Department of Defense
Pharmacoeconomic Center

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Fort Sam Houston, TX 78234-5081

MCCS-GPE **5 March 2003**

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 5 March 2003 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC	Air Force
COL Mark Nadeau, MC (For COL Bill Sykora, MC)	Air Force
LtCol George Jones, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CAPT Robert Rist	Coast Guard
Mike Valentino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
COL Mike Heath, MS	Army Pharmacy Consultant Chair, DoD Pharmacy Board of Directors
MAJ John Howe, BSC	Defense Supply Center Philadelphia
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Kathy Tortorice	Department of Veterans Affairs, PBM
Capt Cherie-Anne Mauntel, BSC	USAF AFIT Student
CPT Tamba Dauda, MS	Pharmacy Resident, WHMC/BAMC
Capt Glenn L. Laird, BSC	Pharmacy Resident, WHMC/BAMC
Capt Agnes Kim, BSC	Pharmacy Resident, WHMC/BAMC
CPT Larry Ricks, MS	Pharmacy Resident, WHMC/BAMC

3. REVIEW MINUTES OF LAST MEETING

The minutes from the last meeting were accepted as written.

4. ADMINISTRATIVE ISSUES

A. *Membership and Meeting Frequency*: The Council discussed potential changes in its membership and the need to conduct additional Council meetings via teleconference in order to make timely decisions regarding joint VA/DoD pharmaceutical procurement strategies. The Council concluded that the charter that governs the DoD P&T Committee and Executive Council should be revised. COL Remund will develop an initial draft of a new charter.

The Council welcomed new members COL Doreen Lounsbery and CDR Mark Richerson, taking the place as voting members for COL Rosa Stith and CDR Kevin Cook, respectively.

B. *Clinical Reviews:* A Clinical Workgroup comprised of three members each from the VA PBM and the PEC are working to integrate and standardize the processes for completing clinical reviews of drug classes and drug monographs for new molecular entities.

C. *Rx NET:* RxNET is a web forum that the PEC established to facilitate communication among health care professionals involved in the delivery and management of drug therapy in the Military Health System. Dave Bretzke serves

as the administrator for RxNET. Council members are encouraged to use the forum that has been established for the DoD P&T Council within RxNET.

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENT (BPA) AWARD, RENEWALS AND TERMINATIONS

A. New joint DoD/VA contracts were awarded for permethrin cream (West-ward), tretinoin topical cream (Allergan), and colchicine tablets (West-ward).

B. Joint DoD/VA contracts for erythromycin topical and clindamycin topical were not awarded because the bid prices were higher than existing FSS prices. The hydrochlorothiazide/triamterene joint contract was not awarded due to lack of offers.

C. New joint DoD/VA blanket purchase agreements were awarded for fluticasone (Flonase; Pharmacia), nisoldipine (Sular; 1st Horizon), tolterodine tartrate extended release capsules (Detrol LA; Pharmacia), lansoprazole (Prevacid; TAP), rabeprazole (Aciphex; Janssen), and levothyroxine (Synthroid; Abbott).

6. PROCUREMENT INITIATIVES

A. The following joint DoD/VA contracts are in various stages of solicitation: isosorbide dinitrate, ketoconazole cream, midazolam injectable, pamidronate injectable, and tramadol tablets.

B. A joint DoD/VA solicitation for a "triptan" closed 20 Dec 02, but the solicitation has been protested to the General Accounting Office (GAO).

C. A joint DoD/VA solicitation for bisphosphonates is being developed. A projected issue date is not yet identified.

D. A joint DoD/VA solicitation for angiotensin receptor blockers (ARBs) has been drafted and is currently being reviewed and edited.

E. A joint DoD/VA solicitation for a thiazolidinedione is being developed. A projected issue date is not yet identified.

F. Levothyroxine (Synthroid) – The price for the Synthroid brand of levothyroxine recently increased from $0.02 per tablet to $0.07 per tablet. In light of the price increase, the Council considered the possibility of a contracting action that would compete various levothyroxine products. Synthroid accounts for 97% of the levothyroxine market at MTF pharmacies. None of the levothyroxine tablets marketed by other companies are "A-rated" to Synthroid. A contracting action that caused patients to be switched from Synthroid to another levothyroxine product would result in therapeutic substitutions requiring additional laboratory tests to monitor thyroid levels. The Council unanimously voted not to pursue a contract for a single levothyroxine product on the BCF.

