Force pharmacists are required to review all fentanyl patch prescriptions prior to dispensing.

Based on safety concerns, the P&T Committee recommended that a PA be required for fentanyl patches (15 for, 0 against, 0 abstained, 2 absent). The Committee's primary concern was for safety reasons to ensure that patients receiving fentanyl patches are opioid-tolerant; however the Committee did not want to affect therapy for patients who are receiving fentanyl patches on a chronic basis. Changes to the Pharmacy Data Transaction Service (PDTS) currently in progress will allow the system to "look-back" at the patient's profile to check for prior use of opioid narcotics during a defined period. This allows automation of some PA requirements and targets the PA only to those patients who are the least likely to be opioid tolerant based on previous medication use.

PA Criteria: The P&T Committee agreed on general PA criteria for fentanyl patches with a vote of 15 for, 0 against, 0 abstained, and 2 absent. These criteria are outlined on pages 22-23 of your background reading material. They are based on the safety recommendations in labeling concerning appropriate patient selection, making allowances for the possibility that patients may be opioid tolerant based on prior use not captured by PDTS - for example, medications started as an inpatient or prescriptions filled outside the DoD pharmacy benefit.

Prescriptions for patients meeting automated PA criteria would be processed through the system as normal; providers would not be required to submit any additional information. It's important to note that a patient receiving fentanyl patches on a chronic basis would meet automated PA criteria for each prescription. Patients who do not meet automated criteria would have to go through the standard PA process.

Implementation: Implementation of the fentanyl patch PA depends on modifications to PDTS which are currently in progress. Therefore, the P&T Committee recommended that the PA should have an effective date no sooner than the first Wednesday following a 30-day implementation period, but as soon thereafter as possible, based on availability of the automated PA capability in PDTS. The implementation period would begin immediately following the approval by the Director, TMA.

Major Brockbank will now comment on the Fentanyl patch prior authorization.

(Major Brockbank): (Comments). This concludes the Fentanyl patch Prior Authorization discussion. We will go back to CPT Napier for the new drugs in previously reviewed classes.

(CPT Napier) **NEW DRUGS IN CLASSES PREVIOUSLY REVIEWED FOR UNIFORM FORMULARY STATUS**

(CPT Napier) : We have a new issue to discuss, newly approved drugs in classes where we have already made a Uniform Formulary decision. We have four new drugs to discuss, which can be found on Page 3, Table 2 of your handout. There are two new oral contraceptives, a new antiemetic, and new topical antifungal product. The first section for each drug contains the recommendation made at the meeting, with the bottom section showing the previous decision and how the new drug fits in with the existing products. We'll address the two oral contraceptives first.

SEASONIQUE AND LOESTRIN 24 FE:
(CPT Napier) **Background:** The oral contraceptives were originally reviewed at the May 2006 P& T Committee meeting. We now have two new products, Seasonique and Loestrin 24 Fe.

Seasonique: Seasonique contains 30 mcg of ethinyl estradiol, and you can see from the table there are several products already on the UF with this estrogen content. Seasonique is an extended cycle product that contains 84 days of active tablets, followed by 7 days of low dose estrogen (10 mcg of ethinyl estradiol). Extended cycle products reduce the number of menstrual cycles each year from the usual 12 to only 4. Seasonique is similar to the extended cycle product Seasonale, which was designated as a non-formulary contraceptive back in May. The difference between Seasonale and Seasonique is the substitution of seven low dose estrogen, 10 mcg of ethinyl estradiol tablets in Seasonique with the seven placebo tablets in Seasonale. The rationale for using the very low dose estrogen instead of placebo is to potentially reduce adverse effects that can occur due to estrogen withdrawal, such as migraine headache or withdrawal bleeding. However, this theory has not been definitively proven in a clinical trial with Seasonique. We cannot exactly duplicate the active ingredients of Seasonique with an existing Uniform Formulary contraceptive, however, we have no clinical trials to suggest that Seasonique would differ from other oral contraceptives with 30 mcg of ethinyl estradiol, with respect to preventing pregnancy. Other conventional oral contraceptives can be used in extended cycle regimens by discarding the placebo tablets and starting a new package early.

