5 October 2010

Executive Summary

UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL COMMENTS
23 September 2010

The Uniform Formulary (UF) Beneficiary Advisory Panel (BAP) commented on the recommendations from the DoD Pharmacy & Therapeutics (P&T) Committee August 2010 meeting.

1. **RENIN ANGIOTENSIN ANTIHYPERTENSIVES (RAAs) INCLUDE ANGIOTENSIN RECEPTER BLOCKERS (ARBs), ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIs), DIRECT RENIN INHIBITORs (DRIs) and FIXED DOSE COMBINATIONS of ARBS, ACEIs, and DRIs:** The P&T Committee recommended the following:

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:

a) Losartan (generic Cozaar), losartan/HCTZ (generic Hyzaar), Micardis, and Micardis HCT, remain classified as formulary on the UF, and that Twynsta, Diovan, Diovan HCT, Exforge and Exforge HCT be designated formulary on the UF. Prior authorization (PA) for the RAAs drug class would require a trial of one of these step-preferred drugs for new patients (15 for, 0 opposed, 1 abstained, 0 absent);

b) Tekturna, Tekturna HCT, Atacand, Atacand HCT, Teveten, Teveten HCT, Avapro, Avalide, Benicar, Benicar HCT, Azor, and Valtuna, be designated formulary on the UF (non-preferred) (15 for, 0 opposed, 1 abstained, 0 absent);

c) benazepril, benazepril HCTZ, benazepril/amlodipine, captopril, captopril HCTZ, enalapril, enalapril HCTZ, fosinopril, fosinopril HCTZ, lisinopril, lisinopril HCTZ, quinapril, quinapril HCTZ, ramipril, and trandolapril remain formulary on the UP (15 for, 0 opposed, 1 abstained, 0 absent);

d) The following four ACEs previously designated NF on the UP are now available in cost effective generic formulations and will be designated formulary on the UP: moexipril (Univasc), moexipril HCTZ (Uniretic), perindopril (Aceon), and trandolaprill/verapamil (Tarka) (15 for, 0 opposed, 1 abstained, 0 absent).

e) As a result of the above recommendations, there are no RAAs designated as non-formulary on the UF.

Summary of Panel Vote/Comments:

Dr. Casull commented that the step therapy procedure seems very complicated for patients receiving new prescriptions. He said he understands that the system has to grandfather current users but asked why, for new users, we aren't considering the generic ACEs and ACE

combinations. He thinks that would make more sense. He also thinks that should be automated and would like to hear a discussion about whether that might be a problem. The second preference would be for generic ARBs and their combination and that, too, should be automated. Then everything else would be under a Prior Authorization review.

Dr. Kugler agreed that it has become more difficult, intellectually, but thinks that is a good thing and the recommendations give clinicians the flexibility to deal with the different requirements of different patients appropriately. Dr. Allerman added that the current guideline is to not recommend combination products at first. Dr. Meade said that what Dr. Casull was suggesting would have been absolutely appropriate five years ago. Now, however, there are projections for the ARBs going generic that are significant. Diovan, which is heavily used, is expected to go generic very soon. After analysis of the bids, it turned out that the scenario recommended is the most cost-effective for the MHS. Eight different scenarios were reviewed, but several could not be operationalized effectively. The goal was to make sure that the beneficiary would be able to walk away from the pharmacy with something.

Dr. Salom agreed that the recommendation does not provide for true step therapy. Step therapy would be more restrictive than the recommendation. He would recommend that people start with ACEs before they start with ARBs because of potential adverse reactions. He also agreed that the ACEs and ARBs are all equivalent within their class and that ARBs and ACEs are also probably equivalent. Given the fact that the ARBs are going generic sooner, he would start people on step therapy that would lead to a generic ARB. He objects to the use of combination drugs as first-step products and particularly not a triple drug combination, which he doesn't think should be UF at all. He would prefer to see a true step-therapy process.

Mr. Hutchings and Ms. LeGette asked for clarification on what the operational issue is. Dr. Meade said the concern was with follow-up with patients who enter into step therapy. The system wants to make sure that it has something in place to provide for follow-up.

Dr. Salom asked if there are other drug classes where combination drugs have been put forth for first-line therapy. Ms. LeGette suggested Vytorin and Simvastatin. Dr. Salom agreed that there are people who present with indications that would lead a physician to start with two drugs, but he just can't support the idea of starting a patient on a combination drug, especially where there are mechanisms for step therapy.

Mr. Hutchings wondered if maybe the parent ARB contract might be the reason why the combination scenarios turn out to be cheaper. Dr. Meade replied that the scenarios were constructed to make sure that at least one combination drug was included.

Dr. Schlaifer said she, too, was surprised to see so many drugs included on the first step. She noted that people maybe equating a drug being on the first step as being recommended. She pointed out that just because it's allowed first doesn't mean that it's recommended first. The two concepts shouldn't be confused.

Dr. Casull suggested that the generic ACEs and combinations should be considered when the clinician does the annual review, as opposed at the point of sale. That would allow a seamless

process for the beneficiary. But he doesn't want to minimize the other issue, which is what we should be doing if we're going to be doing true step therapy.

Ms. LeGette said she is still confused about the operational issue. To her, it seems more disruptive to have a beneficiary hit with a step therapy process.

Dr. Meade noted, without going into specifics, that there are some anomalies in the bid process that impact the cost-effectiveness scenarios. These stem from how the various companies want to position their products. There are ISO-degree differences.

Dr. Crum indicated he is inclined to support the recommendation. Although not all of the recommendations reflect commercial best practices, he recognizes that many of the driving factors are based on information that the Panel isn't privy to.

Dr. Casull said he still would like to see the ACEs preferred to the recommended ARBs and would like to see that the combination products require a review.

- Without further discussion the Panel voted as follows: Concur: 7 Non-concur: 3 Abstain: 0 Absent: 1 regarding the recommendation for formulary agents.
    - Dr. Casull commented that his non-concur vote was based on disagreement with the recommendations regarding which agents would be listed as preferred. His view is that the ACEs should be in the same class as the ARBs and the combination agents, especially the three drug combination, should not be preferred.
    - Dr. Salom concurred with these comments.
    - Dr. Schlaifer said she non-concurred because she doesn't agree with the step therapy. She believes that should be taken off
    - Mr. Hutchings said he agrees with all the dissenting comments even though he voted to concur. His concern is that cost considerations took priority in making the recommendations and he believes that clinical outcomes should be first and foremost in importance.

- Without further discussion the Panel voted as follows: Concur: 7 Non-concur: 3 Abstain: 0 Absent: 1 regarding the Prior Authorization (PA) criteria recommendation.
    - The panel members indicated that the reasons given for non-concurring with the UF recommendations also apply to the PA recommendations.

- The Panel voted as follows: Concur: 10 Non-concur: 0 Abstain: 0 Absent 1 regarding the implementation period of 60 days.

