Department of Defense
Pharmacoeconomic Center

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MCCS-GPE **14 November 2001**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1600 hours on 14 November 2001 at the Uniformed Services University of the Health Sciences. The DoD P&T Executive Council is responsible for performing certain inherently governmental functions relevant to the DoD pharmacy benefits program. The Council focuses primarily on issues related to the Basic Core Formulary (BCF), national pharmaceutical contracts, and blanket purchase agreements. The DoD P&T Executive Council is comprised of federal employees who are members of the DoD P&T Committee.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL John R. Downs, MC	Air Force
COL Bill Sykora, MC	Air Force
LtCol (select) George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
COL Mike Heath, MS (representing MAJ Brett Kelly)	Army
COL Rosa Stith, MC	Army
LTC (P) Joel Schmidt, MC	Army
CAPT Chuck Bruner	Coast Guard
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board

MEMBERS ABSENT

Dick Rooney	Department of Veterans Affairs

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
COL Ardis Meier, BSC	Air Force Pharmacy Consultant
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LTC Deborah Bostock, MC	Air Force
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Maria Ionescu	Pharmacy Benefits Division, TMA
MAJ Barb Roach, MC (by teleconference)	DoD Pharmacoeconomic Center
Howard Altschwager	Deputy General Counsel, TMA
Dave Bretzke	DoD Pharmacoeconomic Center
Michael McGregory	Pharmacy Student, Butler University Pharm.D. Program
Shirif Mitry	Pharmacy Student, TMA
Shana Trice	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia

3. REVIEW MINUTES OF LAST MEETING / ADMINISTRATIVE ISSUES

The Council approved the minutes of the last meeting with two corrections:

- The reference to seborrheic keratoses on Page 15 of the Aug 01 DoD P&T Executive Council minutes was changed to actinic keratoses.
- The prescription data in Table 2 on Page 3 of the Aug 01 DoD P&T Executive Council minutes are incorrect. The corrected table is shown below:

Table 2: Prescription fills for COX-2 Inhibitors and Traditional NSAIDs in the MHS, July 2001

	MTF prescriptions	MCSC retail network prescriptions	NMOP prescriptions	Total
COX-2 inhibitors	45,201 (15%)	40,106 (59%)	12,824 (74%)	98,131 (26%)
Traditional NSAIDs	252,134 (85%)	27,857 (41%)	4,480 (26%)	284,471 (74%)
Total	297,335	67,963	17,304	382,602

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4. ADVANCES IN MEDICAL PRACTICE (AMP) PROGRAM

According to prime vendor data, Military Treatment Facilities (MTFs) spent $46.5 million on AMP drugs in FY 2001. Prime vendor data are incomplete for 44 MTFs in the second half of FY 01, so MTFs actually spent more than $46.5 million on AMP drugs during FY 01.

5. SUBCOMMITTEE REPORT: OBTAINING INPUT FROM PROVIDERS

COL Downs reported how the VA uses the Medical Advisory Panel (MAP) and the regionally based formulary management process in the 22 Veterans Integrated Service Networks (VISNs) to systematically obtain input from providers on formulary and contracting issues. The Council noted that most TRICARE regions have not established a regional formulary management process. LCDR Briski reported a lack of consensus among pharmacy officers regarding methods to obtain prescriber input. Some pharmacy officers favor communicating through lead agents, while others favor military service lines of communication.

LtCol (select) George Jones noted that actions of the DoD P&T Committee are a standing agenda item for his local P&T committee, which prompts input and communication. He suggested that MTF P&T Committees should routinely include DoD P&T Committee actions on their meeting agendas. He also noted that the PEC website provides access to DoD P&T Committee documents. (The PEC website is available at www.pec.ha.osd.mil.)

The Council decided to obtain prescriber input primarily by having the PEC communicate with the chairs of MTF and/or regional P&T committees and MTF pharmacy chiefs. The Council did not reach a definitive conclusion regarding the process that will be used to accomplish this type of communication. However, there was support voiced for including lead agent pharmacists and medical directors as integral parts of the process. The PEC agreed to present various process options at the next meeting.

6. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAs)

A. *Contract awards, renewals, and terminations*

- As of November 2001, 54 joint VA/DoD and 3 DoD-only contracts for drugs or pharmaceutical supplies are in effect. A joint VA/DoD returned goods contract is also in effect. Information on national pharmaceutical contracts, including NDC numbers and prices, is available on the DSCP website (www.dmmonline.com).
- Contracts for terazosin, acyclovir, hydroxyurea, pentoxifylline, rifampin, sucralfate, nortriptyline, prazosin, diltiazem XR, ranitidine, insulin, verapamil, and albuterol inhalers were renewed.
- The cimetidine contract was extended until May 02.
- Contracts for cerivastatin, amoxicillin, azathioprine, and omeprazole were cancelled.
- New contracts were awarded for cyclobenzaprine tablets, isosorbide dinitrate tablets, loperamide capsules, methocarbamol tablets, verapamil immediate release tablets, and lactulose syrup.

B. *Financial impact of contracts* – COL Remund reported on the percent reduction in cost per unit for drugs covered by national pharmaceutical contracts (see Table 1).

Table 1: Percent Reduction in Cost per Unit for Drugs Covered by National Pharmaceutical Contracts*

Drug/Drug Class	% Reduction
Diltiazem extended release	48%
Lisinopril	45%
PPIs	36%
Non-sedating antihistamines	36%
Statins	31%
All contracts	33%

*From start dates of contracts to 30 Sep 2001

C. *Status of Contracting Initiative for Leutinizing Hormone Releasing Hormone (LHRH) agonists* – CAPT Torkildson reported that the joint VA/DoD contracting action to select a LHRH agonist for the Basic Core Formulary (BCF) (for the treatment of prostate cancer only) is awaiting completion of updates to the VA clinical review. The VA extended its contract for Zoladex until early 2002 in preparation for a joint VA/DoD contracting initiative. The DoD Blanket Purchase Agreements (BPAs) for Lupron and Zoladex remain in place. The BPA for Zoladex has been modified since the last meeting to remove the market share requirement and to extend the expiration date of the BPA until 30 April 2002. The Lupron BPA has also been modified to maintain the current price until 30 April 2002.

D. *Non-sedating antihistamine contract* – The market share for fexofenadine (as a percent of all prescriptions for non-sedating antihistamines dispensed at MTF pharmacies) increased from 50% prior to the contract to approximately 89% by the end of October 2001. The prescription market shares for fexofenadine and loratadine continue to remain stable in the retail pharmacy networks and the National Mail Order Pharmacy (NMOP), indicating that MTFs are maximizing the use of fexofenadine without shifting loratadine prescriptions into the retail pharmacy network or NMOP. The average cost per non-sedating antihistamine tablet/capsule purchased by MTFs dropped by 36%, from $0.87 (pre-contract) to $0.56 (as of Sep 2001).

E. *Statin Contract* – The Council considered two options regarding the renewal of the simvastatin contract:

Option 1: Renew the simvastatin contract for the final option year (February 2002 to February 2003). The statin class remains "closed" on the BCF. Simvastatin is the only statin on MTF and NMOP formularies.

Option 2: Do not renew the simvastatin contract. The statin class would be "open" on the BCF. MTFs may have additional statins on formulary. DoD P&T Committee decides which statins are on the NMOP formulary.

The Council assessed the relative safety/tolerability of statins; effectiveness in reducing LDL-cholesterol; evidence of effect on cardiovascular morbidity and mortality; ability of simvastatin to meet the clinical needs of the DoD beneficiary population; current statin

costs; likelihood of future price reductions for simvastatin, input from providers; and potential collaboration with the VA on the statin class in the future.

The Council concluded that:

- Simvastatin has a well-established safety and tolerability profile.
- Simvastatin is proven to reduce cardiovascular morbidity and mortality.
- Simvastatin is currently used by > 95% of statin patients at MTFs.
- Non-contracted statins can be provided through the special order process for patients who need them.
- Simvastatin is more cost-effective than other statins in treating patients to LDL goal.
- The cost per dose of statin therapy has decreased by 31% at MTF pharmacies in the first two years of the statin contract. Additional reductions in the cost per dose are more likely to occur if the contract is renewed than if it is not renewed.
- The VA strategy for managing statins is linked to renewal of the DoD statin contract.
- Contract renewal will facilitate joint management of statins by DoD and VA.