G. Statins – A joint DoD/VA solicitation for a high potency statin closed 28 February 2003. The solicitation permits (but does not mandate) the addition of generic lovastatin and/or a non-CYP3A4 metabolized statin (pravastatin or fluvastatin) to the BCF. Lovastatin, pravastatin and fluvastatin have not been on

any MTF formularies since the current closed class statin contract was awarded in August 1999.

1) Lovastatin accounts for less than 1% of statin usage at MTFs. Lovastatin costs $0.26 per tablet (joint VA/DoD contract price), so it does not offer any price advantage compared to the current contract prices for the strengths of simvastatin that achieve similar reductions in LDL-cholesterol. The future contract prices for a high potency statin are expected to be even lower. The Council voted to not add lovastatin to the BCF. Individual MTFs may add lovastatin to their local formularies if they determine there is a need to do so.

2) Pravastatin and fluvastatin together account for less than 1% of MTF statin usage. Pravastatin and fluvastatin prices are higher than the contract prices for the strengths of simvastatin that achieve similar reductions in LDL-cholesterol. Since pravastatin and fluvastatin do not offer an economic advantage, their use should be limited to patients who have a clinical need for a non-CYP3A4-metabolized statin. If pravastatin or fluvastatin were added to the BCF, MTFs would no longer be able to use the non-formulary request process to limit usage to patients who have a specific clinical need for these agents. The Council voted to not add a non-CYP3A4 metabolized statin to the BCF and also to not participate in any contracting initiative that would require addition of pravastatin or fluvastatin to the BCF. Individual MTFs may add either pravastatin or fluvastatin to their local formularies if they determine there is a need to do so.

H. LHRH Agonists – The Council voted to add goserelin acetate (Zoladex) 3.6 mg and 10.8 mg implants to the BCF for the treatment of prostate cancer based on a joint DoD/VA contract that was awarded to Astra Zeneca. The contract specifies that Zoladex is the sole LHRH agonist on the Basic Core Formulary (BCF) **for the treatment of prostate cancer**, and that other LHRH agonist dosage forms used for prostate cancer are not allowed on MTF formularies. MTFs are allowed to have additional LHRH agonist products on their formularies for the treatment of conditions other than prostate cancer. Detailed guidance regarding the Zoladex contract is on the PEC website at:

http://www.pec.ha.osd.mil/Contracts/LHRH_Agonist_Contract_Guidance.htm

I. Prostaglandins – The Council voted at the November 2002 meeting to add a prostaglandin to the BCF utilizing a closed class contracting strategy competing latanoprost, bimatoprost and travoprost, which would not require patients to be switched from one agent to another. The ophthalmology consultants for the three services subsequently expressed disagreement with the Council's decision. The consultants' concerns centered on (1) evidence from clinical trials and clinical experience that bimatoprost and travoprost have a higher incidence of hyperemia than latanoprost and (2) less certainty regarding the safety of bimatoprost and travoprost because they have been on the market for less time than latanoprost.

The Council reviewed safety and tolerability data from clinical trials of ophthalmic prostaglandins, data on adverse effects and discontinuation rates from a phase IV study of bimatoprost, VA and DoD usage data, and information about

a switch from latanoprost to bimatoprost by a Kaiser health plan. After a lengthy discussion the Council passed a motion (by an 8 to 3 vote) to reaffirm its decision to seek a contract for a single ophthalmic prostaglandin. Members voting in favor of the motion tended to agree with the argument that differences in the incidence of hyperemia were unlikely to lead to clinical problems of a magnitude that would make bimatoprost or travoprost an unacceptable choice as the sole ophthalmic prostaglandin on the BCF. Members voting in favor of the motion also acknowledged that the longer a drug is on the market the more we generally know about its safety profile, but they concluded that selection of any of the ophthalmic prostaglandins as the sole agent on the BCF would not pose an unacceptable safety risk.

J. Proton Pump Inhibitors (PPIs) – In December 2002 Janssen communicated that Eisai, the manufacturer of rabeprazole (Aciphex), had decided to raise the price of rabeprazole (Aciphex) to the DoD and VA from $0.22 per unit to $0.35 per unit on 1 January 2003, and then to approximately $1.90 per unit on 1 April 2003. The impending price increases caused DoD and the VA to negotiate vigorously with all manufacturers of branded PPIs. Three of the four current manufacturers of branded PPIs submitted proposals to the DoD and VA.

