18 April 2012

Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS
5 April 2012

The Uniform Formulary Beneficiary Advisory Panel (BAP) commented on the recommendations from the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee February 2012 meeting.

UF CLASS REVIEWS - ANTIPLATELET DRUG CLASS AGENTS

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, recommended Plavix, Effient, Brilinta, Ticlid and generics, Aggrenox, dipyridamole (Persantine, generics), cilostazol (Pletal, generics) and pentoxifylline (Trental, generics) remain formulary on the UF. Although the cost-effectiveness review showed Aggrenox was the least cost-effective drug for stroke, the P&T Committee recommended that it remain formulary on the UF due to the low new user rate and the advanced age of the patient population. Brilinta was also recommended to remain formulary on the UF due to the incremental cost-effective ratio compared to clopidogrel (Ploavix).

Summary of Panel Vote and Comments:

The Chair opened the floor to questions and comment from BAP members.

Dr. Salom asked what is the absolute number of patients on Aggrenox? The answer given was "under ten thousand."

Dr. Crum asked whether there is a chemical variation of Plavix awaiting approval at this time. Dr. Meade said there is not.

Without further discussion the Chair read the UF recommendations for the antiplatelet drug class agents.

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel

Director, TMA

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

UF CLASS REVIEWS – DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

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, recommended sitagliptin (Januvia), sitagliptin/metformin (Janumet), and sitagliptin/simvastatin (Juvisync) be designated step-preferred and formulary on the UF; linagliptin (Tradjenta) be designated non-preferred and formulary on the UF; saxagliptin (Onglyza) and saxagliptin/metformin ER (Kombiglyze XR) be designated non-preferred and NF.

This recommendation implements step therapy, which requires a trial of Januvia, Janumet, or Juvisync (the preferred drugs) prior to using other DPP-4 inhibitors. Prior authorization for the DPP-4 inhibitors would require a trial of metformin or sulfonylurea for new patients.

Summary of Panel Vote and Comments:

The Chair opened the floor for questions of the presenters.

Ms.Fryar asked whether PA criterion (c) would apply specifically to new patients. Dr. Meade replied that is correct.

Dr. Salom noted that the P&T Committee's decision concerning step therapy using metformin is in line with those of major clinical organizations as well.

Dr. Cohoon noted that, in retail and mail order, 67 percent of rejected prescriptions were followed up by a DPP-4 prescription and that 52 percent showed a later prescription for metformin or sulfonylurea but that 12 percent were left unfilled. She asked what MHS was doing with the 12 percent that just walked away from their prescriptions and whether there was any follow-up. Dr. Meade replied that MHS tries to make sure that patients don't just fall through the cracks and has contractors contact the patients in various ways to see what happened and make sure the patient is getting proper treatment. They do this for virtually all step therapy agents.

Without further discussion, the Chair read the UF recommendations for the DPP-4 inhibitors drug class.

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel.

Director, TMA:

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

1. PA CRITERIA - DPP-4 INHIBITORS

The P&T Committee recommended the following PA criteria should apply to the DPP-4 inhibitors subclass. Coverage would be approved if the patient met any of the following criteria:

a) Automated PA criteria:

(1) The patient has received a prescription for metformin or SU at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

(2) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, Juvisync, Onglyza, Kombiglyze XR, or Tradjenta) at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

b) Manual PA criteria for Januvia, Janumet, Juvisync, Onglyza, Kombiglyze XR, or Tradjenta, if automated criteria are not met:

(1) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis (excessive blood acidification).

(2) The patient has experienced the following adverse event while receiving a SU: hypoglycemia (low blood sugar) requiring medical treatment.

(3) The patient has a contraindication to both metformin and a SU.

c) In addition to the above criteria regarding metformin and SU, the following PA criteria would apply specifically to new patients prescribed saxagliptin (Onglyza), saxagliptin/metformin ER (Kombiglyze XR), and linagliptin (Tradjenta):

(1) The patient has experienced an adverse event with sitagliptin-containing products, which is not expected to occur with saxagliptin- or linagliptin-containing products.

(2) The patient has had an inadequate response to a sitagliptin-containing product.

(3) The patient has a contraindication to sitagliptin.

Summary of Panel Vote and Comments:

There were no Panel comments regarding this set of recommendations.

Without further discussion, the Panel voted on the PA Criteria for DPP-4 Inhibitors as follows:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel.

Director, TMA

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

2. DPP-4 INHIBITORS—PANEL VOTE ON IMPLEMENTATION PLAN

The P&T Committee recommended an effective date of the first Wednesday after a 60-day implementation period in all points of service and that TMA send a letter to beneficiaries affected by this UF decision.

Summary of Panel Vote and Comments:

There were no Panel comments regarding this set of recommendations.

Without further discussion, the Panel voted on the Implementation Plan for DPP-4 Inhibitors as follows:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel.

Director, TMA

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

UF CLASS REVIEW - ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS

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, recommended the following:

Formulary Status. For the *stimulants,* that dextroamphetamine (Dexedrine, Dextrostat, Procentra solution, generics), methamphetamine HCl (Desoxyn, generic) methylphenidate CD (Metadate CD), methylphenidate IR (Ritalin, generic) methylphenidate LA (Ritalin LA, generic), methylphenidate ER (Metadate ER, Methylin ER, generics), methylphenidate chewable tablets, solution (Methylin, generic), methylphenidate OROS (Concerta),

methylphenidate SR (Ritalin SR, generic) mixed amphetamine salts IR (Adderall, generic), and mixed amphetamine salts ER (Adderall XR, generic) be retained on the UF.

For the *non-stimulants,* that all non-stimulants, atomoxetine (Strattera), clonidine ER (Kapvay) and guanfacine ER (Intuniv) be retained on the UF.

For the *wakefulness-promoting agents,* that modafinil (Provigil) and sodium oxybate (Xyrem) be retained on the UF.

Non-Formulary Status. For the *stimulants,* that desmethylphenidate ER (Focalin XR), lisdexamphetamine (Vyvanse) and methylphenidate transdermal system (Daytrana) be designated NF.

Summary of Panel Vote and Comments:

The Chair opened the floor for Panel questions.

Dr. Salom noted that the handout indicated that 90 percent of the prescriptions in the wakefulness-promoting drug category were for non-FDA-approved indications and asked how this affected the Prior Approval process. Dr. Meade said the PEC looked into the prescriptions in this category and could not find a diagnosis that would fall under one of the approved indications. The PEC looked at how much data they could find in the literature to support other uses, which is how the PA was put together.

Ms. LeGette asked about the changes from the straight PA that is being used now for Nuvigil and Xyrem, pointing out that, operationally, they will lead to prescription rejections. Ms. Fryar clarified that new users would have to try Provigil first before using either Nuvigil or Xyrem.

Dr. Cohoon commented that it would be helpful if, in the future, the handout material could indicate how the medication is to be taken.

Without further discussion, the Panel voted on the UF recommendations for the wakefulness-promoting agents class that armodafinil (Nuvigil) be designated NF.

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel:

Director, TMA:

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

1. FORMULARY STATUS CHANGE - ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS

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, recommended that dexmethylphenidate IR (Focalin, generic) be moved from NF status to UF status.

Without further discussion, the Panel voted on the Formulary Status Change for ADHD/wakefulness promoting agents.

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel:

Director, TMA:

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

2. PA CRITERIA - ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS

The P&T Committee recommended PA criteria should apply to modafinil (Provigil), armodafinil (Nuvigil), and sodium oxybate (Xyrem). The current PA criteria for modafinil (Provigil) were recommended to be continued without modification. The P&T Committee recommended maintaining the current PA criteria for Nuvigil, with one modification; jet lag would be added to the list of uses not provided. Additionally, the recommendation was that all current and new users of Nuvigil must undergo the PA process. The P&T Committee recommended PA criteria for sodium oxybate, which would be provided only for the current FDA-approved indications. Prior authorization is not intended to apply to modafinil (Provigil) or armodafinil (Nuvigil) use in active duty operational/readiness situations based on established protocols; MTFs should make necessary allowances for such use.

With regard to the existing PA criteria, with a prescription for Nuvigil there must first be a trial use of Provigil prior to using Nuvigil.

Without further discussion, the Panel voted on the PA Criteria for ADHD/wakefulness promoting agents.

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel:

Director, TMA:

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

3. **IMPLEMENTATION PLAN - ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS**

The P&T Committee recommended an effective date of the first Wednesday after a 60-day implementation period in all points of service.

Without further discussion, the Panel voted on the UF and PA Criteria Implementation Plan for ADHD/wakefulness promoting agents.

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel:

Director, TMA:

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

REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

1. **UF CLASS REVIEW - OPHTHALMIC-1 CLASS—ALCAFTADINE OPHTHALMIC SOLUTION 0.25% (LASTACAFT)**

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, recommended alcaftadine ophthalmic 0.25% solution (Lastacaft) remain designated with formulary status on the UF.

Summary of Panel Vote and Comments:

The Panel had no questions of the presenters regarding this drug.

Without further discussion, the Panel voted on the UF recommendation for Ophthalmic-1 Class – Alcaftadine Opthalmic Solutions 0.25% (Lastacaft)

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel:

Director, TMA:

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

2. UF CLASS REVIEW - NARCOTIC ANALGESICS—TAPENTADOL EXTENDED RELEASE TABLETS (NUCYNTA ER)

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, recommended tapentadol extended release (Nucynta ER) remain formulary on the UF. UF status was designated due to the potential for decreased GI intolerance as compared to oxycodone ER, despite the concerns of potential undesirable drug interactions due to norepinephrine reuptake inhibition properties.

Summary of Panel Vote and Comments:

Dr. Crum noted that over the years he has seen lots of narcotics come and go. He asked what the potential is for misuse and diversion of this drug. Dr. Meade answered that it is probably no greater or less than any other of these products.

Ms. LeGette noted that there are now several generics and quite a few sustained release products in this class and asked if there would be an opportunity to re-review the whole class soon. Dr. Meade acknowledged that there are a large number of products in this class on the UF and said there probably would be an opportunity to review the class as a whole with a view to limiting the products on the UF quite soon. The PEC will be looking at this during the summer.

Dr. Cohoon asked whether any thought had been given to adding a PA on this medication. Dr. Meade said that the Committee didn't consider a PA for this particular drug. They would prefer to do it as a class.

Ms. Fryar commented that one of the concerns she has is the potential for GI bleeding. Dr. Meade replied that with this particular drug class, constipation and nausea can be a big problem. This drug helps eliminate some of that. Although it doesn't do it completely, it does better than the other agents. He said there was a long discussion about the IR versus the ER being available.