The Council decided to advise DSCP to renew the contract for simvastatin.

F. *Status of contracting initiative for nasal corticosteroid inhalers* –The Council reviewed an updated analysis of aqueous nasal corticosteroid dosing frequency and input from providers to assess whether or not flunisolide should be included in a solicitation for a closed class contract.

- An analysis of MTF prescription data from Jun 00 to May 01 showed the following percentages of patients who were treated with a single daily dose of an aqueous nasal corticosteroid:

fluticasone	93.7%
mometasone	93.7%
beclomethasone 84mcg	91.9%
triamcinolone	85.5%
budesonide	60.0%
flunisolide	27.2%

- DoD providers report a higher rate of burning and stinging with flunisolide than with other nasal corticosteroid products.

The Council concluded that flunisolide should not be included in the solicitation because it is dosed more than once daily much more frequently than other products and because providers have reported tolerability problems. The Council concluded that budesonide should not be included in the solicitation because it is dosed more than once daily much more frequently than other products. The Council also recommended that:

- The contract should not apply to use of aqueous nasal steroids in patients under 6 years of age. While it is not known whether the nasal corticosteroids differ significantly in their potential to affect the growth and development of pediatric patients, the Council prefers to allow MTFs to select an alternate agent for this patient

population if they so desire. The PEC estimates that less than 4% of all aqueous nasal steroid inhaler prescriptions are for patients who are under 6 years of age, so exclusion of this patient population will not have a negative impact on the contract.

- The contract should specify that all new patient starts must use the contracted agent, but should not dictate that existing patients be switched to the contracted agent.

The Council reiterated its support for a joint VA/DoD solicitation if agreement can be reached on the products that are included in the solicitation. If agreement cannot be reached, the Council recommends that DoD pursue its own contract.

G. *Potential contracting initiative for carbamazepine* – Multiple AB-rated generic products are available for commonly used strengths of carbamazepine. MTF usage of carbamazepine has declined about 20% over the past two years to a current usage rate of 700,000 tablets/month. MTFs spent about $1.5 million on carbamazepine during FY 01 ($1.4 million for the brand name product (Tegretol) and $0.1 million for generic products). The average cost is currently $0.22/tablet for Tegretol and $0.05/tablet for generic carbamazepine.

   Generic versions of carbamazepine currently account for about 20% of total carbamazepine usage at MTFs (up from 5% two years ago). In light of the large cost difference between the brand and generic versions of carbamazepine, the Council asked the PEC to investigate why the usage of the brand name drug continues to predominate at MTFs.

H. *Potential contracting initiative for triptans* – In the absence of information that negates concerns about variability in patient response, the Council is unwilling to support a closed class contract for a single oral triptan. The Council asked the PEC to continue to explore potential contracting initiatives for this drug class.

I. *Potential contracting initiative for angiotensin receptor blockers (ARBs)* – MTF utilization and expenditures for the ARBs are rising, and clinical information concerning these agents is evolving. The PEC is collaborating with the VA Pharmacy Benefits Management Strategic Healthcare Group (VA PBM) on a class review of the ARBs. The Council asked the PEC to continue to work with the VA to complete the class review and explore the feasibility of contracting initiatives in this drug class.

J. *Contracting initiative for fluoroquinolones* – Independent class reviews completed by the VA PBM and the PEC concluded that gatifloxacin (Tequin) and levofloxacin (Levaquin) offer advantages over the other fluoroquinolones in safety and tolerability (side effect and drug interaction profiles), expanded gram-positive spectrum of activity, and once daily dosing. Both reviews concluded that levofloxacin and gatifloxacin are the only two fluoroquinolones that are therapeutically interchangeable and clinically acceptable as a "workhorse" oral fluoroquinolone. Levofloxacin is currently on the BCF in accordance with a BPA.