Loestrin 24 Fe: Loestrin 24 Fe is a contraceptive containing 20 mcg of ethinyl estradiol, which is packaged as a 24 day regimen. Once again there are several products already on the UF with this estrogen content. Loestrin 24 Fe contains 24 active tablets and 3 placebo tablets, instead of the usual 21 active tablets and 7 placebo tablets found in conventional regimens. The 24 days of active tablets results in a shortened period of monthly bleeding, from 7 days down to 3, and potentially reduces the adverse events associated with estrogen withdrawal. This same goal can be accomplished by using the conventionally packaged Loestrin Fe 1/20, and simply starting a new package early. The efficacy of Loestrin 24 Fe was similar to Loestrin Fe 1/20 in one clinical trial.

Utilization: In the period between Apr 2006 and Oct 2006, there were 161 MHS prescriptions for Seasonique, and 2,227 MHS prescriptions for Loestrin 24 Fe.

Clinical effectiveness Conclusion: The Committee concluded, 15 for, 0 opposed, 0 abstained, 2 absent, that Seasonique and Loestrin 24 Fe do not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over the other oral contraceptives included on the UF.

MAJ Tiller will now discuss the cost effectiveness review for the Seasonique and Loestrin 24 Fe.

(MAJ Tiller) **Cost effectiveness:** Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that Seasonique or Loestrin 24 Fe differed with regard to efficacy, safety, tolerability, or clinical outcomes compared to the existing drugs in the contraceptive class. As a result, two cost-minimization analyses, or CMAs were performed to determine the relative cost-effectiveness of Seasonique and Loestrin 24 Fe.

The CMA for Seasonique compared the weighted average cost per cycle across all three points of service to the monophasic oral contraceptives with 30 mcg of ethinyl estradiol. The CMA for Loestrin 24 Fe compared the weighted average cost per cycle across all three points of service to the monophasic oral contraceptives with 20 mcg of ethinyl estradiol

Cost effectiveness Conclusion for Seasonique: The results of the CMA showed that Seasonique is less cost-effective on a per cycle basis than all UF oral contraceptives containing 30 mcg of ethinyl estradiol.

Cost effectiveness Conclusion for Loestrin 24 Fe: The results of the CMA showed that Loestrin 24 Fe is less cost-effective on a per cycle basis than all UF oral contraceptives containing 20 mcg of ethinyl estradiol.

Committee Action: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for Seasonique and Loestrin 24 Fe, and other relevant factors, the P&T Committee, based on its collective professional judgment, voted 15 for, 0 opposed, 0 abstained, 2 absent to recommend that Seasonique and Loestrin 24 Fe be classified as non-formulary under the UF.

Implementation Period: In regards to the implementation plan, the P&T Committee voted, 15 for, 0 opposed, 0 abstained, 2 absent, to recommend an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

Major Brockbank will discuss the P&T Committee member perspective for Seasonique and Loestrin 24 Fe.

(Major Brockbank): (Comments). We are now finished with the new oral contraceptives. CPT Napier will present the clinical effectiveness review for the new antiemetic.

ANTIEMETICS - CESAMET:

(CPT Napier) **Background:** Nabilone, or Cesamet is the new antiemetic reviewed by the Committee. If you look on Page Four of your handout, you can see that the antiemetics were reviewed at the February 2006 Committee meeting. The class was divided into the newer agents, including the 5-HT3 antagonists Zofran and Kytril, and the older antiemetics. Cesamet is a derivative of cannabis which is closely related to the existing UF product dronabinol, or Marinol. Cesamet is indicated for the treatment of chemotherapy-induced nausea and vomiting. There are no studies comparing Cesamet with Marinol, or with the 5-HT3 antagonists. There are some slight advantages of Cesamet over Marinol, primarily dosing frequency and storage requirements. However, clinical use of the older antiemetics has largely been replaced by the 5-HT3 antagonists, due to their proven efficacy and low incidence of adverse effects. There have been 4 prescriptions for Cesamet dispensed in the MHS, all in the Retail network, as of Oct 2006.

Clinical effectiveness Conclusion: The P&T Committee voted, 15 for, 0 opposed, 0 abstained, that while Cesamet offers a slight convenience of dosing frequency compared to Marinol, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over the other older antiemetics included on the UF.

Maj Tiller will give the cost effectiveness presentation for Cesamet.

(MAJ Tiller) **Cost effectiveness:** Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that nabilone (Cesamet) differed with regards to efficacy, safety, tolerability, or clinical outcomes compared to the other antiemetics. As a result, a CMA was performed to determine the relative cost-effectiveness of Cesamet within the antiemetic drug class.

The CMA compared the ranges of cost per day of treatment at all three points of service (at recommended starting doses) for Cesamet versus the other cannabinoid antiemetic dronabinol, or Marinol, which is currently included on the UF

Cost effectiveness Conclusion: The results of the CMA showed that Cesamet has a cost-effectiveness profile that is similar to dronabinol (Marinol).