Without further discussion, the Panel voted on the UF recommendation for Narcotic Analgesics – Tapentadol Extended Release Tablets (Nucyntaer)

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

No further comments from the Panel:

Director/TMA:

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

UTILIZATION MANAGEMENT - XALKORI, ZELBORAF, AND KALYDECO

Summary of Panel Vote and Comments: **XALKORI, ZELBORAF, AND KALYDECO**

Dr. Crum asked about the potential for inappropriate use of these drugs. Dr. Meade replied that the MHS has no real indication of any potential for inappropriate use. Dr. Cieslak said he would have a hard time imagining there might be inappropriate use, especially since an individual; would have to have the specific gene mutation in order to get the drug. He used the cystic fibrosis disorder as an example and said that one in 1,600 Caucasians has it but the patients with this specific mutation are a tiny minority of the overall cystic fibrosis population. The MHS isn't going to release the drug unless the patient has the specific genetic mutation. Dr. Crum said he was thinking that a prior authorization requirement might be unnecessary in this case.

Dr. Salom said he disagrees. He doesn't believe it would be appropriate to require a trial use under these circumstances, especially given the high cost, and would support the approach in the recommendation. He said right now we are seeing what drugs work in a small, specific number of cases. He thinks what we are going to be seeing in the future is what drugs don't work. He cited codeine as an example, where it doesn't work on one in seven Caucasians. This means that large trials will reveal where drugs don't work.

Dr. Cohoon asked whether we are taking steps to ensure that if, down the road, we discover that the drug does work for something else we are not waiting for an FDA approval. She also asked if all the FDA-approved tests are covered by TRICARE.

Dr. Buchta said that these tests are not FDA approved; they are approved under CLIA—the Clinical Amendment Act and are not TRICARE approved. As these drugs come down the pike they are excluded under TRICARE coverage if the tests for them are not FDA approved

1. PA CRITERIA - XALKORI

Crizotinib (Xalkori) is an oral anaplastic lymphoma kinase (ALK) inhibitor indicated for the treatment of patients with ALK-positive non-small cell lung cancer (NSCLC) as detected by a FDA-approved diagnostic test. The FDA has approved a new molecular diagnostic test (Vysis ALK FISH Probe test) designed to identify ALK-positive NSCLC patients for treatment with Xalkori. The P&T Committee recommended the following PA criteria should apply to Xalkori capsules, consistent with the FDA-approved product labeling:

Coverage would be approved for the treatment of patients with documented diagnosis of ALK-positive NSCLC, detected by a FDA- approved test such as Vysis ALK FISH Probe test.

Without further discussion the Panel voted on the PA Criteria for XALKORI

Concur: 6 Non-concur: 1 Abstain: 0 Absent: 0

The non-concurring vote commented that this PA isn't necessary.

Director, TMA:

☒ *These comments were taken under consideration prior to my final decision*

2. PA CRITERIA - ZELBORAF

Vermurafenib (Zelboraf) is an oral kinase inhibitor indicated for the treatment of patients with inoperable or metastatic melanoma with $BRAF^{v600E}$ mutation. Zelboraf is not recommended for use in wild-type BRAF melanoma. The FDA also approved a new molecular diagnostic test (to identify patients likely to respond to Zelboraf therapy. The P&T Committee recommended the following PA criteria should apply to Zelboraf tablets, consistent with the FDA-approved product labeling.

a) Coverage will be approved for the treatment of patients with documented diagnosis of unresectable or metastatic melanoma with $BRAF^{v600E}$ mutation, detected by a FDA-approved test such as Cobas 4800.

b) Coverage will not be approved for patients with wild-type BRAF melanoma.

Without further discussion the Panel voted on the PA Criteria for ZELBORAF

Concur: 6 Non-concur: 1 Abstain: 0 Absent: 0

The non-concurring vote again commented that this PA isn't necessary.

Director, TMA:

These comments were taken under consideration prior to my final decision

3. PA CRITERIA - KALYDECO

Ivacaftor (Kalydeco) is a new oral agent that targets a specific subgroup of patients with Cystic Fibrosis (CF). Kalydeco is indicated for the treatment of CF in patients aged 6 years of age and older who have a G551D mutation in the CFTR gene. This rare mutation occurs in about 4% of CF patients. In patients for whom the genotype is unknown, a FDA-approved test should be used to detect the presence of this mutation. Kalydeco is not effective in patients with the mutation, which occurs in about 90% of CF patients. There are several FDA-approved in-vitro molecular diagnostic tests designed to simultaneously detect and identify mutations in the CFTR gene. The P&T Committee recommended the following PA criteria should apply to Kalydeco tablets, consistent with the FDA-approved product labeling:

a) Coverage will be approved for the treatment of CF patients aged 6 years and older who have a G551D mutation in the CFTR gene, detected by a FDA-approved test.

b) Coverage will not be approved for patients who are homozygous for the F508del mutation in the CFTR gene.

Without further discussion the Panel voted on the PA Criteria for KALYDECO

Concur: 6 Non-concur: 1 Abstain: 0 Absent: 0

The non-concurring vote commented that this PA isn't necessary.

Director, TMA:

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

4. PA IMPLEMENTATION PERIOD FOR XALKORI, ZELBORAF, AND KALYDECO

The P&T Committee recommended an effective date of the first Wednesday after a 30-day implementation period in all points of service.

Without further discussion the Panel voted on the PA Implementation plan for XALKORI, ZELBORAF, AND KALYDECO.

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

Director, TMA:

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

Uniform Formulary Beneficiary Advisory Panel (BAP)

Meeting Summary
April 5, 2012
Washington, D.C.

Panel Members Present:

- Deborah Fryar, National Military Family Association, representing The Military Coalition, Chairperson
- Kathryn Buchta, Medical Professional, Health Net Federal Services
- Barbara Cohoon, National Military Family Association, representing The Military Coalition
- John Crum, Medical Professional, Humana Military Healthcare Services, Inc.
- Lisa Le Gette, Medical Professional, Express-Scripts, Inc.
- Katherine O'Neill-Tracy, Military Officers Association of America, representing The Military Coalition
- Ira Salom, Medical Professional, Indian Health Service

The meeting was held at the Naval Heritage Center Theater, 701 Pennsylvania Ave., N.W., Washington, D.C. CDR Joseph Lawrence, the Designated Federal Officer (DFO), called the proceedings to order at 9:00 A.M. CDR Lawrence indicated the Panel has been convened to review and comment on the therapeutic drug class recommendations resulting from the February 16 and 17, 2012 Department of Defense (DoD) Pharmacy and Therapeutic (P&T) Committee meeting held in San Antonio, TX.

Agenda

The agenda for this meeting of the Panel is:

- Welcome and opening remarks
- Public citizen comments
- Review and Panel discussion of P&T Committee recommendations for the following therapeutic drug classes:
  - *Drug Class Reviews:*
    - Antiplatelet Agents
    - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
    - Attention Deficit Disorder Hyperactivity Disorder (ADHD)/Wakefulness Promoting Agents
  - *Designated Newly Approved Drugs:*
    - Opthalmic-1 Class—Alcaftadine ophthalmic solution (Lastacaft)
    - Narcotic Analgesics—Tapentadol extended release tablets (Nucynta ER)

- *Utilization Management:*
  - Crizotinib (Xalkori) for non-small cell lung cancer Prior Authorization
  - Vermurafenib (Zelboraf) for metastatic melanoma Prior Authorization
  - Ivcaftor (Kalydeco) for cystic fibrosis Prior Authorization

Opening Remarks

The DFO began by indicating that Title 10 United States Code (U.S.C.) section 1074g subsection b requires the Secretary of Defense to establish a DoD Uniform Formulary (UF) of pharmaceutical agents, and establishes the P&T Committee to review the formulary on a periodic basis and make additional recommendations regarding the formulary as the Committee determines necessary and appropriate.

In addition, 10 U.S.C. section 1074g subsection c also requires the Secretary to establish a UF Beneficiary Advisory Panel (BAP) to review and comment on the development of the UF. The Panel includes members that represent non-governmental organizations and associations that represent the views and interests of a large number of eligible covered beneficiaries. Comments of the Panel must be considered by the Director, TRICARE Management Activity (TMA) before establishing the UF or implementing changes to the UF. The Panel's meetings are conducted in accordance with the Federal Advisory Committee Act (FACA).

The duties of the Uniform Formulary Beneficiary Advisory Panel include:

- To review and comment on the recommendations of the P&T Committee concerning the establishment of the UF and subsequent recommended changes. Comments to the Director, TMA, regarding recommended formulary status, pre-authorizations, and the effective dates for changing drugs from "formulary" to "non-formulary" status must be reviewed by the Director, TMA 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 DFO in consultation with the Chairperson 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.

As guidance to the Panel regarding this meeting, CDR Lawrence said the role of the BAP is to comment on the UF 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 14 hours conducting its reviews of the drug class 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 the Director's decisions will be available on the TRICARE website in approximately four to six weeks.

The DFO next provided the ground rules for conducting the meeting:

- All discussions take 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 the minutes accurately reflect relevant facts, regulations or policy.

Private Citizen Comments

The DFO opened the meeting for private citizen comments but there were none.

CDR Lawrence then introduced the individual Panel members (see list above), noted housekeeping considerations, then turned the meeting over to the Panel Chairperson, Ms. Deborah Fryar.

Chairperson's Opening Remarks

The Chair welcomed the audience and thanked everyone for coming. She reminded the Panel that its function is to represent the beneficiaries by reviewing the P&T Committee's recommendations, asking questions, offering input, voting to concur or not and making comments as appropriate; however the Panel cannot make recommendations on its own. Those must come from the P&T Committee.

Ms. Fryar then turned the meeting over to Dr. Meade of the Pharmacoeconomic Center (PEC) to begin the drug class presentations.

DRUG CLASS REVIEW PRESENTATIONS

(PEC Script)

I'm Dave Meade, Director of Clinical Operations at the Pharmacoeconomic Center. Joining me today from the PEC is LCDR Olaitan Ojo, our Navy Pharmacist consultant. Also joining us today is COL Ted Cieslak, a pediatric physician and one of the DoD P&T Committee members who will provide the physician perspective and comment on the recommendations made by the P&T Committee. Dr Kugler, the chairmen of the P&T Committee and a retired Army Colonel and physician, is also here. Joining us from the TMA is the TMA Chief of Staff, CAPT Nita

Sood of the Pharmaceutical Operations Directorate.

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).

We are here to present an overview of the analyses presented to the DoD P&T Committee. 32 Code of Federal Regulation (C.F.R.) establishes procedures for inclusion of pharmaceutical agents on the Uniform Formulary based upon both relative clinical effectiveness and relative cost effectiveness.