The Council voted unanimously to accept blanket purchase agreements offered by Eisai/Janssen for Aciphex and TAP Pharmaceuticals for lansoprazole (Prevacid). Aciphex will remain on the BCF, and Prevacid will be added to the BCF.

7. Place In Therapy (PIT) Recommendations – PIT recommendations are intended to aid practitioners in the appropriate use of selected medications. The Council reviewed and accepted the revised PIT recommendations for angiotensin II receptor blocker (ARBs). The ARB PIT recommendations will be disseminated to MTFs.

The PEC is developing PIT recommendations for topical immunomodulators (TIMS) and overactive bladder (OAB). The draft PIT recommendations will be disseminated to Council members through RxNET or email. Council members will have a 10-day period to review and comment. The PEC will then modify the PIT recommendations as necessary and disseminate them to MTFs.

8. FORMULARY DECISION FOLLOW-UP

A. *Evista* — Evista was added to the BCF in May 2002. The PEC analyzed prescription data from PDTS to determine the extent to which patients who obtained Evista from retail pharmacies before it was added to the BCF subsequently obtained Evista from MTF pharmacies. An analysis of 11,108 patients who obtained Evista from retail network pharmacies between 1 March 2002 and 1 June 2002 showed that:

- 864 patients (8%) subsequently obtained Evista from MTF pharmacies between 1 September 2002 and 6 December 2002
- 10,244 patients (92%) continued to obtain Evista only from retail network pharmacies between 1 September 2002 and 6 December 2002

The PEC repeated the analysis after dividing the 11,108 patients into two groups. Group 1 included 3,092 patients who obtained prescriptions for drugs other than Evista from MTF pharmacies between 1 March 2002 and 1 June 2002. Group 2 included 8,016 patients who obtained prescriptions for drugs other than Evista at retail network pharmacies only between 1 March 2002 and 1 June 2002. The analysis showed that:

- 693 (22%) of the patients in Group 1 obtained Evista from MTF pharmacies between 1 September 2002 and 6 December 2002
- 171 (2%) of the patients in Group 2 obtained Evista from MTF pharmacies between 1 September 2002 and 6 December 2002

B. *Advair* — Advair was added to the BCF February 2002. The PEC analyzed prescription data from PDTS to determine the extent to which patients who obtained Advair from retail pharmacies before it was added to the BCF subsequently obtained Advair from MTF pharmacies. An analysis of 9,853 patients who obtained Advair from retail network pharmacies between 1 December 2001 and 1 March 2002 showed that:

- 1,874 patients (19%) subsequently obtained Advair from MTF pharmacies between 1 June 2002 and 20 February 2003
- 7,979 patients (81%) continued to obtain Advair only from retail network pharmacies between 1 June 2002 and 20 February 2003

The PEC repeated the analysis after dividing the 9,853 patients into two groups. Group 1 included 2,838 patients who obtained prescriptions for drugs other than Advair from MTF pharmacies between 1 December 2001 and 1 March 2002. Group 2 included 7,015 patients who obtained prescriptions for drugs obtained at retail network pharmacies only between 1 December 2001 and 1 March 2002. The analysis showed that:

- 1,457 (51%) of the patients in Group 1 obtained Advair from MTF pharmacies between 1 June 2002 and 20 February 2003
- 417 (6%) of the patients in Group 2 obtained Advair from MTF pharmacies between 1 June 2002 and 20 February 2003

9. DRUG CLASS EVALUATIONS TO DETERMINE CLINICALLY ACCEPTABLE CONTRACTING/FORMULARY STRATEGIES:

A. *Cholinesterase Inhibitors* — Cholinesterase inhibitors are the primary treatment for cognitive symptoms and functional disability of Alzheimer's disease (AD). Four cholinesterase inhibitors are currently available in the United States: tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). The VA plans to conduct a clinical review of the class to determine potential contracting opportunities. The BCF does not include a cholinesterase inhibitor. CDR Graham presented a brief overview of cholinesterase inhibitors to assist the Council in deciding whether or not a cholinesterase inhibitor should be added to the BCF.

Efficacy: Cholinesterase inhibitors have been shown to delay neuropsychiatric, cognitive and functional decline in patients with mild to moderate AD. Long-term studies on outcomes such as patient quality of life, institutionalization, and caregiver burden have not been conducted, but short-term trials have shown that cholinesterase inhibitors delay nursing home placement and reduce costs of care in the home.