- Mr. Hutchings commented that he absolutely agrees in every single way with the people who non-concurred even though he voted for the recommendations because of what goes on behind the scenes. He expressed concern as to whether the comments and concerns of the Panel are taken into account when the decisions are made.

- Ms. Fryar explained again that the Panel is required to vote on the recommendations presented to it by the P&T Committee. It is free to non-concur and add comments, which are provided to the decision maker (Dr. Taylor) and, she assured the Panel, are looked at and taken into consideration. However, the Panel does not have the ability to change the recommendations.

- The DFO also assured the Panel that the complete minutes of both the P&T Committee meeting and the BAP meeting are provided to Dr. Taylor along with any comments. Additionally, someone representing the BAP is at the discussion and can discuss any comments and concerns raised by the Panel.

- Mr. Hutchings said he doesn't want to leave the impression that only three people agree with the comments. He believes it would be more than that. His vote to concur was based solely on the belief that there is something he is not seeing that went on contractually behind the scenes. But if it weren't for that, he would change his vote to "non concur" based on his agreements with the views and comments of other Panel members.

- Dr. Salom noted that the Panel has to vote based on the information that is given to it.

- Dr. Schlaifer added a comment that she is disappointed in the way that the designations "preferred" and "non-preferred" are being used in relation to the formulary. She said it doesn't make a lot of sense to her. It isn't so much that she has problems with the drugs themselves, it is the concept she objects to.

- Dr. Meade explained that the concept has to do with what drugs are kept in stock at the MTFs. If something is put on formulary, it will be available at the MTFs. If it's not on formulary, it isn't supposed to be available. The goal is to have a robust formulary for the providers and the beneficiaries. The "preferred" designation simply indicates to all where the system wants them to go in order to be most cost-effective. He also said that when the changes are sent out, it is accompanied by documentation. The Panel's points can be included in that documentation.

- Dr. Casull asked about whether the MTF commander has the opportunity to divert funds saved in their pharmacy operations to other uses. Dr. Meade replied that commanders can't divert pharmacy funds to other uses.

- Mr. Chavez commented that, as a beneficiary, he appreciates the process.

Director, TMA:

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

11/10/2010

2. **OPTHALMIC 1-s FOR ALLERGIC CONJUNCTIVITIS:** The P&T Committee recommended the following:

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:

a) Antihistamines and Dual Action AH/MCS: azelastine (Optivar, generics), bepotastine (Bepreve), emedastine (Emadine), epinastine (Elestat), olopatadine 0.1 % (Patanol), and olopatadine 0.2% (Pataday) remain designated formulary on the UF;

b) Mast Cell Stabilizers: cromolyn (generic), lodoxamide (Alomide), nedocromil (Alocril), and pemirolast (Alamast) remain designated formulary on the UF;

c) Ophthalmic-l NSAIDs: bromfenac 0.09% (Xibrom), diclofenac 0.1% (Voltaren, generic), flurbiprofen 0.03% (Ocufen, generic), ketorolac 0.4% (Acular IS, generic), ketorolac 0.45% (Acuvail), ketorolac 0.5% (Acular, generic), and nepafenac 0.1% (Nevanac) remain designated formulary on the UF.

Summary of Panel Vote/Comments:

Ms. Fryar thanked the P&T Committee for considering the beneficiaries when reviewing this drug class and not just automatically placing drugs on the non-formulary.

Dr. Salom noted that figure 5 on page 6 of the handout, which shows a big jump in the use of Keterolac 0.45 % (Acuvail) and a decrease in Keterolac 0.4 % (Acular LS generic). He asked if the PEC knew the reason for this. Dr. Meade pointed out that the Acuvail came out shortly before the Acular went generic. Other than that, he doesn't know why the Acuvail went up so much higher.

Mr. Hutchings said that years ago a drug went generic and caused problems, so now ophthalmologists are hypersensitive to drugs going generic. Consequently, as soon as Acular went generic, ophthalmologists switched completely to Acuvail. He then asked about the differences between the subclasses. Dr. Meade explained that many of the agents are not used chronically.

- The Panel voted as follows: Concur: 10 Non-concur: 0 Abstain: 0 Absent: 1
  - o One BAP member commented for the record that annual expenditures for this drug class are $19 million. In a commercial setting, the only choice offered would be generic products. Nothing else would be there. However, with the ophthalmologists voting the way they do, he understands leaving that situation the way it is.

- Mr. Hutchings asked about another drug. Dr Allerman said that one is now gone and is only available locally.

***Director, TMA*:**

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

11/10/2010

Uniform Formulary Beneficiary Advisory Panel (BAP)

Meeting Summary
September 23, 2010
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
- Brian Casull, Medical Professional, TriWest Healthcare Alliance.
- Santiago Chavez, Association of Military Surgeons of the United States, representing The Military Coalition
- John Crum, Medical Professional, Humana Military Healthcare Services, Inc.
- Rance Hutchings, Medical Professional, Uniformed Services Family Health Plan
- 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, Clinical Associate Professor, Mt. Sinai School of Medicine
- Marissa Schlaifer, Medical Professional, Academy of Managed Care Pharmacy

The meeting was held at the Naval Heritage Center Theater, 701 Pennsylvania Ave., N.W., Washington, D.C. LTC Stacia Spridgen, the Designated Federal Officer (DFO), called the proceedings to order at 8:30 A.M.

LTC Spridgen said the meeting of the Panel has been convened to review and comment on the recommendations of the Department of Defense (DoD) Pharmacy and Therapeutic (P&T) Committee meeting held August 11 and 12, 2010 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 classes:
  - Renin Angiotensin Antihypertensives (RAAs)
    - Angiotensin Receptor Blockers (ARBs)
    - Angiotensin Converting Enzyme (ACE) Inhibitors
    - Direct Renin Inhibitors (DRIs)
    - Fixed Dose Combinations of the ARBs, ACE Inhibitors, and DRIs
  - Opthalmic 1-s
    - Opthalmic Anthistimines

- Opthalmic dual action Antihistimines/Mast Cell Stabilizers
- Opthalmic Mast Cell Stabilizers
- Opthalmic Non-steroidal anti-inflammatory drugs (NSAIDs)

Opening Remarks

LTC Spridgen 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 are:

- 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 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, LTC Spridgen 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 20 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 that the minutes accurately reflect relevant facts, regulations or policy.

LTC Spridgen then noted the housekeeping considerations pertaining to the meeting.

Private Citizen Comments

The DFO opened the meeting for private citizen comments. No individuals signed up in advance and there were no individuals present at the meeting who wished to address the Panel.

Chairperson's Opening Remarks

The BAP Chair, Ms. Fryar, thanked people for coming and participating in today's meeting and turned the podium back to the PEC staff for the presentations.

DRUG CLASS REVIEW PRESENTATIONS

Dr. Meade gave a brief opening statement in which he noted that the agenda for today's meeting does not have very many items for presentation and discussion. He did indicate, however, that the agenda for the next meeting in January would be very full.