   Ciprofloxacin is dosed twice daily, has poor coverage for *S. pneumoniae*, and has several clinically significant drug interactions. The Council concluded that ciprofloxacin is not therapeutically interchangeable with gatifloxacin or levofloxacin. The Council noted that

ciprofloxacin is the only fluoroquinolone currently approved for post-exposure prophylaxis of anthrax, but the proposed contract initiative would not affect the availability of usage of ciprofloxacin for anthrax exposures.

The DoD P&T Executive Council agreed to support a contracting initiative to choose a workhorse oral fluoroquinolone for the BCF.

7. MTF REQUESTS FOR BCF CHANGES

A. *Request to remove cromolyn sodium oral inhaler and solution for inhalation from the BCF* –An Army pharmacist provided the following rationale for the request:

> Cromolyn is relatively infrequently used in clinical practice. Cromolyn is a weak anti-inflammatory agent and is rarely prescribed. Inhaled steroids are used almost exclusively for this indication and are now acceptable in patients <2years of age with use of a spacer mask.

The mast cell stabilizers (cromolyn and nedocromil) produce only minor side effects (nasal congestion, cough, sneezing, dry throat). Nedocromil has an unpleasant taste. Mild-persistent asthma can be controlled with cromolyn in approximately 60 to 75% of patients, but 4 to 6 weeks of usage four times a day may be needed to attain maximum benefit. The mast cell stabilizers are not as effective as the inhaled corticosteroids, which are the agents of choice for long-term control of persistent asthma.

The PEC requested provider input on this issue and received 129 responses: 70 favoring removal from the BCF; 42 against removal from the BCF; 13 unsure; and 4 wanted to remove the MDI, but keep the nebulizer solution. Providers made several key points:

- Keeping cromolyn on the BCF may promote less effective, outdated therapy. Removing it from the BCF may encourage providers to more appropriately treat persistent asthma with inhaled corticosteroids.
- Despite parental concerns, studies reporting growth reduction with inhaled corticosteroids do not offer sufficient justification for avoiding the use of inhaled corticosteroids in children with asthma.
- Data suggest that delays in initiating maintenance therapy with inhaled corticosteroids result in less recovery of lung function in children with asthma.
- The best evidence for use of cromolyn is for people whose asthma symptoms are solely induced by exercise and who do not tolerate a long-acting beta agonist like salmeterol.

Prescriptions for cromolyn MDIs at MTFs declined by 52% over the past year, from 3265 prescriptions in Sep 2000 to 1562 prescriptions in Sep 2001. Prescriptions for cromolyn nebulizer solution declined by 55%, from 957 Rxs in Sep 2000 to 434 in Sep 2001.

The Council removed cromolyn sodium oral inhaler and solution for inhalation from the BCF. MTFs can decide whether or not to keep either or both products on their local formularies.

B. *Request to remove oral haloperidol from the BCF* – An Army pharmacist based this request on the relatively infrequent usage of haloperidol at his MTF.

Haloperidol is a potent antipsychotic with a high propensity to cause adverse effects. MTFs currently fill about 500 haloperidol prescriptions per month. Newer agents such as risperidone, olanzapine, and quetiapine are used more frequently than haloperidol. Primary care providers in the outpatient setting do not commonly prescribe antipsychotics. The Council removed oral haloperidol from the BCF. MTFs can decide whether or not to keep oral haloperidol on their local formularies.

C. *Request to add a no to extremely low androgen oral contraceptive to the BCF* – An Army pharmacist originally requested the addition of Desogen, a monophasic oral contraceptive (OCP) to the BCF. The request was subsequently clarified to be for the addition of a "3rd generation" monophasic OCP classified as having no to low androgenic side effects and 35 mcg of ethinyl estradiol. These OCPs contain the progestin desogestrel (Desogen, Ortho-Cept, Apri) or norgestimate (Ortho-Cyclen).

