Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **20 November 2002**

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 1515 hours on 20 November 2002 at the Uniformed Services University of the Health Sciences, Bethesda, Maryland.

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
MAJ Travis Watson, MS	Army
COL John R. Downs, MC (via VTC)	Air Force
COL Bill Sykora, MC	Air Force
LtCol George Jones, BSC	Air Force
CAPT Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
CAPT Robert Rist	Coast Guard
Kathy Tortorice (Representing Dick Rooney)	Department of Veterans Affairs

VOTING MEMBERS ABSENT

Physician	Army

OTHERS PRESENT

COL Geoffrey W. Rake, MC	Medical Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
COL Mike Heath	Army Pharmacy Consultant Chair, DoD Pharmacy Board of Directors
MAJ John Howe, BSC	Defense Supply Center Philadelphia
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
Paul Vasquez	Defense Supply Center Philadelphia
Vincent Valinotti	Defense Supply Center Philadelphia
LTC Marc Caouette, MS	Joint Readiness Clinical Advisory Board
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
COL Doreen Lounsbery, MC	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC (via VTC)	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC (via VTC)	DoD Pharmacoeconomic Center
LT Chad McKenzie, MSC (via VTC)	DoD Pharmacoeconomic Center, Idaho State PharmD Internship
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke (via VTC)	DoD Pharmacoeconomic Center
Eugene Moore (via VTC)	DoD Pharmacoeconomic Center
Angela Allerman (via VTC)	DoD Pharmacoeconomic Center
CAPT Sandra Yerkes, MC	Deputy, Chief Medical Corps BUMED
LTC Emery Spaar, MS	U.S. Army Officer resident at AMCP
Michael Valentino	Department of Veterans Affairs, PBM

3. REVIEW MINUTES OF LAST MEETING

The minutes from the last meeting were accepted as written.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

A. *Membership*: Currently the DoD P&T Executive Council has 12 voting members and the DoD P&T Committee has 13 voting members. All other members are listed as others present. COL Remund will send out a copy of the existing charter to all members and recommendations for changes to the charter regarding membership should be sent to the chairs prior to the March meeting. The Council will decide at that time whether changes need to be made to the charter.

B. *Venlafaxine extended release capsules (Effexor XR) blanket purchase agreement (BPA):* At the August 2002 meeting, the Council voted to add venlafaxine extended release 37.5, 75, and 150 mg capsules to the BCF, contingent on the signing of a BPA between Wyeth-Ayerst and Defense Supply Center Philadelphia (DSCP). The BPA was recently signed, so Effexor XR is now on the BCF and facilities are required to include it on their formularies.

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

Contract awards, renewals, and terminations

- New joint DoD/VA contracts were awarded for albuterol inhaler and lisinopril (West-ward; bottles of 100 effective November 21, 2002 and bottles of 1000 effective March 2003).
- The following joint DoD/VA contracts were not awarded because the bid prices were higher than existing FSS prices: penicillin, amoxicillin, dicloxacillin, and cephalexin.
- The following joint DoD/VA contract is in various stages of solicitation: tretinoin cream.

6. PENDING PROCUREMENT INITIATIVES

A. Status of contracting initiatives

- The joint DoD/VA solicitation for a leutinizing hormone releasing hormone (LHRH) agonist has closed. An award is expected in January 03.
- A joint DoD/VA solicitation will not be issued for a nasal corticosteroid. A DoD/VA incentive agreement for fluticasone (Flonase) is being developed and will likely be finalized in December 02.
- A joint DoD/VA solicitation for a "triptan" has been issued and is scheduled to close in early December.
- A revision of the current incentive agreement for levofloxacin is being negotiated.
- A joint DoD/VA solicitation is being developed for an angiotensin receptor blocker (ARB) and is scheduled to be issued during the first quarter of CY 03.
- A joint DoD/VA solicitation for a "statin" is scheduled to be issued in late December 02.
- A joint DoD/VA solicitation for a thiazolidinedione is being developed. A projected issue date is not yet identified.
- The lisinopril contract has been awarded. Details are available at: http://www.dmmonline.com/pharm/indivdrugs.asp?id=83

B. Proposed BPA for tolterodine extended release capsules (Detrol LA) – In June 2001 the Council discussed the drugs used for treating overactive bladder (OAB) in response to several requests to add Detrol LA to the Basic Core Formulary (BCF). At that time the Council concluded that none of the drugs should be added to the BCF because none of them offered sufficient clinical benefit to justify their significantly higher cost compared to oxybutynin immediate release. Pharmacia is now offering a BPA that would reduce the price of Detrol LA if it were added to the BCF.