Safety/Tolerability: Generally the agents are well tolerated with common adverse effects managed with titration and dose adjustments. Common adverse effects are related to excessive cholinergic activity consisting of nausea, diarrhea, vomiting, and occasionally excessively vivid dreaming. Tacrine (Cognex) use has been limited due to associated risks of hepatotoxicity.

Other factors: The following table displays FSS cost of cholinesterase inhibitors.

	Tacrine	Donepezil	Rivastigmine	Galantamine
FSS Price/Unit	$0.80/cap	$2.54/tab	$1.30/tab	$1.30/tab
Dosage Frequency	QID	QD	BID	BID
Cost/day	$3.20/day	$2.54/day	$2.60/day	$2.60/day
Cost/month	$96.00/month	$76.20/month	$78.00/month	$78.00/month

PDTS data from October 2002 to January 2003 show that donepezil (Aricept) has the majority of the DoD market share in all three points of service, with a steady increase in prescription fills for donepezil, rivastigmine, and galantamine in all three points of service. MTFs are currently spending nearly $100,000 per month on cholinesterase inhibitors.

A Council member expressed the opinion that the cholinesterase inhibitors are very expensive compared to the relatively modest clinical benefits they offer. The Council voted 10 to 1 not to consider the addition of a cholinesterase inhibitor to the BCF.

B. *Parkinson's Disease*

Carbidopa/ levodopa immediate release (Sinemet IR) formulation is currently the only drug on the BCF for the treatment of Parkinson's disease. The Council addressed the following questions:

- Should carbidopa/levodopa controlled release (Sinemet CR) be added to the BCF or replace carbidopa/levodopa immediate release on the BCF?
- Should adjunctive therapy agents (anticholinergic agents and amantadine) be added to the BCF?
- Should one or more of the dopamine agonists (bromocriptine, pergolide, pramipexole, ropinirole) be added to the BCF?

Carbidopa/levodopa controlled release: Carbidopa/levodopa is the most effective drug for the symptomatic treatment of idiopathic Parkinson's disease. There is no

evidence of a clinical advantage for the controlled release (CR) form of carbidopa/levodopa compared to the immediate release (IR). The daily cost of therapy with the CR is substantially higher, ranging from $1.00 to $2.50 vs $0.20 to $0.80 for the immediate release (IR). The Council unanimously voted to not add carbidopa/levodopa CR to the BCF.

Adjunctive therapy: Adjunctive treatment for Parkinson's disease includes anticholinergic agents (trihexyphenidyl, benztropine) and amantadine. Adjunctive therapy agents are effective monotherapy treatment for tremors in patients under the age of 70 in whom akinesia is not a significant problem. Additionally, they may be useful in patients with more advanced disease that have persistent tremor despite treatment with carbidopa/levodopa or dopamine agonists.

- Anticholinergic agents: There is little evidence to suggest that one anticholinergic agent is superior to another. Trihexyphenidyl is the most widely prescribed anticholinergic agent in the MTFs, with benztropine being reserved for use in the management of antipsychotic drug-induced Parkinsonism. The adverse effects of the anticholinergic medications are common and often limit their use, especially in the elderly population.
- Amantadine is an antiviral agent that has mild antiparkinsonian activity with its main advantage being a lower side effect profile than the anticholinergic agents. All three agents are available as generics and are inexpensive.

Since the goal of treatment for Parkinson's is control of symptoms, and no drug gives excellent relief by itself, the Council voted to add these three medications to the BCF.