   The purported advantages of OCPs with no to low androgenic effects are lower incidences of weight gain, edema, bloating hirsutism and acne. MAJ Barb Roach reported that she could not find empirical evidence that OCPs differ significantly in androgenic side effects. Head-to-head trials are not available. Most reviewers acknowledge that there is no evidence of significant differences in side effects or efficacy for any of the OCPs, regardless of the progestin contained in the pill or their classification as mono-, bi-, tri-, or estro-phasic products. However, the same reviewers then go on to discuss differences in androgenic side effects with different progestins (apparently based primarily on *in vitro* characteristics of the progestins). A number of providers commented on the propensity for misconception in this therapeutic category.

   All OCPs are associated with an increased risk of venous thromboembolism. Some studies suggest an increased potential for venous thromboembolism with the 3rd generation OCPs compared to other OCPs, but the evidence is inconclusive.

   The 3rd generation OCPs cost from $10.20 to $15.28 per cycle—much more than most other OCPs. The Council decided not to add a 3rd generation OCP to the BCF because there is insufficient evidence that an incremental clinical benefit exists that would justify the incremental cost.

8. FORMULARY STATUS OF TRETINOIN

Tretinoin cream is indicated for the treatment of acne, and is also commonly used for the treatment of various skin cancers, precancerous conditions (e.g., actinic keratoses), and other dermatological conditions. Tretinoin products are also used for cosmetic treatment of photoaged skin (wrinkles and liver spots). One brand of tretinoin cream, Renova, is specifically indicated for mitigation of fine wrinkles, mottled hyperpigmentation and tactile skin roughness in patients who use comprehensive skin care and sunlight avoidance programs.

Topical retinoids are first line agents for acne. More than 95% of MTFs already have tretinoin cream on formulary. The Council decided to add tretinoin cream 0.025% and 0.05% to the BCF, but excluded products specifically indicated for wrinkles only (e.g., Renova). The Council noted that MTFs may adopt guidelines or retain existing guidelines designed to prevent usage of tretinoin products for cosmetic treatment of photoaged skin.

The NMOP statement of work does not allow tretinoin prescriptions to be filled for patients over the age of 35. The rule exists only in the NMOP statement of work—not in the Code of Federal Regulations or TRICARE policy. PDTS data show that tretinoin prescriptions are routinely filled in MTF and retail pharmacies for patients over the age of 35. The Council considered a proposal to remove the NMOP age restriction so that tretinoin would be more uniformly available to patients across all points of service. Some attendees expressed concern about taking an action that would require modification of the NMOP contract. After extensive discussion, the vote to remove the NMOP age restriction on tretinoin ended in a tie. The age restrictions on tretinoin remain in the NMOP. .

9. REVIEW OF ANXIOLYTICS FOR THE BCF

CAPT Torkildson reported on the PEC review of drugs for the treatment of anxiety disorders: generalized anxiety disorder (GAD), panic disorder/agoraphobia, acute/post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), specific phobia, and social phobia. These six conditions share a common dimension of poor response to stress leading to frequent and intense episodes of negative affect. This dimension is shared with depressive disorders, and is primarily responsible for the observed comorbidity among the anxiety disorders and between these disorders and depression. Each disorder also contains a unique component that distinguishes it from the others, with the possible exception of GAD.

Pharmacotherapy for anxiety disorders includes serotonin reuptake inhibitors [selective serotonin reuptake inhibitors (SSRIs) and venlafaxine]; benzodiazepines; buspirone; tricyclic antidepressants (TCAs); imipramine; clomipramine; trazodone; and nefazodone. Of these, buspirone, imipramine, trazodone, and four SSRIs are on the BCF.

Serotonin Reuptake Inhibitors – This classification includes the SSRIs and venlafaxine. There is growing support for using this group of drugs as first line therapy for many of the anxiety disorders. SSRIs are now considered the treatment of choice for panic disorder and post-traumatic stress disorder, and as first choice in conjunction with psychotherapy for OCD, specific phobia, and social phobia. Usage of SSRIs for treatment of GAD is increasing. Despite differences in FDA-approved indications, the SSRIs appear similar in safety and efficacy for these conditions. There are already four SSRIs (citalopram, fluoxetine, paroxetine, sertraline) on the BCF.