The goal of this presentation is not to provide you with the same in-depth analyses presented to the DoD P&T Committee but a summary of the processes and analyses presented to the DoD P&T Committee. These include:

1) A brief overview of the relative clinical-effectiveness analyses considered by the DoD P&T Committee.
2) A brief 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 is based upon its collective professional judgment when considering the analyses from both the relative clinical and relative cost-effectiveness evaluations. The Committee reviewed two Uniform Formulary drug classes – Antiplatelet Agents and Attention Deficit Hyperactivity Disorder (ADHD)/Wakefulness-Promoting drug classes. Additionally, we'll present the Uniform Formulary recommendations review for the Dipeptidyl Peptidase-4 (DPP-4) Inhibitors subclass– the clinical effectiveness of the Non-Insulin Diabetes class was presented at a previous meeting. Two newly approved drugs that were reviewed were Alcaftadine (Lastacaft) and Tapentadol extended release (Nucynta ER).
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; these are found on pages 2 through 10. There are tables and utilization figures for all the drug classes. We'll be using trade names as much as possible, so you can refer to your handout throughout the presentation.

At this time I'd like to introduce LCDR Ojo who will present the antiplatelet agents class.

I. UF CLASS REVIEWS—ANTIPLATELET AGENTS

(PEC Script)

ANTIPLATELET DRUG CLASS AGENTS — RELATIVE CLINICAL EFFECTIVENESS

(LCDR Ojo):

Background Relative Clinical Effectiveness— The P&T Committee evaluated the relative clinical effectiveness of the Antiplatelet Drugs which are used for treating acute coronary syndromes, stroke, and peripheral artery disease. The individual drug members of the class are listed in Table 1 of the Handout on page 2. Military Health System (MHS) expenditures for antiplatelet agents exceed $260 million annually.

The class as a whole has not been previously reviewed.

The two newest entrants to the class are Effient and Brilinta. Generic formulations of Plavix are expected in May 2012.

Figure 1 of the handout on p 2 shows the utilization of the agents. Plavix has the highest usage.

In order to support the clinical and cost-effectiveness evaluations in this class, the Pharmacy Outcomes Research Team (PORT) conducted an analysis to define a typical MHS Aggrenox user. A total of 13,341 users with an average age of 76 years were identified. Over 82% of patients had received Aggrenox in the last 180 days, with a new user rate of 13%–18%, suggesting that patients had been on Aggrenox for extended periods.

Moving on to the P&T conclusions:

The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) to accept the following conclusions regarding the antiplatelet drugs: (Table 1 of the Handout):

For acute coronary syndromes, the following conclusions were made:

1. Several large clinical trials have shown the effectiveness of Plavix in decreasing the incidence of major cardiovascular (CV) events in patients with acute coronary syndrome (ACS) which includes myocardial infarction (heart attack) and unstable angina (chest pain).
2. Effient and Brilinta have a faster onset of action and exhibit more complete platelet inhibition, compared to Plavix.
3. Guidelines from professional cardiology groups recommend Plavix, Effient, or Brilinta as first-line options for treating ACS patients requiring percutaneous coronary intervention (PCI) which includes balloon procedure or stent placement.
4. Effient and Brilinta are approved solely for ACS; however, Effient is limited to patients whose coronary anatomy is known and suitable for PCI.
5. In one landmark trial, Effient was more effective than Plavix in reducing the composite endpoint of cardiovascular death, non-fatal myocardial infarction (MI), and stroke in ACS patients undergoing PCI. There was no significant difference between Effient and Plavix for the single endpoint of CV death.
6. A subgroup analysis showed Effient was superior to Plavix in patients who are

diabetic, those with prior stent thrombosis (clotted stent), and those younger than 65 years.

7. In another major trial, Brilinta was more effective than Plavix in reducing the composite endpoint of CV death, non-fatal MI, and stroke in ACS. Brilinta was more effective than Plavix in reducing the single endpoints of CV death and non-fatal MI, although the trial was not designed to assess differences in mortality.
8. A subgroup analysis of the 1,413 U.S. patients found no significant difference between Brilinta and Plavix for major coronary events. This was attributed to the higher aspirin dose utilized in North America versus the rest of the world. Brilinta should only be used with aspirin doses lower than 100 mg.
9. Definitive statements about comparative clinical effectiveness between Effient and Brilinta are difficult to make because there are no head-to-head trials.

For stroke, the following conclusions were made:

1. A systematic review concluded there was no significant difference between Aggrenox and Plavix for all-cause mortality, CV mortality, and recurrent stroke, in patients with ischemic stroke (stroke from a clot), based on the PROFESS trial.
2. A systematic review concluded there was no significant difference between ticlopidine and Plavix on outcomes of all-cause mortality, CV death, or cerebral infarction (stroke from a burst blood vessel) in stroke patients.

For peripheral arterial disease (PAD – narrowing of arteries leading to the brain and heart), the following conclusions were made:

1. Cilostazol is the recommended first-line agent to improve walking distance in patients with PAD, while pentoxifylline is the second-line alternative, based on professional guidelines.
2. Plavix and aspirin are recommended to reduce the risk of MI, stroke or vascular death in patients with symptomatic PAD.

With regards to safety and tolerability, the following conclusions were made:

1. In the one trial Effient had a significantly higher rate of bleeding, including non-coronary artery bypass grafting (CABG) related bleeding and fatal bleeding, compared to Plavix. Additional risk factors that increase the bleeding risk with Effient include low weight (<60 kg), age greater than 75 years, and prior history of stroke and transient ischemic attack (TIA – temporary blood flow blockage in the brain).
2. Brilinta had a similar rate of major and fatal bleeding compared to Plavix; however, the rate of non-CABG-related major bleeding was significantly higher with Brilinta than Plavix. Brilinta was associated with a higher rate of non-hemorrhagic adverse events (AEs), including dyspnea (shortness of breath), and increases in serum creatinine and uric acid levels.
3. Unlike Plavix and Brilinta, Effient is contraindicated in patients with previous stroke or TIA.
4. Ticlopidine's therapeutic use is greatly limited by its adverse event profile, including

risk of neutropenia and aplastic anemia, which are both blood disorders.

5. In stroke patients, Plavix had a lower rate of major bleeding and withdrawal due to AEs, compared with Aggrenox.

ANTIPLATELET DRUG CLASS AGENTS — RELATIVE COST EFFECTIVENESS

(Dr. Meade)

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of the antiplatelet agents for secondary prevention in acute coronary syndrome (ACS) for secondary prevention of stroke, and for PAD. CMAs were performed for the antiplatelet drugs used for stroke and PAD (Aggrenox, ticlopidine, cilostazol, dipyridamole, and pentoxifylline). Cost-effectiveness analyses (CEAs) and CMAs were used to analyze antiplatelet agents for ACS (Plavix, Effient, and Brilinta), as efficacy differences between the agents were noted in the clinical review.

Refer to Table 1 on page 2 for the drugs in this class.

CMA and BIA were used to assess the potential impact of cost scenarios where selected antiplatelet agents were designated with formulary or NF status on the UF. The impact of generic Plavix availability was modeled in the BIA scenarios.

For the antiplatelet drugs prescribed following ACS, CEAs and CMAs were used to assess the potential impact of the occurrence rates of CV and bleeding events, based on differences highlighted in the clinical review.

Two separate cost-effectiveness models were constructed in the analyses of antiplatelet agents for ACS secondary prevention: prasugrel (Effient) versus Plavix and ticagrelor (Brilinta) versus Plavix. Analysis was based on direct comparisons of relevant trial data. The models compared the annual cost per CV event avoided (the composite of nonfatal MI, nonfatal stroke, and death from CV cause).

Relative Cost-Effectiveness Conclusion—Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 against, 0 abstained, 2 absent) the following:

1. **Antiplatelet agents for ACS**—CEA results showed that prasugrel (Effient) and ticagrelor (Brilinta) provide reasonable clinical benefit for the increase in treatment cost.

2. **Antiplatelet agents for stroke**—CMA results showed that aspirin/dipyridamole ER (Aggrenox) was the least cost-effective agent, based on analysis of the average weighted price per day of therapy at all three POS.

3. **Antiplatelet agents for PAD**—CMA results showed that pentoxifylline and cilostazol are similarly cost-effective therapy options.

4. **All antiplatelet agents**—BIA results showed the scenario where all current UF agents were retained on the UF, and aspirin/dipyridamole ER (Aggrenox) and ticagrelor (Brilinta) were

designated NF resulted in the lowest projected cost compared to current MHS expenditures.

ANTIPLATELET DRUG CLASS AGENTS — UF RECOMMENDATIONS

(Dr. Meade)

Antiplatelet: UF Recommendation—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (14 for, 3 opposed, 0 abstained, 1 absent) Plavix, Effient, Brilinta, Ticlid and generics, Aggrenox, dipyridamole (Persantine, generics), cilostazol (Pletal, generics) and pentoxifylline (Trental, generics) remain formulary on the UF. Although the cost-effectiveness review showed Aggrenox was the least cost-effective drug for stroke, the P&T Committee recommended that it remain formulary on the UF due to the low new user rate and the advanced age of the patient population. Brilinta was also recommended to remain formulary on the UF due the results of the CMA, compared to Plavix.

At this time Dr. Cieslak will present physician comments.

ANTIPLATELET DRUG CLASS AGENTS — COMMITTEE PHYSICIAN'S PERSPECTIVE

Dr. Cieslak began by indicating that he is a pediatrician and infectious disease specialist by training, where he doesn't deal with these drugs too often, but he is also currently serving as the Chief of Clinical Services for the Army's Medical Command and is the Army's at-large representative on the P&T Committee, in which capacity he has had plenty of opportunity to look at these drugs. He believes the choice of this class to review was a wise one. One reason is that this is a drug class on which the MHS spends $260 million—one of its largest classes. Another is that Plavix, which has been widely used for years, is going generic next month, presenting an opportunity to save what will certainly be in the high tens of millions of dollars.

He said there was nothing controversial in the reviews. The vote was 14 to 3 and the three dissenting votes simply preferred non-formulary status for a couple of the agents. Aggrenox, for example, which is a relatively cost-ineffective drug is actually a combination of two inexpensive drugs and physicians could just use those two drugs in place of brand-name Aggrenox. But the Committee opted in favor of convenience for the beneficiaries, especially because the patients using these drugs, and Aggrenox in particular, are elderly—most are 70 years old or older. The Committee didn't want elderly patients being turned away, so it erred on the side of approval and included all of the agents on the UF.