[PEC Script]

(Dave Meade): I'm Dave Meade, Director of Clinical Operations at the Pharmacoeconomic Center Director and a retired Air Force Lieutenant Colonel pharmacist. Joining me today from the PEC are Angela Allerman, one of the PEC clinical pharmacists, and Lieutenant Colonel Cindy Lee, the Air Force Pharmacy Consultant to the PEC. Also with us today is Dr. John Kugler, the chairman of the P&T Committee, who will provide the physician perspective and comment on the recommendations made by the Committee.

The DoD Pharmacoeconomic Center (PEC) supports the DoD P&T Committee by conducting the relative (relative meaning in comparison to the other agents defined in the same class)

clinical-effectiveness analyses and relative cost-effectiveness analyses of drug classes under review and consideration by the DoD P&T Committee for the Uniform Formulary (UF).

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 general overview of the relative cost-effectiveness analyses. This overview will be general in nature since we are unable to disclose the actual costs used in the economic models. This overview will include the factors used to evaluate the costs of the agents in relation to the safety, effectiveness, and clinical outcomes.
3) The DoD P&T Committee's Uniform Formulary recommendation based upon its collective professional judgment when considering the analyses from both the relative clinical and relative cost-effectiveness evaluations of two Uniform Formulary drug classed – the Renin Angiotensin Antihypertensive Drugs, and the Ophthalmic 1 drugs for allergic conjunctivitis.
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 9. 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.

Dr. Allerman will now start with the relative clinical effectiveness evaluations for the drugs reviewed by the DoD P&T Committee.

(Angela Allerman:) *We'll now discuss our first UF drug class review.*

I. RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs)

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — RELATIVE CLINICAL EFFECTIVENESS

(PEC Script) Angela Allerman

The P&T Committee evaluated the relative clinical effectiveness of the Renin Angiotensin Antihypertensives (or RAAs) drug class. Please turn to Table 1 on page 2 of the handout, where you'll see the table of the 40 drugs in the class. The class is comprised of the Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARBs), the Direct Renin Inhibitors, and their fixed-dose combination products with hydrochlorothiazide (HCTZ), calcium channel blocker, or other RAAs. All the drugs in the RAAs class are FDA-

approved for treating hypertension.

The ARBs were previously reviewed by the P&T Committee in May 2007 and February 2005; the ACE Inhibitors were previously reviewed in August 2005; and the fixed-dose combination ACE Inhibitor/CCB products were previously reviewed in February 2006. The clinical review included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

In terms of overall Military Health System (MHS) expenditures, the RAAs class is ranked within the top 5 most costly MHS drug classes, with expenditures exceeding $300 million annually.

If you turn to page 3 of the handout, and look at Figure 1, you'll see that the ACE Inhibitors have the highest utilization in the Military Health System, at 58% of the market share, followed by the ARBs at 36%, and then the fixed dose combination products, which comprise 6% of the market share for the RAAs. Figure 2 on page 3 shows the utilization of the ARBs and the Direct Renin Inhibitors, plus their combinations with the diuretic HCTZ. Losartan (Cozaar) and its HCTZ combination (Hyzaar) have the highest utilization in the MHS. Generic formulations of Cozaar were launched in April 2010; none of the other ARBs are off-patent. Telmisartan (Micardis) and valsartan (Diovan) have the 2nd and 3rd highest MHS utilizaiton.

Figure 3 on page 4 of the handout shows the utilization of the RAAs combinations with the calcium channel blocker amlodipine (Norvasc). The ACE inhibitor/CCB amolodipine combination benazepril/amolodipine (Lotrel and generics) have the highest utilization of this subclass, followed by valsartan/amlodipine (Exforge). We didn't show the utilization of the ACE inhibitors, since they are all available as generic products, however, generic lisinopril is number 1 in terms of prescriptions dispensed.

Relative Clinical Effectiveness Conclusion — The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) the following conclusions for the RAAs:

1. For treating hypertension, the ARBs reduce blood pressure to a similar degree. At maximum recommended doses, they reduce systolic blood pressure by 8 mm mercury, and reduce diastolic blood pressure by 5 mm mercury.
2. The ACE inhibitors, ARBs, and the DRI Tekturna reduce BP to a similar degree, based on the conclusions from two systematic reviews.
3. Adding the diuretic HCTZ increases the BP-lowering effect. The current Joint National Committee (JNC) 7 hypertension guidelines recommend multidrug regimens include a thiazide diuretic (e.g., HCTZ).
4. Hypertension studies show that the fixed dose combination drugs produce significantly greater BP reductions than their individual components. Additional benefits of combination products include potential increased patient compliance, and simplified medication regimens. Disadvantages include loss of flexibility for dosage initiation and titration.
5. All the ARBs are FDA-approved for treating hypertension; some of the ARBS have evidence for positive clinical outcomes in other conditions. Micardis is FDA-approved to reduce the risk of cardiovascular mortality and morbidity in patients who are at high risk for CV events and are intolerant of ACE inhibitors. Atacand and Diovan are FDA-approved in patients with chronic heart failure to

reduce the risk of death and hospitalization. Cozaar and Avapro are FDA-approved in patients with Type 2 diabetes and kidney disease to delay the progression to end-stage renal disease, doubling of serum creatinine, or death.

6. Although Cozaar is currently not FDA-approved for treating chronic heart failure, data from one trial reported Cozaar at a dose of 150 mg reduced the risk of death or hospitalization due to heart failure.

7. There are two unpublished studies with Benicar that evaluated clinical outcomes in type 2 diabetes. The first study (ORIENT) did not find a delayed progression to end-stage renal disease, doubling of serum creatinine, or death. The second trial (ROADMAP) did find a benefit in the surrogate outcome of delaying progression to microabluminuria, which is a marker for kidney disease. Benicar is only approved to treat hypertension.

8. The ACE inhibitor/calcium channel blocker drug benazepril/amlodipine (Lotrel) was superior to the ACE inhibitor/diuretic product benazepril/HCTZ (Lotensin HCT) in reducing of CV mortality and morbidity in high-risk hypertension patients (ACCOMPLISH trial). Lotrel is the only RAA/CCB combination product that has evidence for positive clinical outcomes, in addition to reducing BP.

9. There is no data to suggest that there are clinically relevant differences in the BP-lowering efficacy of the ARB/CCB combination products Azor, Twynsta, or Exforge. For adverse events, adding an ARB to the calcium channel blocker amlodipine results in a lower incidence of peripheral edema than that reported with CCB monotherapy.

10. Valsartan/amlodipine/HCTZ (Exforge HCT) is the first triple combination antihypertensive drug to obtain FDA approval. It is more effective at reducing BP than administering two antihypertensive drugs, but has a higher incidence of orthostatic hypotension and dizziness than two-drug regimens.

11. The direct renin inhibitor Tekturna reduces BP by suppressing plasma renin activity, which is a different mechanism than the ARBs or ACE inhibitors. Tekturna is effective at reducing BP, but the BP effects are similar to that achieved with the diuretics, ARBs, or ACE inhibitors. Tekturna is approved solely for treating hypertension; clinical outcomes trials are ongoing. Current JNC guidelines do not address the place in therapy for the DRIs. The adverse event profile for Tekturna appears similar to the ARBs.

