Correction - The next meetings of the DoD P&T Committee have been changed to Tuesday 13 July and Wednesday 14 July, 2004.

Department of Defense Pharmacoeconomic Center

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Fort Sam Houston, TX 78234-5081

MCCS-GPE **20 APRIL 2004**

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

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

1. A meeting of the DoD P&T Committee convened at 0800 hours on 20 April 2004 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
CAPT Terrance Egland, MC (via VTC)	DoD P& T Committee Co-chair
COL Mike Heath, MS (For MAJ Travis Watson)	Army
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
LtCol Gordon Wright Bates, Jr, MC	Air Force
Col Phil Samples, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Mark Richerson, MSC	Navy
CDR Patrick Marshall	Coast Guard
Rance Hutchings, Pharm.D. (For Dr. Trevor Rabie)	Uniformed Services Family Health Plans (USFHP)
Joe Canzolino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

Col James E. Cox, Jr. MC	Air Force

OTHERS PRESENT

COL William Davies, MS, USA	DoD Pharmacy Program Director, TMA
CAPT Patricia Buss, MC, USN	Chief Medical Officer Representative, TMA
COL James Young, BSC, USAF	DoD Pharmacy Program Assistant Director, TMA
COL Kent Maneval, MS, USA	Joint Readiness Clinical Advisory Board
CDR Denise Graham, MSC, USN	DoD Pharmacoeconomic Center
CDR Ted Briski, MSC, USN (via TC)	DoD Pharmacoeconomic Center
CDR Don Nichols, MC, USN	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC, USAF	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC, USAF	DoD Pharmacoeconomic Center
CPT Jill Dacus, MC, USA	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Elizabeth Hearin	DoD Pharmacoeconomic Center
Lisa LeGette	Express Scripts
Elaine Furmaga	Department of Veterans Affairs
Four pharmacists	Iraq Ministry of Health

3. **REVIEW MINUTES OF LAST MEETING** – The minutes from the last meeting were accepted as written.

4. **INTERIM/ADMINISTRATIVE DECISIONS** – None

5. **UNIFORM FORMULARY (UF) PROPOSED RULE** – COL William Davies, DoD Pharmacy Program Director, TMA, updated the Committee on the current status of the Uniform Formulary. The final Uniform Formulary Rule was published 1 Apr 2004. It is available at: http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2004/04-7129.htm.

6. **TRICARE RETAIL PHARMACY (TRRx) UPDATE –** Libby Hearin (PEC) updated the Committee on the status of the TRICARE Retail Pharmacy (TRRx) Program implementation. TRRx establishes a retail pharmacy network that will provide outpatient prescription services to TRICARE beneficiaries throughout the United States, Guam, Puerto Rico, and the U.S. Virgin Islands. Express-Scripts, Inc (ESI) is the contractor for TRRx. ESI is also the contractor for the TRICARE Mail Order Pharmacy (TMOP).

   Beneficiary and provider information concerning TRRx is currently available on the TRICARE Pharmacy site (www.tricare.osd.mil/pharmacy) and on ESI's site at www.express-scripts.com. ESI marketing materials include benefit guides, pharmacy information cards, and introductory letters with a list of network pharmacies closest to beneficiaries. Mail-outs to beneficiary households, TRICARE Service Centers, and placement on the TRICARE SMART site (www.tricare.osd.mil/smart) for MTFs begin 22 Apr 2004.

7. **BCF AND TRICARE MAIL ORDER PHARMACY (TMOP) FORMULARY ISSUES** – The Committee determined the TMOP formulary status, TMOP or retail network formulary restrictions (quantity limits or prior authorization), and Basic Core Formulary (BCF) status for two new drugs and one new combination product. The Committee also confirmed the status of two new formulations of existing products (see Appendix A).

7. **ENFUVIRTIDE (FUZEON)** – The manufacturer of enfuvirtide (Fuzeon) has discontinued the controlled distribution program for this product. Under the controlled distribution program, enfuvirtide was previously available in the retail network only through a specialty pharmacy (Chronimed) and was not available in the TMOP. MTFs could purchase enfuvirtide through a special arrangement with Chronimed, but were not able to use the prime vendor system to obtain the product.

   The manufacturer reports that shipping to wholesalers started 14 Apr 2004. The product is expected to be available through U.S. retail and specialty pharmacies staring 26 Apr 2004. MTFs should be able to order Fuzeon from wholesalers as of 26 Apr 2004. Additional information is available at www.pec.ha.osd.mil/Controlled_Distribution_Drugs.htm or from the manufacturer's website (www.fuzeon.com) or help line (1-877-438-9366).