Committee Action: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for Cesamet and other relevant factors, the P&T Committee, based on its collective professional judgment, voted 15 for, 0 opposed, 0 abstained, 2 absent to recommend that Cesamet be classified as formulary on the UF.

Now back to Major Brockbank once again.

(Major Brockbank): (Comments). This concludes the section on the new antiemetic. Now back to CPT Napier, for the new topical antifungal clinical effectiveness review.

TOPICAL ANTIFUNGALS - VUSION:

(CPT Napier) **Background:** Vusion is an ointment containing 0.25% miconazole, 15% zinc oxide, and 81.35% white petrolatum. Miconazole as a stand alone product is available as a prescription product and over the counter in higher concentrations of 2%. Since miconazole is available over the counter, it has a low incidence of adverse effects at the 2% concentration. If you look back on Page 4, near the bottom of the page, miconazole (Monistat Derm), clotrimazole (Lotrimin), ketoconazole (Nizoral) and nystatin (Mycostatin) were classified as Uniform Formulary when the topical antifungals were reviewed in May 2005.

Vusion has a very specific indication, treatment of diaper rash confirmed to be caused by the fungus *Candida albicans*, in pediatric patients with functioning immune systems who are four weeks of age and older. It is likely that Vusion will be used for off label uses, most likely for diaper rash not confirmed to be caused by Candida.

Vusion is the first product labeled for use in diaper rash in infants as young as four weeks of age. However, it is not clear that Vusion is the only topical antifungal that can be used for this purpose. Mycostatin can be used in infants and neonates, and the package insert states that it is well tolerated. Both Monistat and Lotrimin can be used in children as young as two years of age. Additionally, the UF topical antifungals are FDA-approved to treat a wide range of fungal infections in addition to diaper rash, including jock itch, athlete's foot, and ringworm.

There are no published trials comparing Vusion with other prescription products containing miconazole in 2% concentrations, or other topical antifungal agents. The clinical trials used to gain FDA approval only compared Vusion with a zinc oxide/petrolatum vehicle. The incidence of adverse events with Vusion was similar to that of the ointment vehicle.

Utilization: As of Oct 2006, there have been 581 prescriptions for Vusion in the MHS.

Clinical effectiveness Conclusion: The Committee concluded, 15 for, 0 opposed, 0 abstained, 2 absent, that although Vusion is labeled for a specific type of diaper rash in infants as young as four weeks of age, it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome, over the other topical antifungals included on the UF.

MAJ Tiller will discuss the cost effectiveness conclusion for Vusion.

(MAJ Tiller) **Cost effectiveness:** Based on the information reported from the relative clinical effectiveness evaluation, there was insufficient evidence to suggest that Vusion differed significantly with regard to efficacy, safety, tolerability, or clinical outcomes compared to the existing drugs in the topical antifungal class. As a result, a CMA was performed to determine the relative cost-effectiveness of Vusion within the topical antifungal drug class.

The CMA for Vusion compared the weighted cost per treated utilizer across all three points of service to other antifungal agents previously analyzed during the DoD P&T Committee's August 2005 review of topical antifungals. Comparative antifungals used specifically for diaper rash

included clotrimazole, miconazole, and nystatin. Other topical antifungals compared included cyclopirox, sertaconazole, oxiconazole, naftifine, butenafine, sulconazole, econazole, and ketoconazole.

Cost effectiveness Conclusion: The results of the CMA showed that Vusion is the least cost-effective of all comparators, when analyzed on a cost per utilizer basis.

Committee Action: Taking into consideration the conclusions from the relative clinical effectiveness and relative cost effectiveness determinations for Vusion, and other relevant factors, the P&T Committee, based on its collective professional judgment, voted 15 for, 0 opposed, 0 abstained, 2 absent to recommend that Vusion be classified as non-formulary under the UF.

Implementation Period: The P&T Committee voted, 15 for, 0 opposed, 0 abstained, 2 absent, to recommend an effective date of the first Wednesday following a 60-day implementation period. The implementation period will begin immediately following approval by the Director, TMA.

Now, for Maj Brockbank's comments.

(Major Brockbank). (Comments) This concludes the section on newly approved drugs in previously reviewed classes. Dave Bretzke will review previous formulary decisions made by the P&T Committee.

(Dave Bretzke). (Presentation). MAJ Tiller will give the concluding remarks.

MAJ Tiller