Venlafaxine inhibits both serotonin and norepinephrine reuptake (similar to TCAs). It was approved by the FDA for depression in 1993, and for GAD in 1999. It has been shown to be effective for GAD with and without coexisting depression. Venlafaxine appears to have a rapid onset of action with a safety profile similar to the SSRIs. Venlafaxine appears to be less costly on a cost per day basis than fluoxetine, paroxetine, or sertraline. It is currently on approximately 88% of MTF formularies, but it is not on the BCF.

The Council decided not to change the SSRIs on the BCF, but instructed the PEC to investigate the potential for addition of venlafaxine extended-release to the BCF as a cost-effective alternative to the SSRIs for the treatment of anxiety disorders.

Benzodiazepines – Benzodiazepines are effective in treating anxiety disorders, including GAD, panic disorder, and social anxiety disorder. The long-term use of benzodiazepines for anxiety disorders is controversial. All benzodiazepines share a risk of sedation, motor vehicle accidents, industrial accidents, and dependence. Rebound anxiety occurs in approximately 15% of patients upon discontinuation. The benzodiazepines are Pregnancy Category D due to the risk of cleft lip/palate. There are currently no benzodiazepines on the BCF.

All benzodiazepines used for treatment of anxiety disorders are available as generics. All strengths of these benzodiazepines are available for less than $0.10 per tablet or capsule. As Schedule IV medications, the administrative burden associated with stocking and record keeping must be considered in adding any of them to the BCF.

Psychiatrists identified clonazepam as a drug that should be considered for the BCF because of a lower abuse potential and more utility in other conditions (e.g., some seizure disorders). Almost all MTFs (99%) are filling prescriptions for the 0.5 mg strength of clonazepam. Some MTFs appear to carry only the 0.5 mg strength.

According to the PEC Formulary database, 100% of facilities have diazepam on their local formulary. About 97% of prescriptions for oral diazepam tablets are for the 5 mg strength.

The Council decided to add clonazepam 0.5 mg and diazepam 5 mg to the BCF. MTFs may have other strengths or formulations of these medications on their formularies.

Buspirone – The utility of buspirone is limited primarily to treatment of GAD. Buspirone has a superior safety profile compared to the benzodiazepines, but a significantly slower onset of action. Many think buspirone is less efficacious than other agents, but under-dosing might be the problem. Buspirone is already on the BCF and MTF pharmacies dispensed nearly 6 million tablets in the first 9 months of FY 01. The Council agreed that buspirone should remain on the BCF.

Tricyclic Antidepressants – Imipramine is useful primarily in GAD. Clomipramine is used to treat OCD. The usefulness of these agents is limited by their side effect profile and potential for accidental or deliberate overdose. SSRIs are equally efficacious, safer, and much better tolerated. Imipramine is already on the BCF. There is no provider support for the addition of clomipramine. The Council made no changes in this drug class.

Trazodone – Trazodone is a heterocyclic antidepressant. Anxiolytic use has been confined primarily to GAD. Although trazodone has no significant safety, tolerability, or efficacy advantages over other active agents, it is relatively inexpensive. Trazodone also has some utility in treating insomnia resulting from SSRI therapy. Trazodone is already on the BCF. The Council made no change to the formulary status of trazodone.

Nefazodone – Nefazodone is an antidepressant with a unique mechanism of action. It was FDA-approved in 1994 for treatment of depression, but is used off-label to treat panic disorder, PTSD, and social phobia. The major advantage of nefazodone is its somewhat superior safety profile, but the daily cost per day of therapy is $1.06 to $3.18. Nefazodone is not on the BCF. Providers expressed no interest in the addition of nefazodone to the BCF and usage in the Military Health System (MHS) is relatively low. The Council made no change in the formulary status of nefazodone.

10. EVALUATION OF THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS (CURE) TRIAL

The CURE trial randomized approximately 12,500 patients (500 patients in the U.S. arm) with unstable angina and non-ST-segment elevation myocardial infarction (MI) presenting within 24 hours of symptom onset to clopidogrel (300 mg load, followed by 75 mg daily, plus aspirin in doses ranging from 75 to 325 mg daily) or aspirin plus placebo. Patients were treated for 3 to 12 months (average of 9 months).