12. Adding HCTZ to Tekturna reduces blood pressure to a greater extent than Tekturna alone. The addition of HCTZ is consistent with JNC guidelines, due to the diuretic component. There is limited published information for aliskiren/HCTZ (Tekturna HCT).

13. Aliskiren/valsartan (Valturna) is the first DRI/ARB combination FDA-approved for hypertension; it provides another option for patients requiring multidrug antihypertensive regimens. However, there are only limited published studies available; it is approved solely for treating hypertension, and the benefits of dual RAA inhibition are debatable, due to an increased risk of adverse events.

14. All of the ACE inhibitors, with the exception of Univasc, have evidence for positive clinical outcomes (e.g., decreased risk of major CV events or death in high-CV risk patients, those with heart failure, in patients with Type 2 diabetic renal disease, or in the post-myocardial (MI) setting), in addition to lowering BP.
15. For the ARBs, it is unlikely that there are clinically relevant differences in their adverse event profiles. Clinical trials show similar adverse event rates as with placebo.
16. The FDA is evaluating the association of ARBs and an increased risk of cancer, which was reported in a recent meta-analysis (Sipahi, et al., Lancet Oncology 2010). The FDA maintains the benefits of ARBs currently outweigh their risk.
17. The FDA is evaluating the risk of increased CV death with Benicar reported in Type 2 DM patients from the ROADMAP and ORIENT trials. FDA is currently reviewing the data for Benicar and has not concluded that it increases the risk of death.
18. For the ACE inhibitors, the major adverse events are hyperkalemia, increased serum creatinine, and cough. One systematic review comparing the ARBs with the ACE inhibitors reported the overall incidence of ACE inhibitor-induced cough as ranging between 0%–23% (mean 10%).
19. A survey of Military Treatment Facility (MTF) providers regarding the place in therapy using RAAs for hypertension revealed the ACE inhibitors are considered first-line, the ARBs are second-line, and the DRIs are third-line. The majority of providers responded that ARBs are interchangeable for treating hypertension. Most respondents did not agree that FDC products were necessary to treat the majority of their hypertensive patients

COMMITTEE ACTION: The P&T Committee voted to accept the clinical effectiveness conclusion stated above.

LtCol Lee will now discuss the RAAs cost effectiveness conclusion, and Uniform Formulary and Automated Prior Authorization recommendations.

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — RELATIVE COST-EFFECTIVENESS

(PEC Script) (Lt. Col. Lee):

The P&T Committee evaluated the relative cost-effectiveness of the RAAs. Cost-minimization analyses (CMAs) and budget impact analyses (BIAs) were performed based on clinical findings that the efficacy, safety, tolerability, and other factors among the RAAs subclasses of ACE inhibitors, ARBs, DRIs, and combination products with HCTZ, CCBs, or other RAAs were similar with regard to treating hypertension. For the cost effectiveness analysis, the combination products were compared with their parent RAA. Products containing Tekturna were analyzed and incorporated into the CMA and BIA used to evaluate the ARB subclass.

Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

ACE Inhibitors and their combinations with HCTZ and/or CCBs: Because all ACE inhibitors are now available in generic formulations, comparisons were made against the ARBs, ARB/combinations, DRIs, and DRI/combinations in the form of an ACE inhibitor step-therapy model. BIA was used to assess the potential impact of cost scenarios where ACE inhibitors or their combination agents were designated as the step-preferred agents on the UF prior to filling a prescription for ARBs, DRIs, or their respective combination products. Cost scenarios evaluating the impact of designating ACE inhibitors or ACE inhibitors/combinations as BCF agents prior to the use of ARBs, DRIs, or their respective combinations were also considered. BIA results showed that requiring an ACE inhibitor prior to using any ARB, DRI, or their respective combinations would be cost effective. Due to existing prescribing practices in the MHS, the P&T Committee agreed that use of an ACE inhibitor as a required step-preferred therapy could not be operationalized in an Automated Prior Authorization (PA).

ARBs, ARB/combinations, DRIs, and DRI/combinations: BIA was used to assess the potential impact of cost scenarios where selected ARBs, ARB/combinations, DRIs, and DRI/combinations were designated as formulary or NF on the UF. Cost scenarios evaluating the impact of designating selected agents on the BCF were also considered. BIA results for the ARBs and DRIs showed the scenario placing losartan (generic Cozaar), losartan/HCTZ (generic Hyzaar), Micardis, Micardis HCT, Twynsta, Diovan, Diovan HCT, Exforge, and Exforge HCT as step-preferred agents, while placing all other ARBs, ARB/combinations, DRIs, and DRI/combinations on the UF was the most cost-effective scenario and operationally-appropriate choice.

Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 1 abstained, 0 absent) to accept the relative cost-effectiveness analysis of the RAAs

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — UNIFORM FORMULARY RECOMMENDATION

(PEC Script) (Lt. Col. Lee):

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:

a) Losartan (generic Cozaar), losartan/HCTZ (generic Hyzaar), Micardis, and Micardis HCT, remain classified as formulary on the UF, and that Twynsta, Diovan, Diovan HCT, Exforge and Exforge HCT be designated formulary on the UF. Prior authorization (PA) for the RAAs drug class would require a trial of one of these step-preferred drugs for new patients (15 for, 0 opposed, 1 abstained, 0 absent);

b) Tekturna, Tekturna HCT, Atacand, Atacand HCT, Teveten, Teveten HCT, Avapro, Avalide, Benicar, Benicar HCT, Azor, and Valturna, be designated formulary on the UF (non-preferred) (15 for, 0 opposed, 1 abstained, 0 absent);

c) benazepril, benazepril HCTZ, benazepril/amlodipine, captopril, captopril HCTZ, enalapril, enalapril HCTZ, fosinopril, fosinopril HCTZ, lisinopril, lisinopril HCTZ,

quinapril, quinapril HCTZ, ramipril, and trandolapril remain formulary on the UF (15 for, 0 opposed, 1 abstained, 0 absent);

d) The following four ACEs previously designated NF on the UF are now available in cost-effective generic formulations and will be designated formulary on the UF: moexipril (Univasc), moexipril HCTZ (Uniretic), perindopril (Aceon), and trandolapril/verapamil (Tarka) (15 for, 0 opposed, 1 abstained, 0 absent).

e) As a result of the above recommendations, there are no RAAs designated as non-formulary on the UF.

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — PRIOR AUHORIZAATION CRITERIA

(PEC Script) (Lt. Col. Lee):

The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 2 absent) the following PA criteria should apply to the non-preferred RAAs, aliskiren (Tekturna), aliskiren/HCTZ (Tekturna HCT), aliskiren/valsartan (Valturna), candesartan (Atacand), candesartan/HCTZ (Atacand HCT), eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), and olmesartan/amlodipine (Azor). Coverage would be approved if the patient met any of the following criteria:

II. Automated PA criteria:

(1) The patient has received a prescription for losartan, losartan/HCTZ, telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT) telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), or valsartan/amlodipine/HCTZ (Exforge HCT) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

b) Manual (paper) PA criteria, if automated criteria are not met:

(1) The patient has tried one of the preferred RAAs and was unable to tolerate treatment due to adverse effects.

(2) The patient has tried one of the preferred RAAs and has had an inadequate response.

(3) The patient has a contraindication to the preferred RAAs, which is not expected to occur with the non-preferred RAAs (e.g., history of angioedema).

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — UNIFORM FORMULARY IMPLEMENTATION PLAN

(PEC Script) (Lt. Col. Lee):

The P&T Committee recommended (13 for, 0 opposed, 1 abstained, 2 absent) an effective date after the minutes are signed corresponding to a 60-day implementation period in all points of service.

(Lt. Col. Lee): Dr. Kugler will now give the physician perspective for the RAAs.

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — PHYSICIAN PERSPECTIVE

Dr. Kugler noted that none of the agents reviewed in this class were recommended for non-formulary placement. The Committee recognized that having a wide array of antihypertension drugs available is desirable. The Committee did recommend the use of prior authorization as a means of steering patients to the preferred drugs in this class: losartan, micardis and diovan, which has now become the preferred ARB. The recommendations also include the combinations of these preferred drugs, such as losartan/HCTz and valsartan/amlodipine/HCTZ) to increase compliance where appropriate. He also noted that role of Direct Renin Inhibitors is still unclear but he expects the JNC report in 2011 to clarify that situation.

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — BAP QUESTIONS AND DISCUSSION

Dr. Casull commented that the step therapy procedure seems very complicated for patients receiving new prescriptions. He said he understands that the system has to grandfather current users but asked why, for new users, we aren't considering the generic ACEs and ACE combinations. He thinks that would make more sense. He also thinks that should be automated and would like to hear a discussion about whether that might be a problem. The second preference would be for generic ARBs and their combination and that, too, should be automated. Then everything else would be under a Prior Authorization review.

Dr. Kugler agreed that it has become more difficult, intellectually, but thinks that is a good thing and the recommendations give clinicians the flexibility to deal with the different requirements of different patients appropriately. Dr. Allerman added that the current guideline is to not recommend combination products at first. Dr. Meade said that what Dr. Casull was suggesting would have been absolutely appropriate five years ago. Now, however, there are projections for the ARBs going generic that are significant. Diovan, which is heavily used, is expected to go generic very soon. After analysis of the bids, it turned out that the scenario recommended is the most cost-effective for the MHS. Eight different scenarios were reviewed, but several could not be operationalized effectively. The goal was to make sure that the beneficiary would be able to walk away from the pharmacy with something.

Dr. Salom agreed that the recommendation does not provide for true step therapy. Step therapy would be more restrictive than the recommendation. He would recommend that people start with ACEs before they start with ARBs because of potential adverse reactions. He also agreed that the ACEs and ARBs are all equivalent within their class and that ARBs and ACEs are also probably equivalent. Given the fact that the ARBs are going generic sooner, he would start people on step therapy that would lead to a generic ARB. He objects to the use of combination drugs as first-step products and particularly not a triple drug combination, which he doesn't think

should be UF at all. He would prefer to see a true step-therapy process.

Mr. Hutchings and Ms. LeGette asked for clarification on what the operational issue is. Dr. Meade said the concern was with follow-up with patients who enter into step therapy. The system wants to make sure that it has something in place to provide for follow-up.

Dr. Salom asked if there are other drug classes where combination drugs have been put forth for first-line therapy. Ms. LeGette suggested Vytorin and Simvastatin. Dr. Salom agreed that there are people who present with indications that would lead a physician to start with two drugs, but he just can't support the idea of starting a patient on a combination drug, especially where there are mechanisms for step therapy.

Mr. Hutchings wondered if maybe the parent ARB contract might be the reason why the combination scenarios turn out to be cheaper. Dr. Meade replied that the scenarios were constructed to make sure that at least one combination drug was included.

Dr. Schlaifer said she, too, was surprised to see so many drugs included on the first step. She noted that people maybe equating a drug being on the first step as being recommended. She pointed out that just because it's allowed first doesn't mean that it's recommended first. The two concepts shouldn't be confused.

Dr. Casull suggested that the generic ACEs and combinations should be considered when the clinician does the annual review, as opposed at the point of sale. That would allow a seamless process for the beneficiary. But he doesn't want to minimize the other issue, which is what we should be doing if we're going to be doing true step therapy.

Ms. LeGette said she is still confused about the operational issue. To her, it seems more disruptive to have a beneficiary hit with a step therapy process.

Dr. Meade noted, without going into specifics, that there are some anomalies in the bid process that impact the cost-effectiveness scenarios. These stem from how the various companies want to position their products. There are 180-degree differences.

Dr. Crum indicated he is inclined to support the recommendation. Although not all of the recommendations reflect commercial best practices, he recognizes that many of the driving factors are based on information that the Panel isn't privy to.

Dr. Casull said he still would like to see the ACEs preferred to the recommended ARBs and would like to see that the combination products require a review.

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — BAP VOTE ON UF RECOMMENDATIONS

Ms. Fryar introduced the vote by noting that she would take a vote on the actual recommendations from the P&T Committee. Members may provide comments after the vote regarding their concurrence or non-concurrence. She then read the P&T Committee's UF recommendations for the record.

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:

a) Losartan (generic Cozaar), losartan/HCTZ (generic Hyzaar), telmisartan (Micardis), and telmisartan/HCTZ (Micardis HCT), remain classified as formulary on the UF, and that telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge) and valsartan/amlodipine/HCTZ (Exforge HCT) be designated formulary on the UF. Prior authorization (PA) for the RAAs drug class would require a trial of one of these step-preferred drugs for new patients;

b) Aliskiren (Tekturna), aliskiren/HCTZ (Tekturna HCT), candesartan (Atacand), candesartan/HCTZ (Atacand HCT), eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), olmesartan/amlodipine (Azor), and valsartan/aliskiren (Valturna), be designated formulary on the UF (non-preferred);

c) benazepril, benazepril HCTZ, benazepril/amlodipine, captopril, captopril HCTZ, enalapril, enalapril HCTZ, fosinopril, fosinopril HCTZ, lisinopril, lisinopril HCTZ, quinapril, quinapril HCTZ, ramipril, and trandolapril remain formulary on the UF;

d) The following four ACEs previously designated NF on the UF are now available in cost-effective generic formulations and will be designated formulary on the UF: moexipril (Univasc), moexipril HCTZ (Uniretic), perindopril (Aceon), and trandolapril/verapamil (Tarka).

e) As a result of the above recommendations, there are no RAAs designated as non-formulary on the UF.

Without further discussion the Panel voted as follows:

Concur: 7 Non-concur: 3 Abstain: 0 Absent: 1

Panel Comments

Dr. Casull commented that his non-concur vote was based on disagreement with the recommendations regarding which agents would be listed as preferred. His view is that the ACEs should be in the same class as the ARBs and the combination agents, especially the three-drug combination, should not be preferred.