ANTIPLATELET DRUG CLASS AGENTS — PANEL QUESTIONS AND COMMENTS

The Chair opened the floor to questions and comment from BAP members.

Dr. Salom asked what is the absolute number of patients on Aggrenox? The answer given was

"under ten thousand."

Dr. Crum asked whether there is a chemical variation of Plavix awaiting approval at this time. Dr. Meade said there is not.

ANTIPLATELET DRUG CLASS AGENTS — PANEL VOTE ON UF RECOMMENDATIONS

The Chair read the UF recommendations for the antiplatelet drug class agents.

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, recommended Plavix, Effient, Brilinta, Ticlid and generics, Aggrenox, dipyridamole (Persantine, generics), cilostazol (Pletal, generics) and pentoxifylline (Trental, generics) remain formulary on the UF. Although the cost-effectiveness review showed Aggrenox was the least cost-effective drug for stroke, the P&T Committee recommended that it remain formulary on the UF due to the low new user rate and the advanced age of the patient population. Brilinta was also recommended to remain formulary on the UF due to the incremental cost-effective ratio compared to clopidogrel (Ploavix).

The Panel then voted as follows:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

There were no Panel comments regarding this recommendation.

II. UF CLASS REVIEWS— DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

DPP-4 INHIBITORS—RELATIVE CLINICAL EFFECTIVENESS *(PEC Script)*

(LCDR Ojo):

Relative Clinical Effectiveness—The P&T Committee evaluated the clinical effectiveness of DPP-4 inhibitors. Table 2 on page 3 of the handout shows the drugs in this subclass. Two new products, sitagliptin/metformin ER (Janumet XR) and linagliptin/metformin (Jentadueto) will be reviewed at an upcoming meeting. The DPP-4 inhibitors were previously reviewed in November 2010 as a subclass of the Non-insulin Diabetes Drug Class. Prior Authorization (PA) criteria and step therapy require a trial of metformin or sulfonylurea (SU) prior to using a DPP-4 inhibitor. MHS expenditures exceed $119 million annually for DPP-4 inhibitors.

Figure 2 on page 3 of the handout shows that Januvia and Janumet are the most utilized agents.

Relative Clinical Effectiveness Conclusion—The P&T Committee voted (18 for, 0 against, 0

abstained, 0 absent) to accept the following clinical effectiveness conclusions:

1. Clinical practice guidelines, including the DoD/Veterans Affairs guidelines for diabetes mellitus, do not currently recommend DPP-4 inhibitors for a specific place in therapy but list the class as alternative agents. Metformin remains the recommended first line agent for most patients who do not have a contraindication for metformin therapy.
2. One head-to-head trial did not show clinically relevant differences in efficacy or safety between Januvia and Onglyza.
3. Januvia, Onglyza, and Tradjenta show similar effects of lowering hemoglobin A1c (which is the standard blood test for diabetics) when used as monotherapy, ranging from 0.4% to 0.9%. When a DPP-4 inhibitor is combined with metformin, the mean decrease in A1c from baseline ranges from 0.4% to 2.5%; when combined with a thiazolidinedione (TZD), the mean decrease in A1c ranges from 0.7% to 1.06%; and when combined with a SU, the mean decrease in A1c ranges from 0.5% to 0.6%.
4. DPP-4 inhibitors are weight neutral, lipid neutral, and have minimal impact on blood pressure.
5. Tradjenta has not been directly compared with Onglyza or Januvia in a clinical trial. A meta-analysis showed the A1c-lowering effect of linagliptin plus metformin was non-inferior to sitagliptin plus metformin. Tradjenta is the only DPP-4 inhibitor that does not require dose adjustments due to renal or hepatic impairment.
6. Juvisync is a fixed-dose combination product containing sitagliptin (Januvia) with the cholesterol-lowering drug simvastatin. There are no clinical trials evaluating Juvisync; it obtained FDA approval based on bioequivalence with the individual components. Juvisync may provide a dosing convenience in patients who require both Januvia and a statin.
7. In terms of commonly reported adverse events, there are no clinically relevant differences between Januvia, Onglyza, and Tradjenta. Drug interaction profiles are also similar between agents. Pancreatitis has been reported with both Januvia and Onglyza. Acute renal failure has been reported with Januvia.
8. There is a high degree of therapeutic interchangeability between Januvia, Onglyza, and Tradjenta.

DPP-4 INHIBITORS—RELATIVE COST EFFECTIVENESS

(Dr. Meade):

Relative Cost-Effectiveness Conclusion—CMAs and budget impact analyses (BIA) were used to evaluate the relative cost-effectiveness of the DPP-4 inhibitors. Based on the results of the cost analyses and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the following:

1. BIA was used to assess the potential impact of cost scenarios where selected DPP-4 inhibitors were designated with formulary status on the UF. The analysis included an evaluation of the potential impact of cost scenarios where DPP-4 inhibitors were designated with preferred product status (step therapy) on the UF; i.e., a trial of a

preferred DPP-4 inhibitor would be required before using other DPP-4 inhibitors on the UF.

2. BIA results showed the scenario where sitagliptin (Januvia), sitagliptin/ metformin (Janumet), and sitagliptin/simvastatin (Juvisync) are step-preferred on the UF, linagliptin (Tradjenta) is non-preferred on the UF, and saxagliptin (Onglyza) and saxagliptin/metformin (Kombiglyze XR) are non-preferred and NF was determined to be the most cost-effective.

DPP-4 INHIBITORS—UF RECOMMENDATIONS

(Dr. Meade):

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, recommended (16 for, 1 opposed, 1 abstained, 0 absent): sitagliptin (Januvia), sitagliptin/metformin (Janumet), and sitagliptin/simvastatin (Juvisync) be designated step-preferred and formulary on the UF; linagliptin (Tradjenta) be designated non-preferred and formulary on the UF; saxagliptin (Onglyza) and saxagliptin/metformin ER (Kombiglyze XR) be designated non-preferred and NF.

This recommendation implements step therapy, which requires a trial of Januvia, Janumet, or Juvisync (the preferred drugs) prior to using other DPP-4 inhibitors. Prior authorization for the DPP-4 inhibitors would require a trial of metformin or sulfonylurea for new patients.

DPP-4 INHIBITORS—PA CRITERIA

(Dr. Meade):

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following PA criteria should apply to the DPP-4 inhibitors subclass. Coverage would be approved if the patient met any of the following criteria:

a) Automated PA criteria:

(1) The patient has received a prescription for metformin or SU at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

(2) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, Juvisync, Onglyza, Kombiglyze XR, or Tradjenta) at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

b) Manual PA criteria for Januvia, Janumet, Juvisync, Onglyza, Kombiglyze XR, or Tradjenta, if automated criteria are not met:

(1) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis (excessive blood acidification).

(2) The patient has experienced the following adverse event while receiving a SU: hypoglycemia (low blood sugar) requiring medical treatment.

(3) The patient has a contraindication to both metformin and a SU.

c) In addition to the above criteria regarding metformin and SU, the following PA criteria would apply specifically to new patients prescribed saxagliptin (Onglyza), saxagliptin/metformin ER (Kombiglyze XR), and linagliptin (Tradjenta):

(1) The patient has experienced an adverse event with sitagliptin-containing products, which is not expected to occur with saxagliptin- or linagliptin-containing products.

(2) The patient has had an inadequate response to a sitagliptin-containing product.

(3) The patient has a contraindication to sitagliptin.

DPP-4 INHIBITORS—UF AND PA IMPLEMENTATION PLAN

(Dr. Meade):

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service and that TMA send a letter to beneficiaries affected by this UF decision.

DPP-4 INHIBITORS—COMMITTEE PHYSICIAN'S PERSPECTIVE

Dr. Cieslak noted that this is another large drug class that accounts for a considerable amount of MHS expenditures. He said the Panel would be hearing a lot more about this class as there are two additional agents already in the pipeline and he anticipates that there will be more DPP-4 inhibitors combined with metformin or other therapeutic agents.

There was nothing controversial in the P&T Committee's deliberations on this class of drugs. Nearly all of its decisions in this class were unanimous. The one dissenting vote had to do with the step therapy requirement. He said that, in general, the Committee is not is favor of putting any roadblocks in the physician's ability to prescribe drugs for their patients. However, in this case, the Committee felt strongly that it was necessary to have the first step of metformin or a sulfonylurea before moving on to a second step.

DPP-4 INHIBITORS—PANEL QUESTIONS AND COMMENTS

The Chair opened the floor for questions of the presenters.

Ms.Fryar asked whether PA criterion (c) would apply specifically to new patients. Dr. Meade replied that is correct.

Dr. Salom noted that the P&T Committee's decision concerning step therapy using metformin is in line with those of major clinical organizations as well.

Dr. Cohoon noted that, in retail and mail order, 67 percent of rejected prescriptions were followed up by a DPP-4 prescription and that 52 percent showed a later prescription for metformin or sulfonylurea but that 12 percent were left unfilled. She asked what MHS was doing with the 12 percent that just walked away from their prescriptions and whether there was any follow-up. Dr. Meade replied that MHS tries to make sure that patients don't just fall through the cracks and has contractors contact the patients in various ways to see what happened and make sure the patient is getting proper treatment. They do this for virtually all step therapy agents.

DPP-4 INHIBITORS—PANEL VOTE ON UF RECOMMENDATIONS

The Chair read the P&T Committee's UF recommendations for the DPP-4 inhibitors drug class.

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, recommended sitagliptin (Januvia), sitagliptin/metformin (Janumet), and sitagliptin/simvastatin (Juvisync) be designated step-preferred and formulary on the UF; linagliptin (Tradjenta) be designated non-preferred and formulary on the UF; saxagliptin (Onglyza) and saxagliptin/metformin ER (Kombiglyze XR) be designated non-preferred and NF.

This recommendation implements step therapy, which requires a trial of Januvia, Janumet, or Juvisync (the preferred drugs) prior to using other DPP-4 inhibitors. Prior authorization for the DPP-4 inhibitors would require a trial of metformin or sulfonylurea for new patients.

The Panel vote was:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

There were no Panel comments regarding this recommendation.

DPP-4 INHIBITORS—PANEL VOTE ON PA CRITERIA

The Chair next read the PA criteria recommendations for this drug class.

The P&T Committee recommended the following PA criteria should apply to the DPP-4 inhbitors subclass. Coverage would be approved if the patient met any of the following criteria:

a) Automated PA criteria:

(1) The patient has received a prescription for metformin or SU at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

(2) The patient has received a prescription for a DPP-4 inhibitor (Januvia, Janumet, Juvisync, Onglyza, Kombiglyze XR, or Tradjenta) at any MHS pharmacy POS (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

b) Manual PA criteria for Januvia, Janumet, Juvisync, Onglyza, Kombiglyze XR, or Tradjenta, if automated criteria are not met:

(1) The patient has experienced any of the following adverse events while receiving metformin: impaired renal function that precludes treatment with metformin or history of lactic acidosis (excessive blood acidification).

(2) The patient has experienced the following adverse event while receiving a SU: hypoglycemia (low blood sugar) requiring medical treatment.

(3) The patient has a contraindication to both metformin and a SU.

c) In addition to the above criteria regarding metformin and SU, the following PA criteria would apply specifically to new patients prescribed saxagliptin (Onglyza), saxagliptin/metformin ER (Kombiglyze XR), and linagliptin (Tradjenta):

(1) The patient has experienced an adverse event with sitagliptin-containing products, which is not expected to occur with saxagliptin- or linagliptin-containing products.

(2) The patient has had an inadequate response to a sitagliptin-containing product.

(3) The patient has a contraindication to sitagliptin.

The Panel voted:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

There were no Panel comments regarding this recommendation.

DPP-4 INHIBITORS—PANEL VOTE ON IMPLEMENTATION PLAN

The Chair then read the implementation plan recommendation for the DPP-4 inhibitors.

The P&T Committee recommended an effective date of the first Wednesday after a 60-day implementation period in all points of service and that TMA send a letter to beneficiaries

affected by this UF decision.

The Panel voted:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

The Panel had no comments regarding this recommendation.

III. UF CLASS REVIEWS—ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS—RELATIVE CLINICAL EFFECTIVENESS

(PEC Script)

(LCDR Ojo):

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of the ADHD and Wakefulness-Promoting Agents Class, which was previously reviewed in November 2006. The drugs in this class are comprised of the following three subclasses: 1) ADHD stimulants, 2) ADHD non-stimulants, and 3) wakefulness-promoting agents.

The ADHD stimulants include lisdexamphetamine (Vyvanse), and long- and short-acting formulations of methylphenidate, amphetamine, and mixed amphetamine salt products. The full list of the drugs in the subclass and the classification of long- and short-acting stimulants are found in Table 3 on page 4 of your handout. Since the November 2006 review, dexmethylphenidate IR (Focalin), mixed amphetamine salts ER and IR (Adderall XR; Adderall), and methylphenidate long-acting (LA) (Ritalin LA) are now available in generic formulations. There is one authorized generic for methylphenidate osmotic-controlled release oral delivery system (OROS), which is produced by the manufacturer of Concerta.

The ADHD non-stimulants subclass is comprised of atomoxetine (Strattera), clonidine ER (Kapvay), and guanfacine ER (Intuniv). The wakefulness-promoting subclass includes modafinil (Provigil), armodafinil (Nuvigil), and sodium oxybate (Xyrem). Generic formulations of modafinil are expected in the 2nd quarter of 2012. Prior Authorization is currently required for modafinil and armodafinil.

Figure 3 on page 5 shows that the long acting ADHD stimulant subclass is the most utilized and out of this subclass, Concerta (Brand) has the highest utilization in the MHS followed very closely by Adderall XR (Brand), as seen in figure 4. Figure 5 on page 6 shows that the mixed amphetamine salts is the most utilized in the Short Acting Stimulant Subclass. For the Non stimulant Subclass, Figure 6 on page 6 demonstrates that Strattera has the highest utilization followed closely by Intuniv which is showing an upward trend. Lastly, we have the Wakefulness-promoting Subclass; from Figure 7 on page 7, we see that Nuvigil has the highest

utilization followed by Provigil.

Relative Clinical Effectiveness Conclusion

1. The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) on the following conclusions regarding the ADHD stimulants and non- stimulants:
   a) Methylphenidate IR is more effective than placebo in improving ADHD symptoms in preschool-aged children (4–5 years of age) who do not respond to parental behavior training.
   b) Based on a systematic review, the following conclusions apply in children and adolescents aged 6–17 years:
      - There are no clinically relevant differences between the IR stimulant formulations.
      - There are no clinically relevant differences between IR stimulant formulations when compared to sustained release (SR) stimulants (Ritalin SR, Metadate CD).
      - There is conflicting evidence when methylphenidate IR is compared with methylphenidate OROS (Concerta). Two double-blinded studies showed no difference in efficacy, while two open-label studies favored methylphenidate OROS.
      - There are no clinically relevant differences when SR stimulant formulations are compared to other SR formulations. Minor differences include that methylphenidate CD (Metadate CD) and dexmethylphenidate ER (Focalin XR) show greater response in the morning, while methylphenidate OROS (Concerta) shows greater response in the evening.
      - Lisdexamphetamine (Vyvanse) treatment resulted in similar scores on AHDH rating scales when compared to mixed amphetamine salts ER (Adderall XR).
      - Transdermal methylphenidate (Daytrana) produced similar scores on investigator, teacher, and parent rating scales when compared to methylphenidate OROS (Concerta) over a 7-week period.
   c) In adults (18 years of age and older), there are no clinically relevant differences in efficacy when switching to methylphenidate OROS (Concerta) versus continuing with methylphenidate IR.
   d) With regards to safety, package labeling for all stimulants contains a black box warning for potential abuse and dependency.
   e) Use of mixed amphetamine salts (Adderall IR, generic) is associated with a higher incidence of weight loss and insomnia than methylphenidate IR.
   f) One large randomized controlled trial, the Multimodal Therapy Study of ADHD, reported stimulants caused a decrease in growth velocity in children at 36 months.

g) Stimulants do not significantly increase the risk of serious cardiovascular events in children, adolescents, or adults (up to age 64), based on two large cohort studies.

h) The stimulants with suggested low potential for abuse/diversion are Vyvanse, Daytrana, and Concerta. In adolescents, American Academy of Pediatrics guidelines recommend prescribing non-stimulants or stimulants with the lowest potential for abuse/diversion, compared to the other stimulant products.

i) For patients with swallowing difficulties, Vyvanse is dissolvable in water. Ritalin LA, Metadate CD, Adderall XR, and Focalin XR are formulated in capsules that can be opened and sprinkled on food.

2. The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) on the following conclusions regarding the ADHD non-stimulants:

a) A systematic review concluded atomoxetine (Strattera) is associated with efficacy outcomes similar to methylphenidate IR. Methylphenidate OROS (Concerta) and mixed amphetamine salts ER (Adderall XR, generic) are superior to atomoxetine in terms of response rates.

b) There are no head-to-head trials comparing clonidine ER (Kapvay) or guanfacine ER (Intuniv) with other ADHD drugs. Placebo-controlled studies with clonidine ER showed modest benefit when used as add-on or monotherapy. Placebo-controlled studies with guanfacine ER (Intuniv) showed modest benefit up to 8 hours after dosing.

c) With regards to safety, the package labeling for atomoxetine (Strattera) contains a black box warning for suicidal ideation. Atomoxetine has a higher incidence of vomiting, nausea, and somnolence compared to stimulants.

d) Clonidine ER (Kapvay) and guanfacine ER (Intuniv) are associated most commonly with somnolence and fatigue, although there are no comparative data with other ADHD drugs.

3. The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 1 absent) on the following conclusions regarding the wakefulness-promoting drugs:

a) There is one head-to-head trial comparing modafinil 200 mg with armodafinil 150 mg in patients with excessive sleepiness due to shift work sleep disorder. There was no significant difference between the two drugs in terms of percentage of responders at 12 weeks.

b) There are no head-to-head trials comparing modafinil with armodafinil in patients with (excessive sleepiness or sleep attacks) narcolepsy or obstructive sleep apnea (pauses in breathing during sleep).

c) The manufacturer of armodafinil (Nuvigil) submitted data to the FDA requesting approval for patients with jet lag, but the application was denied.

d) The manufacturer of sodium oxybate (Xyrem) sought FDA approval for use in fibromyalgia, but was denied due to abuse potential and safety concerns.

e) With regards to safety and tolerability, there are no clinically relevant differences in the safety profiles between modafinil and armodafinil.

f) Sodium oxybate (Xyrem) has a black box warning for abuse/misuse/diversion potential. A restricted distribution program limits dispensing to one centralized pharmacy.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS—RELATIVE COST EFFECTIVENESS

(Dr. Meade):

Relative Cost-Effectiveness—The P&T Committee evaluated the relative cost-effectiveness of ADHD long-acting stimulants, short-acting stimulants, and non- stimulants, and the wakefulness-promoting agents. CMAs were performed to compare average daily cost of therapy for all branded and generic drugs within each of the respective subclasses. BIAs of varying formulary scenarios where various agents moved between BCF, UF, and NF status were performed for the long-acting stimulants, the non-stimulants, and the wakefulness-promoting drugs.

ADHD—BIA was used to evaluate the long-acting stimulants, with corresponding sensitivity analyses. For relative comparison with the long-acting stimulants, a composite average daily cost for the short-acting stimulants was also calculated.

Wakefulness-promoting agents—CMA and BIAs were used to evaluate the drugs in this subclass, with corresponding sensitivity analyses. BIAs also considered the potential impact of cost scenarios where current armodafinil (Nuvigil) users were grandfathered (and prior authorization would only apply to new users) versus a no-grandfathering scenario with prior authorization applicable to all users. Sodium oxybate (Xyrem) was not included in the CMA or BIAs due to restricted distribution from one pharmacy. Generic pricing estimates for modafinil (Provigil) were used in the cost analyses based on its anticipated generic availability.

Relative Cost-Effectiveness Conclusion—Based on the results of the economic analysis and other clinical and cost considerations, the P&T Committee concluded the following for the ADHD and wakefulness-promoting agents:

1. The P&T Committee agreed (17 for, 0 opposed, 1 abstained, 0 absent) on the following conclusions regarding the long-acting stimulants: CMA results showed the following ranking, from least costly to most costly: mixed amphetamine salts ER < Ritalin LA < Vyvanse < Focalin XR < Concerta < Daytrana. BIAs results showed that scenarios where the current branded NF long-acting stimulants remained NF generated greatest cost avoidance.
2. The P&T Committee agreed (17 for, 0 opposed, 1 abstained, 0 absent) on the following conclusions regarding the short-acting stimulants: CMA results showed the following ranking, from least costly to most costly: methylphenidate

IR (Ritalin generic) < dextroamphetamine tablets (Dexedrine generic) < mixed amphetamine salts (Adderall generic) < dexmethylphenidate (Focalin generic) < methylphenidate SR (Ritalin SR generic) < Metadate CD < Methylin chewable tablet < dextroamphetamine spansules (Dexedrine generic) < Procentra liquid < Desoxyn. Composite costs results showed the short-acting stimulants were more cost-effective than the long-acting stimulants.

3. The P&T Committee agreed (18 for, 0 opposed, 0 abstained, 0 absent) on the following: for the non-stimulants, Strattera was most cost-effective, followed by Intuniv; Kapvay was least cost-effective. BIAs results showed minimal differences in cost-avoidance between branded NF and UF non-stimulants.
4. The P&T Committee agreed (18 for, 0 opposed, 0 abstained, 0 absent) on the following: for the wakefulness-promoting agents, CMA showed the estimated generic modafinil was most cost-effective, followed by Provigil; Nuvigil was least cost-effective. BIAs results showed that scenarios where Nuvigil changes to NF status and all current and new users of Nuvigil undergo the PA process (e.g., not grandfathered) generated greatest cost-avoidance; this scenario also included maintaining the existing PA for Provigil.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS—UF RECOMMENDATIONS

(Dr. Meade):

ADHD and Wakefulness-Promoting Agents Class – UF Recommendation—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended the following:

For the *stimulants* class (15 for, 1 opposed, 1 abstain and 1 absent) that dextroamphetamine (Dexedrine, Dextrostat, Procentra solution, generics) methamphetamine HCl (Desoxyn, generic) methylphenidate CD (Metadate CD) methylphenidate IR (Ritalin, generic) methylphenidate LA (Ritalin LA, generic) methylphenidate ER (Metadate ER, Methylin ER, generics) methylphenidate chewable tablets solution (Methylin, generic) methylphenidate OROS (Concerta) methylphenidate SR (Ritalin SR, generic) mixed amphetamine salts IR (Adderall, generic) and mixed amphetamine salts ER (Adderall XR, generic) be retained on the UF and that desmethylphenidate ER (Focalin XR) lisdexamphetamine (Vyvanse) and methylphenidate transdermal system (Daytrana) be designated NF and that dexmethylphenidate IR (Focalin, generic) be moved from NF status to UF status.

For the *non-stimulants* class (16 for, 0 opposed, 1 abstain and 1 absent) that all non-stimulants, atomoxetine (Strattera) clonidine ER (Kapvay) and guanfacine ER (Intuniv) be retained on the UF. (*Note*: Clonidine IR tablets and transdermal system (Catapress, Catapress patch, generic) and guanfacine IR (Tenex, generics) are designated UF in the Miscellaneous Anti-hypertensive Agents Drug Class.)

For the *wakefulness-promoting agents* class (16 for, 0 opposed, 1 abstain and 1 absent) that

modafinil (Provigil) and sodium oxybate (Xyrem) be retained on the UF and that armodafinil (Nuvigil) be designated NF.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS—PA CRITERIA

(Dr. Meade):

ADHD and Wakefulness-Promoting Agents Class – PA Criteria—The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) PA criteria should apply to modafinil (Provigil), armodafinil (Nuvigil), and sodium oxybate (Xyrem). The current PA criteria for modafinil (Provigil) were recommended to be continued without modification. The P&T Committee recommended maintaining the current PA criteria for Nuvigil, with one modification; jet lag would be added to the list of uses not provided. Additionally, the recommendation was that all current and new users of Nuvigil must undergo the PA process. The P&T Committee recommended PA criteria for sodium oxybate, which would be provided only for the current FDA-approved indications. Prior authorization is not intended to apply to modafinil (Provigil) or armodafinil (Nuvigil) use in active duty operational/readiness situations based on established protocols; MTFs should make necessary allowances for such use.

(Off script) **Dr. Meade:**

The full recommended PA criteria for the wakefulness-promoting drugs —provigil, nuvigil and Xyrem—are shown in a table on page 29 of the information handout and lists the coverage provided for the treatment of various indications as well as those for which coverage is not provided. Each of the indications was reviewed to make sure that the literature supports the use of the drug in those instances. In addition, there must first be a trial of provigil.

(PEC Script)

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS—IMPLEMENTATION PLAN

(Dr. Meade):

ADHD and Wakefulness-Promoting Agents – UF and PA Implementation Plan—
The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) an effective date of the first Wednesday after a 60-day implementation period in all points of service.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS —COMMITTEE PHYSICIAN'S PERSPECTIVE

Dr. Cieslak again provided the Panel with the Committee physician's perspective on this drug class review. He noted that the Committee looked at these drugs in three different categories: stimulants, non-stimulants and wakefulness-promoting drugs. As a pediatrician, he is very

familiar with the stimulants and non-stimulant drugs. In all of medicine, but especially in pediatrics, there are two factors that drive drug development. One concerns the dosing interval; physicians don't want to have the school nurse giving extra doses of medication during the school day, so the extended release formulations are especially important in pediatrics. The other concerns alternative formulations, particularly the inability of children to swallow tablets. Those considerations drove some of the P&T Committee's deliberations. Additionally, there are a lot of options in this class that raise situations could take away from prescribing pediatricians. With Concerta, for example, the analysis would lead one to conclude that it is not cost-effective but the Committee concluded that it should remain on the formulary as it is widely used in the MHS and its removal would have a huge disruptive effect on beneficiaries. Although the Committee recognized that the Daytrana patch, Vyvanse and Focalin XR were alternative formulations, they were very cost ineffective compared to other agents and there were a lot of options available.

There was no controversy with the non-stimulant ADSHD drugs. They are not as widely used as the stimulant drugs and the BIA revealed that there wouldn't be significant savings by making any of them NF. Consequently, all were left on the UF.

In the wakefulness-promoting category, there may some big news on the near-term horizon: generics are becoming available. One generic Provigil was approved this week, in fact.

The Committee's vote in all these categories was unanimous or near unanimous.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS —PANEL QUESTIONS AND COMMENTS

The Chair opened the floor for Panel questions.

Dr. Salom noted that the handout indicated that 90 percent of the prescriptions in the wakefulness-promoting drug category were for non-FDA-approved indications and asked how this affected the Prior Approval process. Dr. Meade said the PEC looked into the prescriptions in this category and could not find a diagnosis that would fall under one of the approved indications. The PEC looked at how much data they could find in the literature to support other uses, which is how the PA was put together.

Ms. LeGette asked about the changes from the straight PA that is being used now for Nuvigil and Xyrem, pointing out that, operationally, they will lead to prescription rejections. Ms. Fryar clarified that new users would have to try Provigil first before using either Nuvigil or Xyrem.

Dr. Cohoon commented that it would be helpful if, in the future, the handout material could indicate how the medication is to be taken.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS —PANEL VOTE ON UF RECOMMENDATION

Ms. Fryar read the P&T Committee's UF recommendations for the ADHDS/Wakefulness-Promoting agents drug class.

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, recommended the following:

Formulary Status. For the *stimulants,* that dextroamphetamine (Dexedrine, Dextrostat, Procentra solution, generics), methamphetamine HCl (Desoxyn, generic) methylphenidate CD (Metadate CD), methylphenidate IR (Ritalin, generic) methylphenidate LA (Ritalin LA, generic), methylphenidate ER (Metadate ER, Methylin ER, generics), methylphenidate chewable tablets, solution (Methylin, generic), methylphenidate OROS (Concerta), methylphenidate SR (Ritalin SR, generic) mixed amphetamine salts IR (Adderall, generic), and mixed amphetamine salts ER (Adderall XR, generic) be retained on the UF.

For the *non-stimulants,* that all non-stimulants, atomoxetine (Strattera), clonidine ER (Kapvay) and guanfacine ER (Intuniv) be retained on the UF.

For the *wakefulness-promoting agents,* that modafinil (Provigil) and sodium oxybate (Xyrem) be retained on the UF.

Non-Formulary Status. For the *stimulants,* that desmethylphenidate ER (Focalin XR), lisdexamphetamine (Vyvanse) and methylphenidate transdermal system (Daytrana) be designated NF.

For the *wakefulness-promoting agents* class that armodafinil (Nuvigil) be designated NF.

The Panel voted as follows:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

The Panel had no comments regarding this recommendation.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS —PANEL VOTE ON FORMULARY STATUS CHANGE

The Chair next read the Committee's recommendations for a UF status change.

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, recommended that dexmethylphenidate IR (Focalin, generic) be moved from NF status to UF status.

The Panel vote was:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

There were no comments on this recommendation.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-

PROMOTING AGENTS —PA CRITERIA

The Chair next called for a Panel vote on the Committee's PA criteria recommendations.

The P&T Committee recommended PA criteria should apply to modafinil (Provigil), armodafinil (Nuvigil), and sodium oxybate (Xyrem). The current PA criteria for modafinil (Provigil) were recommended to be continued without modification. The P&T Committee recommended maintaining the current PA criteria for Nuvigil, with one modification; jet lag would be added to the list of uses not provided. Additionally, the recommendation was that all current and new users of Nuvigil must undergo the PA process. The P&T Committee recommended PA criteria for sodium oxybate, which would be provided only for the current FDA-approved indications. Prior authorization is not intended to apply to modafinil (Provigil) or armodafinil (Nuvigil) use in active duty operational/readiness situations based on established protocols; MTFs should make necessary allowances for such use.

With regard to the existing PA criteria, with a prescription for Nuvigil there must first be a trial use of Provigil prior to using Nuvigil.

The Panel vote was as follows:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

There were no comments on this recommendation.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)/WAKEFULNESS-PROMOTING AGENTS —IMPLEMENTATION PLAN

Ms. Fryar read the P&T Committee's UF and PA Criteria implementation plan recommendations.

The P&T Committee recommended an effective date of the first Wednesday after a 60-day implementation period in all points of service.

The Panel voted:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

There were no comments on this recommendation.

III. REVIEW OF RECENTLY APPROVED U.S. FOOD AND DRUG ADMINISTRATION (FDA) AGENTS

(PEC Script)

OPHTHALMIC-1 CLASS—ALCAFTADINE OPHTHALMIC SOLUTION 0.25% (LASTACAFT)

OPHTHALMIC-1 CLASS—ALCAFTADINE OPHTHALMIC SOLUTION 0.25% (LASTACAFT)—RELATIVE CLINICAL EFFECTIVENESS

(LCDR Ojo):

Relative Clinical Effectiveness—The P&T Committee evaluated the relative clinical effectiveness of a newly approved Alcaftadine (Lastacaft), a dual action ophthalmic antihistamine/mast cell stabilizer. It is dosed once daily to prevent symptoms associated with allergic conjunctivitis (AC). The Ophthalmic-1 Class was evaluated for Uniform Formulary (UF) placement in February 2010.

There are no head-to-head trials with alcaftadine and the other dual action ophthalmic antihistamines. Alcafatidine was superior to placebo in preventing ocular itching associated with AC, but was not superior in relieving conjunctival redness. Alcaftadine's safety profile appears similar to the other ophthalmic antihistamines.

Table 4 on page 8 shows the drugs in the Ophthalmic-1 drug class. Figure 8 shows that Olopatadine 0.1% (Patanol) has the highest MSH utilization, followed by Olopatadine 0.2% (Pataday).

Lastacaft - Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) there is no evidence to suggest alcaftadine ophthalmic solution has a compelling clinical advantage over the other dual action agents for AC on the UF.

OPHTHALMIC-1 CLASS—ALCAFTADINE OPHTHALMIC SOLUTION 0.25% (LASTACAFT)—RELATIVE COST EFFECTIVENESS

(Dr. Meade)

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—Cost minimization analysis (CMA) was performed. The weighted average cost per day at all three points of service (POS) was evaluated for alcaftadine ophthalmic solution in relation to other currently available Ophthalmic-1 agents. Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (16 for, 0 opposed, 0 abstained, 2 absent) that alcaftadine ophthalmic solution was cost-effective when compared to other agents on the UF.

OPHTHALMIC-1 CLASS—ALCAFTADINE OPHTHALMIC SOLUTION 0.25% (LASTACAFT)—UF RECOMMENDATION

(Dr. Meade)

Lastacaft - UF Recommendation —Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (15 for, 0 opposed, 1abstained, 2 absent) alcaftadine ophthalmic 0.25% solution (Lastacaft) remain designated with formulary status on the UF

OPHTHALMIC-1 CLASS—ALCAFTADINE OPHTHALMIC SOLUTION 0.25% (LASTACAFT)—PHYSICIAN'S PERSPECTIVE

Dr. Cieslak informed the Panel that there are over a dozen similar agents on the UF already, but that the cost-effectiveness of this new drug was well within the range of those others and the Committee saw no reason to exclude it. Moreover, it's a once-daily dosing drug. The decision was not controversial.

OPHTHALMIC-1 CLASS—ALCAFTADINE OPHTHALMIC SOLUTION 0.25% (LASTACAFT)—PANEL QUESTIONS AND COMMENTS

The Panel had no questions of the presenters regarding this drug.

OPHTHALMIC-1 CLASS—ALCAFTADINE OPHTHALMIC SOLUTION 0.25% (LASTACAFT)—PANEL VOTE ON UF RECOMMENDATION

The Chair read the UF recommendation.

Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended alcaftadine ophthalmic 0.25% solution (Lastacaft) remain designated with formulary status on the UF.

The BAP vote was:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

The Panel offered no comments on this recommendation.

NARCOTIC ANALGESICS—TAPENTADOL EXTENDED RELEASE TABLETS (NUCYNTA ER)

(PEC Script)

NARCOTIC ANALGESICS—TAPENTADOL EXTENDED RELEASE TABLETS (NUCYNTA ER) —RELATIVE CLINICAL EFFECTIVENESS

(LCDR Ojo):

Relative Clinical Effectiveness—Tapentadol extended release (Nucynta ER) is an opioid analgesic with dual modes of action; it is a mu (pain) receptor agonist with norepinephrine reuptake inhibition properties. Tapentadol ER is a Schedule II narcotic, and is classified as a high potency analgesic in the Narcotic Analgesics Drug Class. The class was last reviewed for UF placement in February 2007. Tapentadol immediate release (IR) (Nucynta) was reviewed in November 2009 and is currently NF. Tapentadol ER is indicated for moderate to severe pain when continuous, around-the-clock opioid analgesia is needed chronically. In two trials, tapentadol ER demonstrated greater reductions in pain scores compared to placebo, and produced similar reductions in pain scores as oxycodone ER (Oxycontin).

The safety profile of tapentadol ER is typical of the other high potency long-acting opioids. The adrenergic (neurologic) properties of the drug create additional safety concerns with respect to serotonin syndrome (a constellation neurologic condition that includes increased heart rate, high blood pressure, twitching, and agitation) and interactions with monoamine oxidase inhibitors. When indirectly compared to oxycodone ER in clinical trials, the frequency of gastrointestinal (GI) adverse events (constipation, nausea, and vomiting) was observed less frequently in the Nucynta ER treatment groups. However, there were more central nervous system (CNS) disorders seen in the Nucynta ER groups.

Table 5 on page 9 shows the drugs in the Narcotic Analgesics drug class, specifically the High-potency single analgesic agents, Long-acting agents. Figure 9 shows that Oxycontin has the highest MSH utilization, followed by Fentanyl patches.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that tapentadol extended release (Nucynta ER) offers another long-acting, high-potency narcotic analgesic treatment option that may have less GI adverse events but more CNS adverse events than oxycodone ER. There is no evidence that pain control with tapentadol ER is superior to oxycodone ER.

NARCOTIC ANALGESICS—TAPENTADOL EXTENDED RELEASE TABLETS (NUCYNTA ER) —RELATIVE COST EFFECTIVENESS

(Dr. Meade)

Relative Cost-Effectiveness Analysis and Relative Cost-Effectiveness Conclusion—CMA was performed. Based on the results of the cost analysis and other clinical and cost considerations, the P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) that tapentadol ER (Nucynta ER) was more costly on an average weighted cost per day of therapy basis than several other comparators in the high potency narcotic analgesics currently on the UF, including generic morphine sulfate IR and fentanyl patches. Tapentadol ER was less costly than morphine sulfate ER (Avinza and Kadian), oxymorphone ER (Opana ER), oxycodone ER (OxyContin), and hydromorphone ER (Exalgo).

NARCOTIC ANALGESICS—TAPENTADOL EXTENDED RELEASE TABLETS (NUCYNTA ER) —UF RECOMMENDATION

(Dr. Meade)

Nucynta ER: UF Recommendation—Taking into consideration the conclusions from the relative clinical effectiveness and relative cost-effectiveness determinations, and other relevant factors, the P&T Committee, based upon its collective professional judgment, recommended (9 for, 8 opposed, 1 abstained, 0 absent) tapentadol extended release (Nucynta ER) remain formulary on the UF. UF status was designated due to the potential for decreased GI intolerance as compared to oxycodone ER, despite the concerns of potential undesirable drug interactions due to norepinephrine reuptake inhibition properties.

NARCOTIC ANALGESICS—TAPENTADOL EXTENDED RELEASE TABLETS (NUCYNTA ER) —PHYSICIAN'S PERSPECTIVE

Dr. Cieslak began by saying this was a tough one. The 9-8 vote was the closest he has ever seen in his years of participation on the Committee. The deciding factor for the majority was the increased possibility of decreased GI intolerance. Several clinicians on the Committee thought that offered an advantage that should be included on the formulary. However, it was by no means the most cost-effective drug in this class; generics are far more cost-effective. Neither is it the least cost-effective drug in this class; several drugs already on the UF are less cost-effective than this one. Some consternation also was expressed that the committee was approving the extended release version of the drug while keeping the immediate release version off of the formulary. This may also have led to some dissenting votes.

NARCOTIC ANALGESICS—TAPENTADOL EXTENDED RELEASE TABLETS (NUCYNTA ER) —PANEL QUESTIONS AND COMMENTS

Ms. Fryar opened the floor for questions by the BAP.

Dr. Crum noted that over the years he has seen lots of narcotics come and go. He asked what the potential is for misuse and diversion of this drug. Dr. Meade answered that it is probably no greater or less than any other of these products.

Ms. LeGette noted that there are now several generics and quite a few sustained release products in this class and asked if there would be an opportunity to re-review the whole class soon. Dr. Meade acknowledged that there are a large number of products in this class on the UF and said there probably would be an opportunity to review the class as a whole with a view to limiting the products on the UF quite soon. The PEC will be looking at this during the summer.

Dr. Cohoon asked whether any thought had been given to adding a PA on this medication. Dr. Meade said that the Committee didn't consider a PA for this particular drug. They would prefer to do it as a class.

Ms. Fryar commented that one of the concerns she has is the potential for GI bleeding. Dr. Meade replied that with this particular drug class, constipation and nausea can be a big problem. This drug helps eliminate some of that. Although it doesn't do it completely, it does better than the other agents. He said there was a long discussion about the IR versus the ER being available.

NARCOTIC ANALGESICS—TAPENTADOL EXTENDED RELEASE TABLETS (NUCYNTA ER) —PANEL VOTE ON UF RECOMMENDATION

Ms. Fryar read the P&T Committee's UF recommendation for Nucynta ER.

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, recommended tapentadol extended release (Nucynta ER) remain formulary on the UF. UF status was designated due to the potential for decreased GI intolerance as compared to oxycodone ER, despite the concerns of potential undesirable drug interactions due to norepinephrine reuptake inhibition properties.

The Panel voted as follows:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

The Panel offered no comments on this recommendation.

Ms. Fryar then asked for the presentation on the next set of recommendations.

IV. UTILIZATION MANAGEMENT

(PEC Script)

(Dr. Meade)

This is really a new area of utilization management that we haven't talked about before. It has three drugs related to FDA tests.

Crizotinib (Xalkori)—PA: Crizotinib (Xalkori) is an oral anaplastic lymphoma kinase (ALK) inhibitor indicated for the treatment of patients with ALK-positive non-small cell lung cancer (NSCLC) as detected by a FDA-approved diagnostic test. The FDA has approved a new molecular diagnostic test (Vysis ALK FISH Probe test) designed to identify ALK-positive NSCLC patients for treatment with Xalkori. The P&T Committee recommended the following PA criteria should apply to Xalkori capsules, consistent with the FDA-approved product labeling:

a) Coverage would be approved for the treatment of patients with documented diagnosis of ALK-positive NSCLC, detected by a FDA- approved test such as Vysis ALK FISH Probe test.

Vermurafenib (Zelboraf)—PA: Vermurafenib (Zelboraf) is an oral kinase inhibitor indicated for the treatment of patients with inoperable or metastatic melanoma with $BRAF^{v600E}$ mutation. Zelboraf is not recommended for use in wild-type BRAF melanoma. The FDA also approved a new molecular diagnostic test (to identify patients likely to respond to Zelboraf therapy. The P&T Committee recommended the following PA criteria should apply to Zelboraf tablets, consistent with the FDA-approved product labeling.

a) Coverage will be approved for the treatment of patients with documented diagnosis of unresectable or metastatic melanoma with $BRAF^{v600E}$ mutation, detected by a FDA-approved test such as Cobas 4800.

b) Coverage will not be approved for patients with wild-type BRAF melanoma.