The primary composite outcome of non-fatal MI, stroke, or death due to cardiovascular causes occurred in 9.3% of patients receiving clopidogrel plus aspirin compared to 11.4% of patients receiving aspirin plus placebo. This equates to a relative risk of 0.80 (95% CI 0.72-0.90, $p<0.001$), or a 20% relative risk reduction. The absolute risk reduction was 2.1%, which yields a number needed to treat of 47. The addition of clopidogrel to aspirin appeared to provide both an early (within 2 hours) and sustained benefit.

If 100 patients analogous to those obtaining benefit in the CURE trial were treated for a 9 month period with clopidogrel plus aspirin and a similar group of 100 patients were treated with aspirin only, drug costs for the clopidogrel plus aspirin group would be about $50,220 ($1.86 per patient per day) compared to about $270 ($0.01 per patient per day) for the aspirin only group. Given outcomes of the CURE trial, 9 patients (9.3%) in the clopidogrel plus aspirin group and 11 (11.4%) in the aspirin only group would be expected to experience the primary outcome of non-fatal MI, stroke, or death. Dividing the incremental cost of clopidogrel therapy ($50,220 - $270) by the number of averted events (2) results in an incremental cost of $25,000 per averted event.

The increased risk of bleeding in the clopidogrel plus aspirin group must also be considered. During the CURE trial, a significantly higher percentage of patients receiving clopidogrel plus aspirin experienced major bleeding compared to those receiving aspirin plus placebo (3.7% vs 2.7%, $p = 0.001$), a number needed to harm of 100. Thus, for every 100 patients treated with clopidogrel plus aspirin, one additional patient would be expected to have a major bleed compared to 100 patients receiving aspirin alone (or one major bleed per two events averted). Combination therapy also resulted in a significantly higher percentage of patients experiencing non-life threatening bleeding, minor bleeding, and bleeding requiring transfusion of $\geq$ 2 units of blood. The percentage of fatal bleeding episodes was 2.2% for clopidogrel plus aspirin compared to 1.8% with aspirin plus placebo (a statistically non-significant difference).

The definitions used in the CURE trial for the various types of bleeding differ from widely accepted definitions used in the ACCP Consensus Conference on Antithrombotic Therapy guidelines published each year in CHEST (the “CHEST guidelines”) and the “Thrombolysis in Myocardial Infarction” (TIMI) trials. The variance in bleeding definitions raises the

concern that the risk of bleeding among patients receiving clopidogrel plus aspirin may have been even larger if the bleeding definitions in the CHEST guidelines and TIMI trials had been used.

The Council decided not to add clopidogrel to the BCF. The Council asked the PEC to request additional information from the manufacturer about the incidence of bleeding found in the CURE trial—ideally information about the bleeding rates using the definitions found in the CHEST guidelines and TIMI trials.

11. PROTON PUMP INHIBITORS

COL Remund reported on a significant shift in proton pump inhibitor (PPI) prescription market shares after omeprazole (Prilosec) was removed and rabeprazole (Aciphex) was added to the BCF on 1 October 2001. By the first week in November, rabeprazole accounted for 54% of MTF PPI prescription fills. The rapid switch to rabeprazole by MTF pharmacies essentially negated the effect of the huge increase in the price of omeprazole. The weighted average cost per unit for PPIs increased significantly during the first part of October, but trended back down to $1.08 per unit by the first week in November (just under the $1.09 cost per unit that existed prior to termination of the omeprazole contract).

12. COX-2 INHIBITORS

MTF prescription fills and expenditures for the COX-2 selective inhibitors (celecoxib and rofecoxib) leveled off over the past six months. Council members speculated that uncertainty about cardiovascular safety and the ability of these agents to significantly reduce the risk of GI events (especially in patients taking aspirin for cardiac prophylaxis) may have played a role.

13. ADJOURNMENT

The meeting adjourned at 1600 hours on 14 Nov 2001. The next meeting will be held at the Non-Commissioned Officers Club, Fort Sam Houston, TX starting at 0800 on 12 Feb 2002. All agenda items should be submitted to the co-chairs no later than 11 Jan 2002.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair