DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

INFORMATION FOR THE UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL

I. Uniform Formulary Review Process

Under 10 United States Code § 1074g, as implemented by 32 Code of Federal Regulations (CFR) 199.21, the DoD Pharmacy and Therapeutics (P&T) Committee is responsible for developing the Uniform Formulary (UF). Recommendations to the Director, TMA, on formulary status, pre-authorizations, and the effective date for a drug's change from formulary to nonformulary (NF) status receive comments from the Beneficiary Advisory Panel (BAP), which must be reviewed by the Director before making a final decision.

II. UNIFORM FORMULARY CLASS REVIEWS—RENIN ANGIOTENSIN ANTIHYPERTENSIVE AGENTS (RAAs)

P&T Comments

A. Renin Angiotensin Antihypertensive Agents—Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the RAAs drug class. The class is comprised of the Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARBs), the Direct Renin Inhibitors (DRIs), and their fixed-dose combination (FDC) products with hydrochlorothiazide (HCTZ), calcium channel blockers (CCBs), or other RAAs. The ARBs were previously reviewed by the P&T Committee in May 2007 and February 2005; 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).

The individual RAAs are listed below:

- **ACE Inhibitors:** benazepril (Lotensin, generic), benazepril/HCTZ (Lotensin HCT, generic), captopril (Capoten, generic), captopril/HCTZ (Capozide, generic), enalapril (Vasotec, generic), enalapril/HCTZ (Vasoretic, generic), fosinopril (Monopril, generic), fosinopril/HCTZ (Monopril HCT, generic), lisinopril (Prinvil, Zestril, generic), lisinopril HCT (Prinzide, Zestoretic, generic), moexipril (Univasc, generic), moexipril/HCTZ (Uniretic generic), perindopril (Aceon, generic), quinapril (Accupril, generic) quinapril/HCTZ (Accuretic, generic), trandolapril (Mavik, generic), and ramipril (Altace, generic)

- **ARBs:** candesartan (Atacand), candesartan/HCTZ (Atacand HCT), eprosartan, (Teveten), eprosartan/ HCTZ (Teveten HCT), irbesartan (Avapro), irbesartan/HCTZ (Avalide), losartan (Cozaar, generic), losartan/HCTZ (Hyzaar, generic), olmesartan (Benicar), olmesartan/HCTZ (Benicar HCT), telmisartan (Micardis), telmisartan/ HCTZ (Micardis HCT), valsartan (Diovan), and valsartan/HCTZ (Diovan HCT)
- **DRIs:** aliskiren (Tekturna), aliskiren/HCTZ (Tekturna HCT), and valsartan/aliskiren (Valturna)
- **Fixed-dose combinations:** (RAAs/CCBs): benazepril/amlodipine (Lotrel, generic), trandolapril/verapamil sustained release (SR) (Tarka, generic), olmesartan/amlodipine (Azor), telmisartan/amlodipine (Twynsta), valsartan/amlodipine (Exforge), and valsartan/amlodipine/HCTZ (Exforge HCT)

The current BCF products are lisinopril, lisinopril/HCTZ, ramipril, and benazepril/amlodipine. The NF agents include perindopril, moexipril +/- HCTZ, trandolapril/verapamil sustained release (SR), eprosartan +/- HCTZ, irbesartan +/- HCTZ, olmesartan +/- HCTZ, valsartan +/-HCTZ, olmesartan/amlodipine, telmisartan/amlodipine, valsartan/amlodipine, and aliskiren/valsartan. The remaining drugs are classified as UF drugs. Generic formulations are available for all the ACE inhibitors and the ACE inhibitor/diuretic products; generic formulations of losartan and losartan/HCTZ entered the market in April 2010. Generic formulations of candesartan, irbesartan, and valsartan are expected in 2012.

The RAAs class is ranked within the top 5 most costly Military Health System (MHS) drug classes, with expenditures exceeding $300 million annually. In terms of utilization, the ACE inhibitors comprise 58% of the RAAs market share, with the ARBs comprising 36%, and the fixed-dose combinations comprising 6%. For expenditures, the ARBs account for 66% of the annual MHS cost for the RAAs.