Dr. Salom concurred with these comments.

Dr. Schlaifer said she non-concurred because she doesn't agree with the step therapy. She believes that should be taken off.

Mr. Hutchings said he agrees with all the dissenting comments even though he voted to concur. His concern is that cost considerations took priority in making the recommendations and he believes that clinical outcomes should be first and foremost in importance.

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — BAP VOTE ON PRIOR AUTHORIZATION RECOMMENDATIONS

The Chair next opened the floor for questions and discussion about the Prior Authorization recommendations.

Dr. Schlaifer asked for confirmation that any beneficiaries already using the non-preferred agents would be grandfathered. The PEC staff indicated that her understanding is correct. Dr. Schlaifer expressed concern that she doesn't see that anywhere in the recommendation and asked whether it needs to be in writing. Dr. Meade said it is covered by the last sentence of the UF recommendation, i.e. "Prior Authorization (PA) for the RAAs drug class would require a trial of one of these step-preferred drugs for *new patients*."

The Chair read the P&T Committee's Prior Authorization recommendations:

The P&T Committee recommended the following PA criteria should apply to the non-preferred RAAs, aliskiren (Tekturna), aliskiren/HCTZ (Tekturna HCT), aliskiren/valsartan (Valturna), candesartan (Atacand), candesartan/HCTZ (Atacand HCT), eprosartan (Teveten), eprosartan/HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), and olmesartan/amlodipine (Azor). 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 losartan, losartan/HCTZ,telmisartan (Micardis), telmisartan/HCTZ (Micardis HCT) telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), or valsartan/amlodipine/HCTZ (Exforge HCT) at any MHS pharmacy point of service (MTFs, retail network pharmacies, or mail order) during the previous 180 days.

b. Manual (paper) PA criteria, if automated criteria are not met:

   (1) The patient has tried one of the preferred RAAs and was unable to tolerate treatment due to adverse effects.

   (2) The patient has tried one of the preferred RAAs and has had an inadequate response.

   (3) The patient has a contraindication to the preferred RAAs, which is not expected to occur with the non-preferred RAAs (e.g., history of angioedema).

Without further discussion the Panel voted as follows:

Concur: 7 Non-concur: 3 Abstain: 0 Absent: 1

Panel Comments

The panel members indicated that the reasons given for non-concurring with the UF recommendations also apply to the PA recommendations.

RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs) — BAP VOTE ON IMPLEMENTATION PLAN RECOMMENDATIONS

The Chair opened the floor for questions and discussion about the Prior Authorization recommendations. Dr. Casull said he believes this set of recommendations should be sent back

for reconsideration. He doesn't see how he can vote to implement something that he personally believes has so many issues that need to be dealt with.

Dr. Salom said he agrees with what Dr. Casull just said. This is a very widely-used class of drugs that is important to the beneficiaries.

Mr. Hutchings indicated that similar issues have come before the Panel in the past. The question to be voted on should be: "If this recommendation goes forward, do you agree with the implementation plan?" Even if we don't agree with the recommendation, the vote should indicate whether the implementation plan is adequate should MHS decide to implement it. Ms. Fryar, agreeing, clarified that the vote should be on the implementation plan recommendations in relation to the UF and PA recommendations from the P&T Committee.

The Chair read the P&T Committee's implementation plan recommendations:

The P&T Committee recommended an effective date after the minutes are signed corresponding to a 60-day implementation period in the retail network and mail order, and at MTFs no later than a 60-day implementation period.

Without further discussion the Panel voted as follows:

Concur: 10 Non-concur: 0 Abstain: 0 Absent: 1

Additional Panel Comments/Discussion

Mr. Hutchings commented that he absolutely agrees in every single way with the people who non-concurred even though he voted for the recommendations because of what goes on behind the scenes. He expressed concern as to whether the comments and concerns of the Panel are taken into account when the decisions are made.

Ms. Fryar explained again that the Panel is required to vote on the recommendations presented to it by the P&T Committee. It is free to non-concur and add comments, which are provided to the decision maker (Dr. Taylor) and, she assured the Panel, are looked at and taken into consideration. However, the Panel does not have the ability to change the recommendations.

The DFO also assured the Panel that the complete minutes of both the P&T Committee meeting and the BAP meeting are provided to Dr. Taylor along with any comments. Additionally, someone representing the BAP is at the discussion and can discuss any comments and concerns raised by the Panel.

Mr. Hutchings said he doesn't want to leave the impression that only three people agree with the comments. He believes it would be more than that. His vote to concur was based solely on the belief that there is something he is not seeing that went on contractually behind the scenes. But if it weren't for that, he would change his vote to "non concur" based on his agreements with the views and comments of other Panel members.

Dr. Salom noted that the Panel has to vote based on the information that is given to it.

Dr. Schlaifer added a comment that she is disappointed in the way that the designations "preferred" and "non-preferred" are being used in relation to the formulary. She said it doesn't make a lot of sense to her. It isn't so much that she has problems with the drugs themselves, it is the concept she objects to.

Dr. Meade explained that the concept has to do with what drugs are kept in stock at the MTFs. If something is put on formulary, it will be available at the MTFs. If it's not on formulary, it isn't supposed to be available. The goal is to have a robust formulary for the providers and the beneficiaries. The "preferred" designation simply indicates to all where the system wants them to go in order to be most cost-effective. He also said that when the changes are sent out, it is accompanied by documentation. The Panel's points can be included in that documentation.

Dr. Casull asked about whether the MTF commander has the opportunity to divert funds saved in their pharmacy operations to other uses. Dr. Meade replied that commanders can't divert pharmacy funds to other uses.

Mr. Chavez commented that, as a beneficiary, he appreciates the process.

Noting that there were no further comments, Ms. Fryar asked for the second drug class presentation.

(Angela Allerman): We'll now move on to our second Uniform Formulary Class Review

II. UNIFORM FORMULARY DRUG CLASS REVIEWS — OPTHALMIC 1-s FOR ALLERGIC CONJUNCTIVITIS

OPTHALMIC 1-s — RELATIVE CLINICAL EFFECTIVENESS

(PEC Script) Angela Allerman

The P&T Committee evaluated the relative clinical effectiveness of the agents in the Ophthalmic-1 drug class. Please turn to page 5 of the handout and look at table 2. You'll see that the class is comprised of four different subclasses: the ophthalmic antihistamines (AHs), mast cell stabilizers (MCS), dual action AH/MCS, and the nonsteroidal anti-inflammatory drugs (NSAIDs). The Ophthalmic-1s have not previously been reviewed for UF placement; all the drugs are currently designated with formulary status on the UF, and there are no BCF or NF drugs. The clinical review focused on use of the Ophthalmic-1s for allergic conjunctivitis and included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

Please turn to the figures on pages 6 and 7, where the utilization of the Ophthalmic-1s subclasses is shown. MHS expenditures for the Ophthalmic-1s exceed $19 million annually. Figure 4 on page 6 shows for the dual action antihistamine/mast cell stabilizers, olopatadine 0.1% (Patanol), which is dosed twice daily, has the highest utilization, followed by olopatadine 0.2% (Pataday), which is dosed once daily. Azelastine (Optivar) has the third highest utilization; generic formulations of Optivar are now available. Figure 5 shows the NSAID utilization. The newest formulation of ketorolac, the 0.45% concentration (Acuvail) has the highest utilization, followed

by Xibrom. Note that the utilization of ketorolac 0.4% concentration (Acular LS), which is now available in a generic, has decreased, since the Acuvail product became available. The ophthalmic mast cell stabilizer utilization is shown in figure 6 – generic cromolyn is the most widely prescribed mast cell stabilizer.