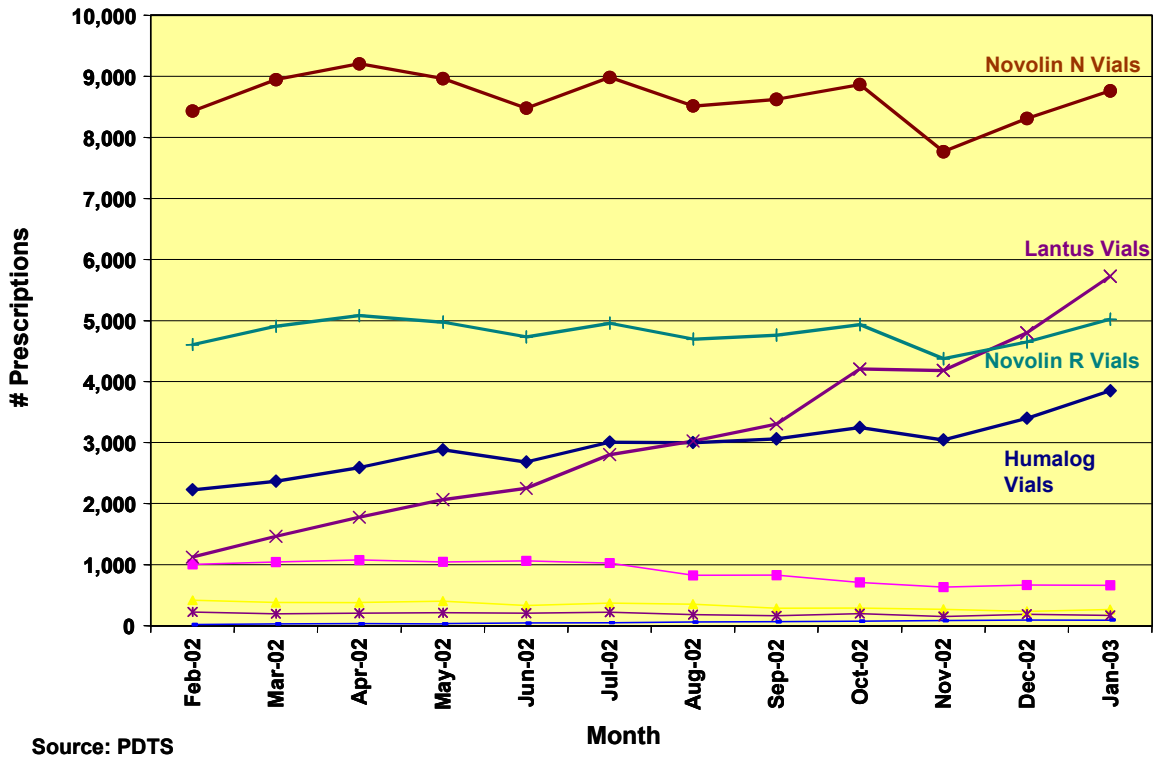
Dopamine agonists: A recent consensus opinion stated that dopamine agents are appropriate for the initial treatment of Parkinson's disease. Controlled trials have shown that bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapax), and ropinirole (Requip) are all effective in patients with advanced Parkinson's disease complicated by motor fluctuations and dyskinesias. Dopamine agonists, however, are ineffective in patients who have shown no therapeutic response to carbidopa/levodopa. Side effects caused by dopamine agonists are similar to those of levodopa and patients who are intolerant of one agonist may tolerate another. The Council requested the PEC conduct a drug class review to determine which, if any, dopamine agonists, to add to the BCF.

C. *Insulin Pens* – CAPT Torkildson discussed the need to consider the addition of insulin pens and/or cartridges to the BCF. This question had been raised following the addition of insulin glargine (Lantus) to the BCF in August 2002. A perception had developed that this would result in an increased utilization of these insulin delivery systems, especially for the pre-prandial administration of short-acting and ultra-short-acting insulins. A joint contract was awarded to Novo Nordisk Pharmaceuticals, Inc. in 1999 to provide the DoD and VA with human regular, NPH, lente, and NPH/regular 70/30 mix insulin products. However, this contract included only the 10 ml vial package size of these products. Since the cost per unit of insulin delivered is much higher for the pen and cartridge delivery systems

compared to vials, and these delivery systems are not included in the current insulin contract, the PEC felt it would be prudent to look at this issue in greater detail.

CAPT Torkildson presented current data regarding insulin utilization within the direct care system (see Figure 1). Two of the top four insulin products by prescription volume (Novolin N and Novolin R) are currently under contract, while the other two products (Lantus and Humalog) are not. The other two contracted insulin products, Novolin L and Novolin 70/30, have no appreciable utilization at MTFs. A similar usage pattern exists in the mail order program.

Figure 1: MTF Prescription Volume for Most Commonly Prescribed Insulin Products

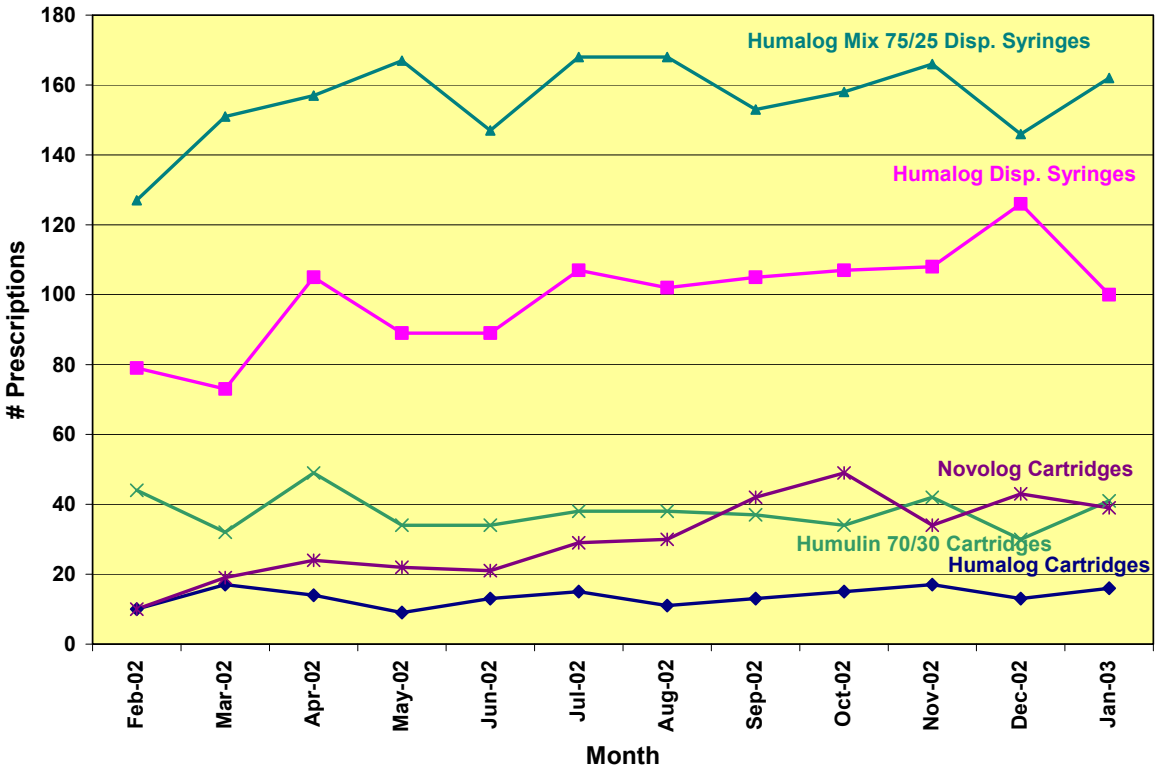


Source: PDTS

The data on utilization of insulin pens and cartridges within the direct care system is presented in Figure 2. Overall, insulin pens and cartridges currently represent a very small fraction of insulin product utilization. For the period 1 March 2002-28 Feb 2003, prescriptions for insulin pens and cartridges represented only 6% of the total number of insulin prescriptions filled in MTFs and the mail order program. However, as can be seen in Figure 2, the number of prescriptions for pen and cartridge delivery systems for ultra-short-acting insulin preparations (Humalog and Novolog) grew by about 50% over this period. In contrast, the prescription volume for other pen and cartridge insulin delivery products remained relatively flat. However, MTF expenditures for insulin pens and cartridges have increased

more rapidly. For example, MTFs spent $15,000 for Humalog pens in January 2003 compared to $5,000 in February 2002.

Figure 2: MTF Prescription Volume for Selected Insulin Disposable Syringe and Cartridge Products



A brief review of the clinical data highlighted the following information: While there are data to support the superiority of the ultra-short-acting insulin products (insulin lispro and insulin aspart) compared to regular insulin in terms of glycemic control, HbA1c levels, and frequency of hypoglycemia; there are currently no data that suggest that one ultra-short-acting insulin product is superior to the other. No data have been published since the award of the current insulin contract to suggest that any significant clinical differences exist between the products that were competed at that time, and no additional manufacturers of the products that are currently under contract have been identified.

From this information, the PEC came to the following conclusions:

- There is substantial and growing use of ultra-short-acting insulin products, primarily Humalog, at MTFs.
- There is almost no utilization of two of the four contracted insulin products, Lente and 70/30.
- There is currently little use of insulin pen devices.

- The monthly MTF expenditures for ultra-short-acting insulin pen devices has more than tripled over the past 12 months, from $6,000 to $20,000/month overall.

The PEC made the following recommendations to the Council:

- The DoD and VA should not exercise the final option year of insulin contract, which would begin on 1 November 2003
- The DoD and VA should instead begin development of a solicitation for a new insulin contract that covers different products than the current contract.
    - Lente insulin and the 70/30 product should not be included in the solicitation
    - The ultra-short-acting products (insulin lispro and insulin aspart) should be included in the solicitation
    - The pen/cartridge delivery system for the ultra-short-acting products only should be included in the solicitation

The Council voted unanimously to accept the PEC's recommendation and forward the above conclusions and recommendations for consideration by the Contracting Officer.

10. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF ADDITION

A. *Atypical antipsychotics* – The PEC is working on a review of the atypical antipsychotics. After the review is completed, the PEC will estimate the relative cost-effectiveness of the atypical antipsychotics and recommend how many of these agents should be added to the BCF.

B. *Ethinyl estradiol 20 mcg / Norelgestromin 150 mcg transdermal system (Ortho Evra)*

A MTF provider requested the addition of Ortho Evra to the BCF due to its unique administration route (topical) and potential for increased compliance.

Efficacy: A head-to-head that trial that compared 812 patients on Ortho Evra to 605 patients on Triphasil (30/40 mcg ethinyl estradiol with 50/75/125 mcg levonorgestrel) found that:

- The mean proportion of each participant's cycles that demonstrated perfect compliance was higher with Ortho Evra than with Triphasil (88.2% vs 77.7%, $p<0.0001$). [Note: Back-up contraception must be used if a patient exceeds a 7-day patch-free interval between Ortho Evra patches.]
- Despite better compliance with Ortho Evra, there was not a statistically significant difference in pregnancies: 5 with Ortho Evra vs 7 with Triphasil; $p=0.57$.

Safety/Tolerability: A higher percentage of patients on Ortho Evra discontinued the study due to adverse events than patients on Triphasil:

- Nausea: 1.8% with Ortho Evra vs 0.8% with Triphasil (p=0.12)
- Headache: 1.5% with Ortho Evra vs 0.3% with Triphasil (p=0.03)
- Dysmenorrhea: 1.5% with Ortho Evra vs 0.2% with Triphasil (p=0.01)
- Breast discomfort 1% with Ortho Evra vs 0.2% with Triphasil (p = 0.09)
- Application site reactions: 2.6% with Ortho Evra—not applicable for Triphasil

Other factors: A pooled analysis of clinical trial data (N=3319, 16,673 cycles) showed that 4.6% of Ortho Evra patches had to be replaced due to complete or partial detachment.

Price and usage: Ortho Evra costs $15.06/cycle, compared to $0.21-$8.00/cycle for oral contraceptives that are on the BCF. Ortho TriCyclen (which is not on the BCF) costs $15.21 per cycle. Ortho TriCyclen is the most commonly used contraceptive in the Military Health System (approximately 32,000 Rxs/month in all 3 points of service), compared to approximately 40,000 Rxs/month for all the oral contraceptives on the BCF combined. As of Jan 03, Ortho Evra had exceeded 10,000 Rxs/month.

The Council concluded that Ortho Evra does not offer any advantages in efficacy or safety/tolerability that justify its higher price compared to oral contraceptives already on the BCF. The Council voted unanimously not to add Ortho-Evra to the BCF.

C. *Topical Immunomodulators (TIMS)*

The PEC is still exploring procurement options for topical immunomodulators, so the Council took no action on these agents.

11. MTF REQUESTS FOR BCF CHANGES

A. *Request to add metoprolol extended release tablets (Toprol XL) to the BCF–* A MTF provider requested the addition of metoprolol succinate extended release tablets (metoprolol XL) to the BCF for congestive heart failure (CHF). The requestor's rationale was that "metoprolol XL is indicated for CHF and is not equivalent to the metoprolol tartrate immediate release preparation (metoprolol IR); additionally the XL formulation provides more dose flexibility by providing low doses to the patient and is the standard of care for CHF patients." No supporting literature was submitted along with the request.

Efficacy: Metoprolol XL is labeled for treating New York Heart Association (NYHA) functional class II/III CHF. A placebo-controlled trial conducted with metoprolol XL (MERIT-HF; Lancet 1999) in approximately 4000 subjects reported that 7.2% of patients receiving the drug died, compared with 11% in the placebo group (34% risk reduction, $p<0.00009$).

Metoprolol IR lacks an FDA-approved indication for CHF. A placebo-controlled trial conducted with metoprolol IR in approximately 400 patients with dilated idiopathic cardiomyopathy (MDC trial; Lancet 1993) found that 13% of patients

receiving the drug died, compared with 20% in the placebo group. The mortality rate of 13% is within range of the mortality rate seen in other beta blocker trials (7%-16%). Due to the small sample size, the survival benefit did not reach statistical significance ($p<0.058$). However, the risk reduction of 34% achieved with the metoprolol IR is similar to the risk reductions reported in other trials of similar design conducted with the beta blockers bisoprolol, carvedilol, and metoprolol XL.