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

1. For treating hypertension, the results of one systematic review reported the ARBs reduce blood pressure (BP) to a similar degree; at maximum recommended doses, the average trough systolic blood pressure reduction is -8 mmHg and the average trough diastolic blood pressure reduction is -5 mmHg.
2. The ACE inhibitors, ARBs, and the DRI aliskiren (Tekturna) reduce BP to a similar degree, based on the conclusions from two systematic reviews.
3. The addition of HCTZ increases the BP-lowering efficacy of the RAAs. 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 FDC products produce significantly greater BP reductions than their individual components. Additional benefits of FDC products include potential enhanced medication compliance, increased patient compliance, and simplified medication regimens. Disadvantages include loss of flexibility for dosage initiation and titration.
5. All the ARBs are U.S. Food and Drug Administration (FDA)-approved for treating hypertension; some of the ARBS have shown evidence for positive clinical outcomes. Telmisartan (Micardis) is FDA-approved to reduce the risk of cardiovascular (CV) mortality and morbidity in patients who are at high risk for CV events and are intolerant of ACE inhibitors (ON-TARGET and TRANSCEND trials). Candesartan (Atacand) and valsartan (Diovan) are FDA-approved for reducing the risk of death and hospitalization in patients with chronic heart failure. Losartan (Cozaar, generic) and irbesartan (Avapro) are FDA-approved to reduce the risk of delaying progression to end-stage renal disease (ESRD), doubling of serum creatinine, or death in patients with Type 2 diabetes mellitus (DM).
6. Although losartan (Cozaar, generic) is currently not FDA-approved for treating chronic heart failure, data from one trial (HEAAL, Lancet 2010) reported losartan 150 mg reduced the risk of death or hospitalization due to heart failure.
7. One unpublished trial (ORIENT) with olmesartan in patients with Type 2 DM did not find a delayed progression to ESRD, doubling of serum creatinine, or death. Another unpublished trial (ROADMAP) evaluating olmesartan in Type 2 DM patients did find a benefit in the surrogate outcome of delaying progression to microabluminuria.
8. For the RAA/CCB products, benazepril/amlodipine (Lotrel, generic) was superior to benazepril/HCTZ (Lotensin HCT, generic) in reducing the composite of CV mortality and morbidity in patients with hypertension who are at high risk for CV events (ACCOMPLISH trial). Benazepril/ amlodipine is the only RAA/CCB FDC product with 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-reducing efficacy of the ARB/CCB FDC products olmesartan/ amlodipine (Azor), telmisartan/amlodipine (Twynsta), or valsartan/ amlodipine (Exforge). Adding an ARB to 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 FDC 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 DRI aliskiren (Tekturna) reduces BP by suppressing plasma renin activity, which is unique among the RAAs. Aliskiren is effective at reducing BP when used as monotherapy or in combination with other antihypertensive drugs, but the BP effects are similar to that achieved with the diuretics, ARBs, or ACE inhibitors. Aliskiren 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 aliskiren appears similar to the ARBs.
12. Adding HCTZ to aliskiren (Tekturna HCT) provides enhanced BP reduction and is consistent with JNC guidelines, due to the diuretic component. There is limited published information for aliskiren/HCTZ.
13. Aliskiren/valsartan (Valturna) is the first DRI/ARB that is 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. For the ACE inhibitors, with the exception of moexipril (Univasc, generics), evidence exists 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 olmesartan reported in Type 2 DM patients from the ROADMAP and ORIENT trials. FDA is currently reviewing the data for olmesartan 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. The DoD Pharmacy Outcomes Research Team (PORT) provided an analysis of RAAs MHS prescription data and reported that ARBs are initiated as first-line therapy in the majority of patients, instead of ACE inhibitors. Additionally, it does not appear that patients with comorbidities (chronic heart failure, DM, left ventricular hypertrophy, post-MI) are prescribed an ARB based on the evidence for positive outcomes data and hypertension.
20. 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.

B. Renin Angiotensin Antihypertensive Agents—Relative Cost-Effectiveness

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 FDC products with HCTZ, CCBs, or other RAAs were similar with regard to treating hypertension. For the cost effectiveness analysis, the FDC products were compared with their parent RAA. Products containing aliskiren 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 step 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, losartan/ HCTZ, telmisartan (Micardis), telmisartan/ HCTZ (Micardis HCT), telmisartan/amlodipine (Twynsta), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), valsartan/amlodipine (Exforge), and valsartan/amlodipine/ HCTZ (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.

C. Renin Angiotensin Antihypertensive Agents—Uniform Formulary 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:

a) losartan, losartan/HCTZ, 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 (15 for, 0 opposed, 1 abstained, 0 absent);

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) (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).

As a result of the above recommendations, there are no RAAs designated as nonformulary on the UF.

D. Renin Angiotensin Antihypertensive Agents—Prior Authorization Requirements

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:

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.

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).

E. Renin Angiotensin Antihypertensive Agents—Uniform Formulary Implementation Plan

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 the retail network and mail order, and at MTFs no later than a 60-day implementation period.

III. UNIFORM FORMULARY CLASS REVIEWS—RAAs

BAP Comments

A. Renin Angiotensin Antihypertensive Agents—Uniform Formulary 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:

a) losartan, losartan/HCTZ, 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).

As a result of the above recommendations, there are no RAAs designated as NF on the UF.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Renin Angiotensin Antihypertensive Agents—Prior Authorization Requirements

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:

b) 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.

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).

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

C. Renin Angiotensin Antihypertensive Agents—Uniform Formulary Implementation Plan

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 the retail network and mail order, and at MTFs no later than a 60-day implementation period.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

IV. UNIFORM FORMULARY CLASS REVIEWS—OPHTHALMIC-1s

P&T Comments

A. Ophthalmic-1s—Relative Clinical Effectiveness

The P&T Committee evaluated the relative clinical effectiveness of the agents in the Ophthalmic-1 drug class. The class is comprised of 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 (AC) and

included, but was not limited to, sources of information listed in 32 CFR 199.21(e)(1).

The individual Ophthalmic-1s are listed below:

- **Antihistamines:** emedastine (Emadine)
- **Dual Action Antihistamine/Mast Cell Stabilizers:** azelastine (Optivar, generics), bepotastine (Bepreve), epinastine (Elestat), olopatadine 0.1% (Patanol), and olopatadine 0.2% (Pataday)
- **Mast Cell Stabilizers:** pemirolast (Alamast), nedocromil (Alocril), cromolyn (Crolom/Opticrom, generic), and lodoxamide (Alomide)
- **Ophthalmic-1 NSAIDs:** ketorolac 0.4% (Acular LS, generic), ketorolac 0.45% (Acuvail), ketorolac 0.5% (Acular, generic), bromfenac (Xibrom), diclofenac (Voltaren, generic), flurbiprofen (Ocufen, generics), and nepafenac (Nevanac)

MHS expenditures for the Ophthalmic-1s exceed $19 million annually. In the MHS, olopatadine 0.2% (Patanol) is the highest utilized Ophthalmic-1 agent.

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. With regard to mechanism of action and pharmacokinetic properties, the antihistamines provide relief of ocular itching, hyperemia, and edema, while MCS have anti-inflammatory effects. The dual action AH/MCS exhibit both properties. MCS have a slower onset of action for providing relief of ocular symptoms than AH/MCS (days to weeks, vs. minutes, respectively). NSAIDs relieve pain and reduce erythema.
2. With regard to FDA-approved indications, dual action AH/MCS and the MCS are approved for treating AC. For the NSAIDs, ketorolac 0.5% (Acular, generic) is approved for AC, and clinical trial data supports use of bromfenac (Xibrom) for this indication.
3. With regard to place in therapy, professional guidelines from the American Academy of Ophthalmology and the American Optometric Association recommend use of AHs or AH/MCS as first-line topical therapy for relief of AC symptoms.
4. With regard to efficacy for the treatment of AC, the results of one meta-analysis reported the following: MCS and AHs are superior to placebo in relieving symptoms of AC; there is no significant difference between the AHs and MCS in terms of proportion of patients with perceived benefit; there is insufficient evidence to demonstrate

superiority of agents within each subclass; and convenience of use, cost and patient preference should guide treatment choice.

5. Interpretation of clinical efficacy differences between the individual dual action AH/MCS and individual MCS is difficult due to small patient enrollment, short-term treatment, use of single-dose studies, and acute course of symptoms. There are no head-to-head trials comparing bepotastine (Bepreve) with another Ophthalmic-1 agent. Overall, for relief of ocular itching, there does not appear to be clinically relevant differences between the dual action AH/MCS and the MCS.
6. With regard to safety and tolerability, published data does not suggest there are clinically relevant differences concerning burning/stinging, headaches, taste perversion, and hyperemia individual dual action AH/MCS and individual MCS in treating AC. The only published available meta-analysis did not assess adverse events, and the head-to-head trials were too small to determine clinically relevant differences individual dual action AH/MCS and individual MCS. The overall adverse event rate is low.
7. Data from the product labeling reports the dual action AH/MCS bepotastine (Bepreve) is associated with taste perversion in 25% of patients. For the MCS, nedocromil (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 other MCS are dosed 4–6 times daily. The NSAID ketorolac 0.5% (Acular) is dosed four times daily for AC.
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.

A request for input from MTF providers revealed that the majority of responders ranked olopatadine 0.2% (Patanol) as the preferred Ophthalmic-1 agent to treat AC and olopatadine 0.1% (Pataday) as the second preference. The majority of responders chose cromolyn (Crolom/Opticrom, generic) as the preferred MCS, and ketorolac 0.5% (Acular, generic) as the preferred NSAID for treating AC.

B. Ophthalmic-1s—Relative Cost-Effectiveness

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 cromolyn 0.4% (generic) 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.

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.

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.

C. Ophthalmic-1s—Uniform Formulary 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:

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).

D. Ophthalmic-1s—Uniform Formulary Recommendation – not applicable

V. UNIFORM FORMULARY CLASS REVIEWS—OPHTHALMIC-1s

BAP Comments

A. Ophthalmic-1s—Uniform Formulary 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:

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.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissentions:

B. Ophthalmic-1s—Uniform Formulary Implementation Plan – Not applicable (no drugs designated as non formulary)