Relative Clinical Effectiveness Conclusion - The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 0 absent) the following clinical effectiveness conclusions for the Ophthalmic-1s:

1. The antihistamines provide relief of ocular itching, hyperemia, and edema, while Mast Cell Stabilizers have anti-inflammatory effects. The dual action antihistamine/mast cell stabilizer drugs exhibit both properties. MCS have a slower onset of action for providing relief of ocular symptoms than the dual action drugs (days to weeks, vs. minutes, respectively). NSAIDs relieve pain and reduce erythema.
2. With regard to FDA-approved indications, the dual action AH/MCS and the MCS are approved for treating allergic conjunctivitis. For the NSAIDs, ketorolac 0.5% (generic Acular) is approved for allergic conjunctivitis, and Xibrom has clinical trial data supporting use for allergic conjunctivitis, although it is not FDA-approved for this indication. The other NSAIDs are approved for use following ocular surgery.
3. With regard to place in therapy, professional guidelines from the American Academy of Ophthalmology and the American Optometric Association recommend use of the antihistamines or dual action agents as first-line therapy for relief of allergic conjunctivitis symptoms.
4. With regard to efficacy for the treatment of allergic conjunctivitis, the results of one meta-analysis reported (1) there was no significant difference between the AHs and MCS in terms of proportion of patients with perceived benefit; (2) there is insufficient evidence to demonstrate superiority of agents within each subclass; and (3) convenience of use, cost and patient preference should guide treatment choice.
5. For relief of ocular itching, there does not appear to be clinically relevant differences between the dual action AH/MCS and the MCS. There are no head-to-head trials comparing Bepreve with another Ophthalmic-1 agent.
6. With regard to safety and tolerability, published data does not suggest there are clinically relevant differences between the individual dual action dual action drugs and individual MCS concerning burning/stinging, headaches, taste perversion, and hyperemia. The overall adverse event rate is low.
7. Data from the product labeling reports the dual action drug Bepreve is associated with taste perversion in 25% of patients. The MCS, Alocril has an incidence of burning/stinging on instillation, plus taste perversion in 10%–30% of patients. The 0.5% concentration of ketorolac (Acular) is associated with burning/stinging in up to 40% of patients.
8. With regard to dosing frequency, olopatadine 0.2% (Pataday) is the only dual action AH/MCS that is dosed once daily; the other AH/MCS are dosed twice daily. For the MCS, nedocromil (Alocril) is dosed twice daily, while the others are dosed 4–6 times daily. The NSAID ketorolac 0.5% (Acular) is dosed four times daily for allergic conjunctivitis.

9. With regard to preservatives, it remains to be determined whether the presence of carboxymethylcellulose instead of benzalkonium chloride (BAK) in ketorolac 0.45% (Acuvail) or the reduced BAK concentration in bepotastine (Bepreve) are associated with a lower risk of adverse events.

Lt Col Lee will now discuss the Ophthalmic-1s cost effectiveness conclusion, and Uniform Formulary and Automated Prior Authorization recommendations.

OPTHALMIC 1-s — RELATIVE COST EFFECTIVENESS

(PEC Script) Lt Col Lee:

The P&T Committee evaluated the relative cost-effectiveness of the agents in the Ophthalmic-1 drug class used in the treatment of allergic conjunctivitis. CMAs and BIAs were performed based on clinical findings that the efficacy, safety, tolerability, and other factors among the Ophthalmic-1 subclasses were similar. Information considered by the P&T Committee included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(2).

Antihistamines and Dual Action AH/MCS: The antihistamine emedastine (Emadine) was analyzed with the dual action AH/MCS subclass. CMA results showed olopatadine 0.1% (Patanol) to be the most cost-effective agent for the treatment of AC, based on the cost per day of treatment. BIA was used to assess the potential impact of cost scenarios where Emedastine (Emadine) and/or dual action AH/MCS were designated formulary or NF on the UF. Cost scenarios evaluating the impact of designating agents on the BCF were also considered. BIA results from this analysis showed the most cost-effective scenario designated bepotastine (Bepreve) and epinastine (Elestat) NF on the UF, and the remaining dual action AH/MCS as formulary on the UF. Follow-up P&T Committee discussion considered the potential for MTF recapture of Bepreve and epinastine Elestat from the retail sector to recommend formulary status for all other antihistamines and dual action AH/MCS agents.

Dual Action Drugs Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (15 for, 0 opposed, 0 abstained, 1 absent) to accept the relative cost-effectiveness analysis of the Antihistamines and Dual Action AH/MCS subclasses.

Mast Cell Stabilizers: BIA was used to assess the potential impact of cost scenarios where selected MCS were designated formulary or NF on the UF. BIA results showed the most cost-effective scenario designated generic cromolyn 0.4% with formulary status on the UF, with all other MCS designated as NF on the UF. However, P&T Committee discussion recommended that all MCS should remain formulary on the UF because they are primarily prescribed by specialists and have low MHS low utilization.

Mast Cell Stabilizers Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the relative cost-effectiveness analysis of the Mast Cell Stabilizers subclass.

Ophthalmic-1 NSAIDs: BIA was used to assess the potential impact of cost scenarios where selected Ophthalmic-1 NSAIDs were designated formulary or NF on the UF. This subclass is more commonly used in the treatment of post-surgical procedures than in the treatment of AC. BIA results showed that the most cost-effective scenario designated all the Ophthalmic-1 NSAIDs formulary on the UF.

Ophthalmic-1 NSAIDs Relative Cost-Effectiveness Conclusion—The P&T Committee, based upon its collective professional judgment, voted (16 for, 0 opposed, 0 abstained, 0 absent) to accept the relative cost-effectiveness analysis of the Ophthalmic-1 NSAIDs subclass.