   Enfuvirtide is approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. It is given via subcutaneous injection twice daily and may be self-administered by the patient. The Committee will consider Fuzeon for addition to the TMOP Covered Injectables List as soon as it is clear that supplies of enfuvirtide are adequate and that the TMOP will have no difficulty obtaining the product.

9. **SERMORELIN (GEREF, SERONO)** – The Geref brand of sermorelin (growth hormone releasing hormone) has been withdrawn from the market. The diagnostic product (Geref Diagnostic) is still available. Since the therapeutic product is no longer available, the Committee removed sermorelin from the TMOP Covered Injectables List.

10. **KETOROLAC ORAL** – Currently, ketorolac (Toradol) tablets are available from the TMOP with a quantity limit of 5 days supply per 30 days. Express-Scripts does not typically make ketorolac tablets available through mail order plans, so they requested that the Committee consider discontinuing availability of ketorolac tablets at the TMOP. In the 6-month period from Oct 2003 to Mar 2004, the TMOP filled 41 prescriptions for ketorolac tablets, none of which exceeded 20 tablets (a 5-day supply at maximum recommended dosing). The Committee decided that since some patients do fill prescriptions for ketorolac tablets through the TMOP and since there is no indication that patients are receiving excessive quantities of ketorolac, ketorolac tablets will remain on the TMOP Formulary with the current quantity limits.

11. **QUININE** – Quinine has historically been used for nocturnal leg cramps, but this has never been an FDA-approved indication. In 1994-1995, the FDA halted the sale and distribution of OTC quinine sulfate for leg cramps due to its serious risks (Federal Register, 22 Aug 1994). In 1995, the FDA sent letters to manufacturers ordering a halt to the promotion of prescription quinine for leg cramps (FDA Consumer, 1995). In 1998, the FDA halted the sale and distribution of OTC quinine for malaria (Federal Register, 20 Mar 1998). In Feb 1999, the DoD P&T Committee excluded quinine from the National Mail Order Pharmacy (the

previous mail order program), based on the FDA's actions. Since a formulary does not exist in the retail network, the Committee could not take similar action in regard to the availability of quinine in the retail network. Quinine continues to be available in the retail network.

The only FDA-approved indication for quinine is as a prescription drug for the second-line treatment of malaria, but the vast majority of quinine prescriptions are most likely for treatment of leg cramps. Quinine is also available in food products and dietary supplements.

The Committee agreed that drugs available in the TMOP and the retail network should be consistent whenever reasonable and possible. The Committee considered three options:

- Make quinine available without formulary restriction in both TMOP & the retail network (TRRx).
- Subject quinine to formulary restrictions in both TMOP and TRRx.
- Maintain the status quo.

Background

Nocturnal leg cramps are a common problem in elderly patients. Nonpharmacological treatments (e.g., stretching, heat, correction of dehydration or electrolyte imbalances) are considered first-line therapies. Besides quinine, medications that have been used to treat nocturnal leg cramps include gabapentin, verapamil, muscle relaxants, vitamin E, magnesium, and B-complex vitamins.

Efficacy

Two systematic reviews of quinine for leg cramps support its efficacy for this condition:

- In 1995, Man-Son-Hing M et al (BMJ 1995; 310:13-7) reviewed six placebo-controlled cross-over trials including 107 patients, mostly elderly. Patients received 200-300mg quinine sulfate/day over 2- 4 weeks. Compared to placebo, quinine resulted in 8.83 fewer cramps over 4 weeks (95% CI 4.16 , 13.49) based on 5 trials in 82 pts, a relative risk reduction of 43% (95% CI 21%, 65%). There was a 27.5% reduction (95% CI 30.6%, 24.4%) in the number of nights with cramps, based on 2 trials in 51 pts. There was no statistically significant change in the severity or duration of cramps.
- In 1998, Man-Son-Hing M & Wells G, (J Gen Intern Med 1998; 13:600-6) published an updated meta-analysis including pooled individual patient data (combined n=659) from 8 randomized, double-blind, placebo-controlled trials (7 cross-over trials), 4 of which were unpublished. Patients taking quinine had 3.6 (95% CI 2.15 , 5.05) fewer leg cramps over 4 weeks compared to placebo, a relative risk reduction of 21% (95% CI 12% , 30%). Investigators concluded that while publication bias was present (almost all published studies reported higher efficacy than unpublished studies), quinine still appeared to be more effective than placebo in reducing the frequency of nocturnal leg cramps.