The metoprolol IR study measured other parameters that showed significant benefits, including a reduced need for cardiac transplantation and improvements in left ventricular ejection fraction and exercise capacity. A head to head mortality study of metoprolol IR in comparison with carvedilol (COMET study) is currently underway in Europe, with results expected in summer 2003.

Safety/Tolerability: The XL formulation produces more consistent blood levels than the IR formulation. More consistent blood levels would theoretically produce more consistent beta-1 receptor blockade and cause fewer adverse events. However, head-to-head trials comparing metoprolol XL and metoprolol IR in small numbers of patients show no difference in safety and tolerability between the two formulations.

Other factors: Metoprolol IR is formulated in tablet strengths required for treating hypertensive patients (50 and 100 mg scored tablets), and is not available in the low doses required for initiating therapy in CHF patients (12.5 –25 mg). Metoprolol IR requires twice daily dosing. Metoprolol XL offers an advantage over metoprolol IR in that it is available in 25 mg scored tablets and is dosed once daily.

An analysis of PDTS prescription data showed that metoprolol XL is responsible for the 2nd highest number of beta blocker prescriptions in the NMOP and Retail Network, second only to atenolol. In the MTF setting, atenolol generates the most beta blocker prescriptions, followed by metoprolol IR, then metoprolol XL.

The Council voted unanimously not to add metoprolol XL to the BCF. Despite the lack of an FDA-approved indication, DoD providers use metoprolol IR for CHF. Although metoprolol XL offers the convenience of once daily administration and dosing flexibility, the absence of a significant difference in efficacy, safety or tolerability compared to metoprolol IR does not justify the higher expense for metoprolol XL ($9.90-$14.70 /month for metoprolol XL vs $0.90-$2.42/month for metoprolol IR). In the absence of a mechanism for MTFs to target the usage of metoprolol XL to patients with CHF, the addition of metoprolol XL to the BCF would likely result in increased use of metoprolol XL for hypertension in lieu of using other less-expensive beta blockers. The Council requested re-evaluation of the use of beta blockers for CHF upon completion of the COMET study.

B. *Request to add chlorthalidone 25 and 50 mg tablets to the BCF–* A MTF provider requested the addition of chlorthalidone, a generic thiazide diuretic, to the BCF in light of the recently completed landmark study (Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALLHAT; JAMA 2002). This study showed that the thiazide diuretic chlorthalidone was equally efficacious to a

calcium channel blocker (amlodipine) and an ACE inhibitor (lisinopril) in reducing blood pressure in hypertensive patients, at a much lower cost than the other agents. Efficacy of chlorthalidone was also proven in the Systolic Hypertension in the Elderly Program (SHEP; JAMA 1991), which showed a reduced incidence of stroke and major cardiovascular events in the diuretic arm.

Chlorthalidone has historically has been used more commonly in Europe than the US. Chlorthalidone may have a higher incidence of hypokalemia than hydrochlorothiazide (HCTZ), however, all patients receiving thiazide diuretics require electrolyte monitoring. The incidence of hypokalemia (serum potassium < 3.5 mEq/L) in patients receiving chlorthalidone in both the ALLHAT and SHEP trials was <10% (8.5% and 7.2%, respectively).

Although current DoD utilization of chlorthalidone is low (10,000 chlorthalidone Rxs in all 3 venues, vs 1 million Rxs for HCTZ), the extensive publicity of the results of ALLHAT may cause usage to increase. HCTZ and chlorthalidone are both very inexpensive, with tablet costs as low as $0.01/tablet. Although the current BCF thiazide diuretic HCTZ meets the needs of the majority of DoD patients, practitioners of evidence-based medicine may want to use chlorthalidone, and its availability should be ensured at MTF pharmacies. Providers should be encouraged to take advantage of a low cost drug with excellent evidence of benefit in the treatment of hypertension. The Council voted unanimously to add chlorthalidone to the BCF.

12. ADJOURNMENT

The meeting adjourned at 1530 hours. The next meeting will be held at Fort Sam Houston, TX at 0800 on Tuesday, 6 May 2003. All agenda items should be submitted to the co-chairs no later than 18 April 2003.

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