Ivacaftor (Kalydeco)—PA: Ivacaftor (Kalydeco) is a new oral agent that targets a specific subgroup of patients with Cystic Fibrosis (CF). Kalydeco is indicated for the treatment of CF in patients aged 6 years of age and older who have a G551D mutation in the CFTR gene. This rare mutation occurs in about 4% of CF patients. In patients for whom the genotype is unknown, a FDA-approved test should be used to detect the presence of this mutation. Kalydeco is not effective in patients with the mutation, which occurs in about 90% of CF patients. There are several FDA-approved in-vitro molecular diagnostic tests designed to simultaneously detect and identify mutations in the CFTR gene. The P&T Committee recommended the following PA criteria should apply to Kalydeco tablets, consistent with the FDA-approved product labeling:

a) Coverage will be approved for the treatment of CF patients aged 6 years and older who have a G551D mutation in the CFTR gene, detected by a FDA-approved test.

b) Coverage will not be approved for patients who are homozygous for the F508del mutation in the CFTR gene.

PA IMPLEMENTATION PERIOD FOR XALKORI, ZELBORAF, AND KALYDECO—The P&T Committee recommended (16 for, 0 opposed, 1 abstain, 1 absent) an effective date of the first Wednesday after a 30-day implementation period in all points of service.

XALKORI, ZELBORAF, AND KALYDECO —PHYSICIAN'S PERSPECTIVE

Dr. Cieslak said that these drugs are fascinating in that they relate to genetic medicine which will someday create designer drugs for each individual's genome. This is the vanguard of that line of thinking. We are now at the point of specific genetic therapy specific to an individual's own genome. The idea is that patients have to have these specific tests performed and will have to be found to have a specific genetic mutation before they would be a candidate for any of these drugs. That's the good news. The bad news is that they are very expensive; the cystic fibrosis one is $65,000 a month. Under these conditions, very few people will be candidates for these drugs. He said he is optimistic that the cost of these things will come down.

XALKORI, ZELBORAF, AND KALYDECO —PANEL QUESTIONS AND COMMENTS

The Chair opened the floor for questions.

Dr. Crum asked about the potential for inappropriate use of these drugs. Dr. Meade replied that the MHS has no real indication of any potential for inappropriate use. Dr. Cieslak said he would have a hard time imagining there might be inappropriate use, especially since an individual; would have to have the specific gene mutation in order to get the drug. He used the cystic fibrosis disorder as an example and said that one in 1,600 Caucasians has it but the patients with this specific mutation are a tiny minority of the overall cystic fibrosis population. The MHS isn't going to release the drug unless the patient has the specific genetic mutation. Dr. Crum said he was thinking that a prior authorization requirement might be unnecessary in this case.

Dr. Salom said he disagrees. He doesn't believe it would be appropriate to require a trial use under these circumstances, especially given the high cost, and would support the approach in the recommendation. He said right now we are seeing what drugs work in a small, specific number of cases. He thinks what we are going to be seeing in the future is what drugs don't work. He cited codeine as an example, where it doesn't work on one in seven Caucasians. This means that large trials will reveal where drugs don't work.

Dr. Cohoon asked whether we are taking steps to ensure that if, down the road, we discover that the drug does work for something else we are not waiting for an FDA approval. She also asked if all the FDA-approved tests are covered by TRICARE.

Dr. Buchta said that these tests are not FDA approved; they are approved under CLIA—the Clinical Amendment Act and are not TRICARE approved. As these drugs come down the pike they are excluded under TRICARE coverage if the tests for them are not FDA approved.

PANEL VOTE ON PA FOR XALKORI

The Chair read the recommendation.

Crizotinib (Xalkori) is an oral anaplastic lymphoma kinase (ALK) inhibitor indicated for the treatment of patients with ALK-positive non-small cell lung cancer (NSCLC) as detected by a FDA-approved diagnostic test. The FDA has approved a new molecular diagnostic test (Vysis ALK FISH Probe test) designed to identify ALK-positive NSCLC patients for treatment with Xalkori. The P&T Committee recommended the following PA criteria should apply to Xalkori capsules, consistent with the FDA-approved product labeling:

> Coverage would be approved for the treatment of patients with documented diagnosis of ALK-positive NSCLC, detected by a FDA- approved test such as Vysis ALK FISH Probe test.

The Panel voted:

Concur: 6 Non-concur: 1 Abstain: 0 Absent: 0

The non-concurring vote commented that this PA isn't necessary.

PANEL VOTE ON PA FOR ZELBORAF

Ms. Fryar next read the recommendation for Zelboraf.

Vermurafenib (Zelboraf) is an oral kinase inhibitor indicated for the treatment of patients with inoperable or metastatic melanoma with $BRAF^{v600E}$ mutation. Zelboraf is not recommended for use in wild-type BRAF melanoma. The FDA also approved a new molecular diagnostic test (to identify patients likely to respond to Zelboraf therapy. The P&T Committee recommended the following PA criteria should apply to Zelboraf tablets, consistent with the FDA-approved product labeling.

a) Coverage will be approved for the treatment of patients with documented diagnosis of unresectable or metastatic melanoma with $BRAF^{v600E}$ mutation, detected by a FDA-approved test such as Cobas 4800.

b) Coverage will not be approved for patients with wild-type BRAF melanoma.

The Panel vote was:

Concur: 6 Non-concur: 1 Abstain: 0 Absent: 0

The non-concurring vote again commented that this PA isn't necessary.

PANEL VOTE ON PA FOR KALYDECO

Ivacaftor (Kalydeco) is a new oral agent that targets a specific subgroup of patients with Cystic Fibrosis (CF). Kalydeco is indicated for the treatment of CF in patients aged 6 years of age and older who have a G551D mutation in the CFTR gene. This rare mutation occurs in about 4% of CF patients. In patients for whom the genotype is unknown, a FDA-approved test should be used to detect the presence of this mutation. Kalydeco is not effective in patients with the mutation, which occurs in about 90% of CF patients. There are several FDA-approved in-vitro molecular diagnostic tests designed to simultaneously detect and identify mutations in the CFTR gene. The P&T Committee recommended the following PA criteria should apply to Kalydeco tablets, consistent with the FDA-approved product labeling:

a) Coverage will be approved for the treatment of CF patients aged 6 years and older who have a G551D mutation in the CFTR gene, detected by a FDA-approved test.

b) Coverage will not be approved for patients who are homozygous for the F508del mutation in the CFTR gene.

The Panel voted:

Concur: 6 Non-concur: 1 Abstain: 0 Absent: 0

The non-concurring vote commented that this PA isn't necessary.

PANEL VOTE ON PA IMPLEMENTATION PERIOD FOR XALKORI, ZELBORAF, AND KALYDECO

The Chair read the implementation plan recommendation.

The P&T Committee recommended an effective date of the first Wednesday after a 30-day implementation period in all points of service.

The Panel vote was:

Concur: 7 Non-concur: 0 Abstain: 0 Absent: 0

There were no Panel comments.

CLOSING COMMENTS

With the agenda completed, Ms. Fryar thanked the presenters for their briefing and thanked the audience for taking the time to come out.

She next summarized the Chairman's report for the past year of BAP activities. Noting that the Panel held four public meetings last year, she indicate that the majority of the time the BAP agree d with the Uniform Formulary recommendations, practically 100% of the time it concurred with Prior Authorization criteria and almost 100% of the time it concurred with the recommended implementation plan. She also thanked all of the support staff and Dr. Dave Meade for organizing the presentations. Ms. Fryar noted that special efforts have been made during the past year to solicit beneficiary input. The efforts of the TRICARE pharmacy benefit process were noted in the May 2011 Consumer Reports article where TRICARE received a 92% rating from consumers. The Panel asks that efforts to educate beneficiaries continue to be a top priority. Although the process for educating beneficiaries has been improved, the Panel asks that this process be continued. One example of improvement has been the inclusion of formulary information and the BAP process in the TRICARE Beneficiary newsletter that is published quarterly and mailed to each DoD household. The Chairs asks that this type of information regarding the Pharmacy benefit and potential future changes with co-pays continue to go out to all DoD households. Furthermore it is essential that efforts to educate the consumers about the benefits of the pharmacy mail order continue.

Ms. Fryar closed by thanking each of the Panel members for the time they devote to the process and for all their dedicated work. She indicated that the next scheduled public meeting of the Panel is June 21, 2012.

CDR Lawrence, the DFO, closed the meeting at 10:50 A.M.

Deborah Fryar

Ms. Deborah Fryar
Chairperson

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 commonly used as acronyms in Panel discussions 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.

- AC—Allergic Conjunctivitis
- ACS — Acute Coronary Syndrome
- ADHD—Attention Deficit Hyperactivity Disorder
- AE — Adverse event
- AHRQ — Agency for Healthcare Research and Quality
- ALK—Anaplastic Lymphoma Kinase inhibitor
- APR — Automated Profile Review
- BAP — Uniform Formulary Beneficiary Advisory Panel (the "Panel" referred to above)
- BCF — Basic Core Formulary
- BIA — Budget Impact Analysis
- CABG—Coronary Artery Bypass Grafting
- CEA — Cost-effectiveness analysis
- CF—Cystic Fibrosis
- CFR — Code of Federal Regulations
- CMA — Cost-Minimization Analysis
- CNS—Central Nervous System
- CPG — Clinical Practice Guideline
- CR — Controlled Release (a drug formulation)
- CV—Cardiovascular
- DFO — Designated Federal Officer
- DoD — Department of Defense
- DPP-4—Dipeptidyl Peptidase-4 inhibitors (A drug class)
- 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
- GI—Gastrointestinal
- HRQoL—Health-related quality of life
- IR — Immediate Release (a drug formulation)
- MHS — Military Health System
- MI—Myocardial Infarction
- MN — Medical Necessity

- NSCLC—Non-Small Cell Lung Cancer
- MTF — Military Treatment Facility
- NF — Non-formulary
- NIH — National Institutes of Health
- OTC — Over the counter
- PA — Prior Authorization
- PAD—Peripheral Arterial Disease
- PAH — Pulmonary Arterial Hypertension
- P&T Committee — DoD Pharmacy and Therapeutics Committee
- PCI—Percutaneous Coronary Intervention
- PDTS — Pharmacy Data Transaction Service
- PEC — DoD Pharmacoeconomic Center
- PORT — Pharmacy Outcomes Research Team
- POS — Point of Service
- RCTs — Randomized Control Trials
- SR — Sustained release (a drug formulation)
- SU—Sulfonylurea
- TMA — TRICARE Management Activity
- TMOP — TRICARE Mail Order Pharmacy
- TPHARM — TRICARE Pharmacy Program
- TRRx — TRICARE Retail Pharmacy Program
- UF — DoD Uniform Formulary
- USC — United States Code
- VA — U.S. Department of Veterans Affairs