OPTHALMIC 1-s — UNIFORM FORMULARY RECOMMENDATIONS

(PEC Script) Lt Col Lee:

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:

a) **Antihistamines and Dual Action AH/MCS:** azelastine (Optivar, generics), bepotastine (Bepreve), emedastine (Emadine), epinastine (Elestat), olopatadine 0.1% (Patanol), and olopatadine 0.2% (Pataday) remain designated formulary on the UF (15 for, 0 opposed, 1 abstained, 0 absent);

b) **Mast Cell Stabilizers:** cromolyn (generic), lodoxamide (Alomide), nedocromil (Alocril), and pemirolast (Alamast) remain designated formulary on the UF (15 for, 0 opposed, 1 abstained, 0 absent);

c) **Ophthalmic-1 NSAIDs:** bromfenac 0.09% (Xibrom), diclofenac 0.1% (Voltaren, generic), flurbiprofen 0.03% (Ocufen, generic), ketorolac 0.4% (Acular LS, generic), ketorolac 0.45% (Acuvail), ketorolac 0.5% (Acular, generic), and nepafenac 0.1% (Nevanac) remain designated formulary on the UF (15 for, 0 opposed, 1 abstained, 0 absent).

OPTHALMIC 1-s — UNIFORM FORMULARY IMPLEMENTATION PLAN

(PEC Script) Lt Col Lee: This is not applicable, since no products were placed non-formulary.

(PEC Script) Lt Col Lee: Dr. Kugler will now give the physician perspective for the Opthalmic 1-s.

OPTHALMIC 1-s — COMMITTEE PHYSICIAN PERSPECTIVE

Dr. Kugler informed the BAP that there was no controversy on the P&T Committee for this class of medications. No products were made non-formulary.

OPTHALMIC 1-s — BAP QUESTIONS AND DISCUSSION

Ms. Fryar thanked the P&T Committee for considering the beneficiaries when reviewing this drug class and not just automatically placing drugs on the non-formulary.

Dr. Salom noted that figure 5 on page 6 of the handout, which shows a big jump in the use of Keterolac 0.45 % (Acuvail) and a decrease in Keterolac 0.4 % (Acular LS generic). He asked if the PEC knew the reason for this. Dr. Meade pointed out that the Acuvail came out shortly

before the Acular went generic. Other than that, he doesn't know why the Acuvail went up so much higher.

Mr. Hutchings said that years ago a drug went generic and caused problems, so now ophthalmologists are hypersensitive to drugs going generic. Consequently, as soon as Acular went generic, ophthalmologists switched completely to Acuvail. He then asked about the differences between the subclasses. Dr. Meade explained that many of the agents are not used chronically.

OPTHALMIC-1s — BAP VOTE ON UF RECOMMENDATIONS

Ms. Fryar next read the P&T Committee's UF recommendations for the ophthalmic-1s drug class, indicating again that the Panel should vote on the Committee's recommendations as presented but feel free to offer comments.

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:

a) **Antihistamines and Dual Action AH/MCS:** azelastine (Optivar, generics), bepotastine (Bepreve), emedastine (Emadine), epinastine (Elestat), olopatadine 0.1% (Patanol), and olopatadine 0.2% (Pataday) remain designated formulary on the UF;

b) **Mast Cell Stabilizers:** cromolyn (generic), lodoxamide (Alomide), nedocromil (Alocril), and pemirolast (Alamast) remain designated formulary on the UF;

c) **Ophthalmic-1 NSAIDs:** bromfenac 0.09% (Xibrom), diclofenac 0.1% (Voltaren, generic), flurbiprofen 0.03% (Ocufen, generic), ketorolac 0.4% (Acular LS, generic), ketorolac 0.45% (Acuvail), ketorolac 0.5% (Acular, generic), and nepafenac 0.1% (Nevanac) remain designated formulary on the UF.

Without further discussion the Panel voted as follows:

Concur: 10 Non-concur: 0 Abstain: 0 Absent: 1

Panel Comments

One BAP member commented for the record that annual expenditures for this drug class are $19 million. In a commercial setting, the only choice offered would be generic products. Nothing else would be there. However, with the ophthalmologists voting the way they do, he understands leaving that situation the way it is.

Mr. Hutchings asked about another drug. Dr Allerman said that one is now gone and is only available locally.

Closing Remarks

In closing, the Chair again thanked everybody for coming, for the high-quality presentations and for the lively discussion and good comments.

Adjournment

The DFO also thanked the presenters and the Panel then announced that the next meeting would be in January 2011, details to be announced.

She adjourned the meeting at 10:15 A.M.

Certified by: Deborah K. Fryar

Ms. Deborah Fryar
Chairperson, Uniform Formulary Beneficiary Advisory Panel

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.

- ACE — Angiotensin Converting Enzyme (a drug subclass)
- AE — Adverse event
- AH — Ophthalmic Anthistamines (a drug subclass)
- APR — Automated Profile Review
- ARB — Angiotensin Receptor Blocker (a drug subclass)
- BAP — Uniform Formulary Beneficiary Advisory Panel (the "Panel" referred to above)
- BCF — Basic Core Formulary
- BIA — Budget Impact Analysis
- BP — Blood pressure
- BPA — Blanket Purchase Agreement
- BPH — Benign Prostatic Hyperplasia
- CCB — Calcium Channel Blocker (a drug subclass)
- CEA — Cost-effectiveness analysis
- C.F.R — Code of Federal Regulations
- CHD — Coronary heart disease
- CMA — Cost-Minimization Analysis
- CR — Controlled Release (a drug formulation)
- CV — Cardiovascular
- DACON — Daily average consumption
- DEA — U.S. Drug Enforcement Administration
- DFO — Designated Federal Officer
- DoD — Department of Defense
- DRI — Direct Renin Inhibitors (a drug subclass)
- ECF — Extended Core Formulary
- ER — Extended Release (a drug formulation)
- ESI — Express-Scripts, Inc.
- FACA — Federal Advisory Committee Act
- FCP — Federal Ceiling Price
- FDA — U.S. Food and Drug Administration
- HCTZ — Hydrochlorothyazide
- HDL — High-density lipoprotein
- IR — Immediate Release (a drug formulation)
- IV — Intravenous

- MCS — Mast Cell Stabilizers (a drug subclass)
- MHS — Military Health System
- MN — Medical Necessity
- MTF — Military Treatment Facility
- NDAA — National Defense Authorization Act
- NF — Non-formulary
- NIH — National Institutes of Health
- NNH — Number Needed to Harm
- NNT — Number Needed to Treat
- NSAIDs — Non-Steroidal Inflammatory Drugs (a drug subclass)
- OTC — Over the counter
- PA — Prior Authorization
- P&T Committee — DOD Pharmacy and Therapeutics Committee
- PDTS — Pharmacy Data Transaction Service
- PEC — DOD Pharmacoeconomic Center
- PORT — Pharmacy Outcomes Research Team
- POS — Point of Service
- RAAs — Renin Angiotensin Antihypertensive agents (a drug class)
- RCTs — Randomized Control Trials
- SR — Sustained release (a drug formulation)
- SQ — Subcutaneously
- TMA — TRICARE Management Activity
- TMOP — TRICARE Mail Order Pharmacy
- TPHARM — TRICARE Pharmacy Program
- TRRx — TRICARE Retail Pharmacy Program
- UF — DOD Uniform Formulary
- U.S.C. — United States Code
- VA — U.S. Department of Veterans Affairs
- VARR — Voluntary Agreement on Retail Rebates