Safety/Tolerability

- The FDA's 1994-1995 regulatory actions were based on 157 reports of quinine-associated adverse drug reactions (1969 through mid-1992), 105 of which involved dosing within recommendations. The reports included 16 deaths and 40 hospitalizations.
- Adverse effects at doses used for leg cramps include dizziness, fever, nausea and vomiting, diarrhea, visual or auditory disturbances, and thrombocytopenia (rare but

potentially fatal). Quinine should NOT be used in pregnancy (Category X), should be used with caution in patients with renal failure, and should be avoided in patients with hepatic failure. Patients with a history of immune mediated thrombocytopenia or G-6-PD deficiency should not receive quinine.

- Brinker & Beitz (Am J Hematol 2002; 70:313-7) reported on a case series of thrombocytopenia associated with quinine. Of 397 adverse drug reactions for quinine reported to the FDA from 1974 – 2000, there were 141 reports of apparently isolated thrombocytopenia. After eliminating cases confounded by disease or drug therapy, investigators focused on 64 reports. The typical presentation of thrombocytopenia appeared to be rapid (median time-to-onset 7 days) and severe (hospitalization in 57 cases). Investigators suggested that clinicians evaluating patients with new-onset thrombocytopenia watch for quinine use, including food and dietary supplements.
- Kojouri et al (Ann Intern Med 2001;135:1047-51) reported that 11% of 132 consecutive cases of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) were associated with quinine. They commented that the toxicity appeared immune-mediated, with a sudden onset. Women may be more susceptible than men.
- Quinine has a long half-life, is protein-bound, and is metabolized by CYP450. It has several potentially dangerous drug-drug interactions, including elevation of digoxin levels and increased effect of anticoagulants.

Other Factors

Various criteria, guidelines, and recommendations from published reviews conclude that while quinine should not be used first-line, cautious use may be justified in patients with severe symptoms who have failed other treatments.

- The VA's nonformulary criteria for use (available at www.vapbm.org) recommend reserving use of quinine for nocturnal leg cramps for patients who have failed other modalities and who have severe symptoms requiring treatment. Patients should be advised of the potential for adverse drug reactions.
- Similar advice is provided by the UK National Health System's PRODIGY guidance, (http://www.prodigy.nhs.uk/guidance.asp?gt=Leg%20cramps) which recommends non-drug treatment first-line, with drug treatment only in people with regular cramps significantly affecting quality of life. The guidance suggests that clinicians monitor the risk-benefit ratio with quinine due to the potentially toxic effects.
- The April 2004 Pharmacist's Letter succinctly summarizes the dilemma, suggesting that pharmacists "help people understand pros and cons and decide for themselves…"

Quinine Utilization

- A total of 28,655 DoD beneficiaries received at least one prescription for quinine at MTFs or retail pharmacies in the six months from Oct 2003 to Mar 2004. Of these, 20,557 received quinine prescriptions in retail pharmacies, 8,369 at MTF pharmacies (does not add to 28,655 because some beneficiaries used both points of services).
- Utilization of quinine is increasing, most likely due to the increased numbers of patients 65 years of age and older using the retail network.

The Committee agreed that the non-availability of quinine in the TMOP probably did not decrease the use of quinine for nocturnal leg cramps, since patients could readily fill these prescriptions at retail network pharmacies. The Committee voted to add quinine to the TMOP Formulary. Quinine will be available from the TMOP and retail network without a prior authorization or other formulary restriction. Considerations included:

- Clinical evidence of efficacy of quinine in the treatment of nocturnal leg cramps and the existence of criteria, guidelines, and reviews supporting cautious use in patients for whom the benefits outweigh the considerable risks.
- The absence of an FDA-mandated special distribution process or special monitoring requirements for quinine.
- The incongruence of denying prescriptions for quinine in the TMOP while filling prescriptions for quinine in retail pharmacies.

The Committee noted that the TMOP provides a patient information insert with all medications, including quinine. Patients using the TMOP have access to a toll-free number for pharmacist consultation. Individual providers and pharmacists should assess the patient-specific benefits and risks of this medication and educate patients accordingly.

12. QUANTITY LIMITS

A. *Follitropin beta (Follistim AQ)* – All injectable gonadotropins, including follitropin, currently have a quantity limit of 3600 IU per 30 days (no refills) in both TMOP and the retail network. These products are also subject to prior authorization. Follistim AQ is a new formulation of follitropin beta in a pre-filled, pre-mixed cartridge for use with the "Follistim Pen." It is supplied in a box containing 4 needles and 1 prefilled cartridge containing either 300 or 600 IU of follitropin beta. The Committee established quantity limits for this new formulation consistent with existing products. These quantity limits apply to both TMOP and retail:

   - 300 IU cartridge: 12 cartridges (3600 IU) per 30 days, no refills
   - 600 IU cartridge: 6 cartridges (3600 IU) per 30 days, no refills

B. *Anakinra (Kineret)*- As of 23 Feb 2004, Amgen stopped selling 7-syringe packs of anakinra. Anakinra is now available only as 28-syringe packs (4 weeks supply). The current quantity limit for anakinra in the TMOP is a 6-week supply (6 packages of 7 syringes). The Committee voted to change the quantity limits for anakinra to the following:

   - TMOP: 56 syringes = 2 packages of 28 syringes per 56 days (8 weeks supply);
   - Retail: 28 syringes = 1 package of 28 syringes per 28 days (4 weeks supply)

   The Committee decided to assess the impact of the increased quantity limit on utilization of anakinra before considering any changes to the current 6-week quantity limits for etanercept (Enbrel) and adalimumab (Humira), which are similar injectable agents also used for the treatment of rheumatoid arthritis and available from the TMOP.

13. PRIOR AUTHORIZATIONS (PAS)

A. *Implementation of the Growth Hormone PA* – The Committee recommended implementation of the PA in both TMOP and the retail network as of 1 Jun 2004 for new patients only (i.e., patients presenting a new growth hormone prescription at a retail

network pharmacy or the TMOP for whom there was no prescription fill for growth hormone in the preceding 180 days).

The Committee recommended that patients who are currently receiving growth hormone in the TMOP and retail network (based on use within the last 180 days) should be required to fulfill PA requirements within 180 days after being notified about the existence of the PA. A method to notify patients who are currently receiving growth hormone from the TMOP or a retail network pharmacy has not been finalized.

A total of 1147 DoD beneficiaries received at least one prescription for growth hormone during the six-month period from Oct 2003 to Mar 2004. Of these, 220 received growth hormone prescriptions in retail pharmacies, 443 at MTF pharmacies, and 506 in the TMOP (does not add to 1147 because some beneficiaries used more than one point of service).

14. ADJOURNMENT – The meeting adjourned at 1130 hours. The next meeting is scheduled for 29 and 30 June at the PEC. All agenda items should be submitted to the co-chairs no later than 4 June 2004.

<signed>
DANIEL D. REMUND
COL, MS, USA
Co-chair

<signed>
TERRANCE EGLAND
CDR, MC, USN
Co-chair

List of Appendices

APPENDIX A: DOD P&T COMMITTEE FORMULARY DECISIONS REGARDING NEWLY APPROVED DRUGS

Generic name (Trade name; manufacturer)	**FDA approval date, drug class, FDA-approved indication**	**TMOP Formulary status**	**TMOP and/or retail network formulary restrictions**	**BCF status**
Amlodipine besylate / atorvastatin tablets (Caduet; Pfizer)	2 Feb 2004. Combination tablet approved for patients for whom treatment with both amlodipine and atorvastatin is appropriate; i.e., hyperlipidemia AND hypertension, chronic stable angina, or vasospastic angina Launch date is 27 Apr 2004.	Not added to the TMOP Formulary Atorvastatin is not on the TMOP Formulary due to provisions of the statin contract; amlodipine is available from the TMOP	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** Nifedipine sustained release, simvastatin (contract statin)
Epinastine HCl 0.05% ophthalmic solution (Elestat; Allergan)	12 Oct 2003 (not launched until Jan 2004). Topically active antihistamine with mast cell stabilizing properties, indicated for the prevention of itching associated with allergic conjunctivitis.	Added to the TMOP Formulary	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** There are no ophthalmic antihistamine products on the BCF.
Tiotropium bromide inhalation powder (Spiriva HandiHaler; Boehringer / Pfizer)	30 Apr 2004 (Launch date is not expected until 11 Jun 2004). Tiotropium bromide is an anticholinergic with specificity for muscarinic receptors. It is indicated for the long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. It is not indicated to relieve dyspnea associated with COPD. The product consists of a capsule containing a dry powder formulation of tiotropium bromide, intended for use with the HandiHaler oral inhalation device.	Added to the TMOP Formulary	**Quantity Limits** TMOP: 90 caps per 90 days (3 packages of 30 caps for inhalation) Retail: 30 caps per 30 days (1 package of 30 caps for inhalation) **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: Albuterol MDI; Ipratropium MDI (Atrovent); albuterol /ipratropium MDI (Combivent); salmeterol / fluticasone (Advair Diskus) and salmeterol DPI (Serevent Diskus)
Mycophenolic acid delayed-release tablets (Myfortic; Novartis)	Immunosuppressant approved for the prophylaxis of organ rejection in patients receiving renal transplants. It is administered in combination with cyclosporine and corticosteroids. This product is a new formulation of mycophenolate mofetil (Cellcept).	Added to the TMOP Formulary as a line extension	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents:** none
Clozapine orally disintegrating tablets (Fazaclo; Alamo Pharmaceuticals)	Clozapine is an atypical antipsychotic agent approved for schizophrenia. This product is formulated as an orally disintegrating tablet.	Not added to the TMOP Formulary. Clozapine is excluded from the TMOP due to monitoring requirements and dispensing restrictions mandated by the FDA.	**Quantity Limits** General rule applies **Prior Authorization** None	Not added to the BCF **Similar BCF agents**: Quetiapine (Seroquel) and risperidone (Risperidal)

APPENDIX B: COMBINED SUMMARY OF FORMULARY CHANGES FROM THE APRIL 2004 DOD P&T EXECUTIVE COUNCIL & DOD P&T COMMITTEE MEETINGS

1. **BCF CHANGES**

   A. *Additions to the BCF - None*

   B. *Deletions, changes, clarifications or exclusions from the BCF*

      1) Fexofenadine (Allegra) was removed from the BCF. There is no longer a second generation antihistamine on the BCF. The BCF now states that MTFs must have at least one second generation antihistamine on their formularies. The Council strongly encourages all MTFs to include loratadine on their formularies.

2. **TMOP FORMULARY CHANGES**

   A. *Additions to the TMOP Formulary*

      1) Epinastine HCl 0.05% ophthalmic solution (Elestat; Allergan)
      2) Tiotropium bromide inhalation powder (Spiriva HandiHaler; Boehringer/Pfizer) – has quantity limits (see Section 3 below)
      3) Mycophenolic acid delayed-release tablets (Myfortic; Novartis)
      4) Quinine

   B. *Exclusions from the TMOP Formulary*

      1) Amlodipine/atorvastatin (Caduet; Pfizer) (combination tablets) – excluded from the TMOP Formulary due to current statin contract
      2) Clozapine orally disintegrating tablets (Fazaclo; Alamo Pharmaceuticals) – excluded from the TMOP Formulary due to monitoring requirements and dispensing restrictions mandated by the FDA
      3) Sermorelin (Geref, Serono) – removed from the TMOP Covered Injectables list

3. **QUANTITY LIMIT CHANGES (RETAIL NETWORK AND TMOP)**

   A. Quantity limits for follitropin beta injection (Follistim AQ) for both TMOP and retail:

      - 300 IU cartridge: 12 cartridges (3600 IU) per 30 days, no refills
      - 600 IU cartridge: 6 cartridges (3600 IU) per 30 days, no refills

   B. TMOP quantity limits for Anakinra (Kineret) were changed to an 8-week rather than a 6-week supply, to accommodate discontinuation of the 7-syringe pack. Anakinra is now available in 28-syringe packs only. Quantity limits in the retail network remain unchanged.

      - TMOP: 56 syringes = 2 packages of 28 syringes per 56 days (8 weeks supply);
      - Retail: 28 syringes = 1 package of 28 syringes per 28 days (4 weeks supply)

   C. Quantity limits for tiotropium bromide inhalation powder (Spiriva)

      - TMOP: 90 caps per 90 days (3 packages of 30 caps for inhalation)
      - Retail: 30 caps per 30 days (1 package of 30 caps for inhalation)

4. **CHANGES TO THE TMOP PRIOR AUTHORIZATION (PA) PROGRAM**

   A. *Growth Hormone* – The Committee recommended implementation of the PA in both TMOP and the retail network as of 1 Jun 2004 for new patients only (i.e., patients presenting a new growth hormone prescription at a retail network pharmacy or the TMOP for whom there was no prescription fill for growth hormone in the preceding 180 days). A method to notify patients who are currently receiving growth hormone from the TMOP or a retail network pharmacy about the existence of the PA has not been finalized.