The Council considered the following information:

- A head-to-head study of Ditropan XL and Detrol LA found that Detrol LA was better tolerated (patients' perceptions reported on a visual analog scale) and slightly more effective (patients' perceptions reported on a 6-point Likert scale)
- An analysis of PDTS data from Jul 01 to Oct 02 showed that 58.4% of patients prescribed Detrol LA obtained at least one refill of their prescription, compared to only 36.7% for Detrol, 36.1% for Ditropan XL, and 30.7% for oxybutynin immediate release. The higher

refill rate for Detrol LA may indicate that patients tolerate it better than other agents and/or that patients perceive that it works better than the other agents.

- Dr. John Fischer, an Air Force urogynecologist, briefed the Council via VTC on his clinical experiences with patients and patient perceptions of benefit. Dr. Fischer recommended that the Council add Detrol LA to the BCF.
- Detrol LA usage has increased much more than other agents for OAB. Data from all outpatient pharmacy points of service in the MHS show that the number of patients getting prescriptions filled for Detrol LA more than tripled from 4,000 patients in Jul 01 to nearly 13,000 patients in Oct 02.

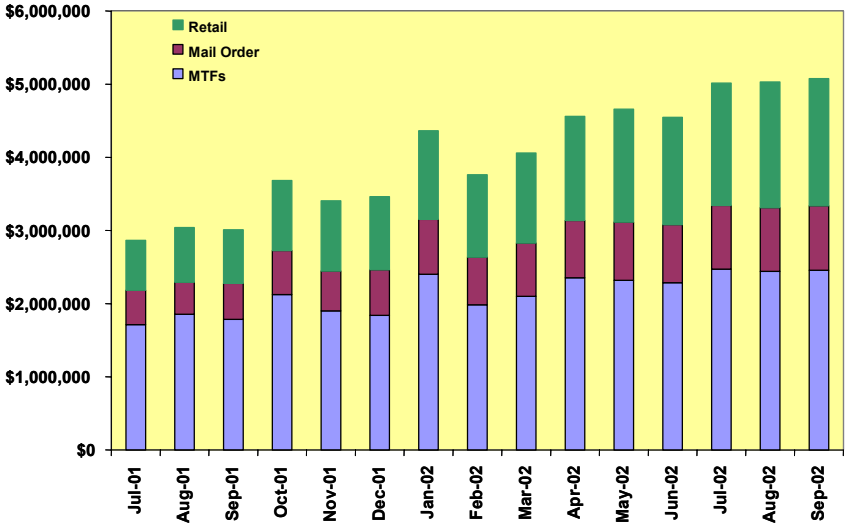
The Council voted to add Detrol LA to the BCF and advise DSCP to accept the proposed BPA.

7. **GENERIC CONTRACTS -** CDR (sel) Ted Briski informed the Council that some solicitations for joint DoD/VA generic contracts do not elicit competitive bids because the generic companies have trouble meeting the large demand from both agencies. He asked the Council whether the need for standardization was still a legitimate reason for pursuing these contracts. Council members stated that standardization is needed by both agencies, particularly to support the use of automation. The Council suggested the two agencies might be more successful by pursuing separate contracts to avoid overwhelming the production capabilities of the generic manufacturers. CDR (sel) Briski stated he would work with the Federal Pharmacy Executive Steering Committee (FPESC) sub-committee for contracting to find viable solutions to the problems encountered. The Council unanimously agreed on the motion to strive to achieve inter-agency standardization through whatever means are available.

8. **ARB Place In Therapy (PIT) Recommendation –** The Council discussed a draft of the Angiotensin II receptor blocker (ARB) place in therapy recommendations. The Council had requested guidelines for ARB use at the last meeting as part of their decision to pursue a procurement strategy to select one of these agents for BCF status, as these agents are significantly more expensive than ACE inhibitors, and their place in therapy is not yet clearly defined. The PIT recommendation is intended to aid practitioners in the appropriate use of the ARBs, and provides a summary of the literature for use in hypertension, congestive heart failure, and diabetic nephropathy. COL Downs expressed concern about the designation of ARBs as the initial agents of choice for diabetic nephropathy in Type 2 diabetes. Members also expressed concern about placement of pricing information at the beginning of the document. The Council asked the Pharmacoeconomic Center (PEC) to work with COL Downs to revise the document and report back at the next meeting.

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

A. *Bisphosphonates* — Oral bisphosphonates are the most frequently prescribed drug therapy for the treatment of osteoporosis. Alendronate and risedronate are currently indicated for the prevention and treatment of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, and Paget's disease. Alendronate is also indicated for osteoporosis in men. Both bisphosphonates are available in daily or weekly dosing formulations. The weekly dosage forms account for the majority of DoD usage. The DoD now spends about $5 million a month on oral bisphosphonates across all outpatient pharmacy points of service. Bisphosphonates rank number 8 in Military Treatment Facility (MTF) overall drug expenditures.



MHS Bisphosphonate Monthly Expenditures

Source: PDTS & Prime Vendor Data

Therapeutic Interchangeability:

- *Efficacy* – There are no head-to-head trials that compare fracture rates for alendronate and risedronate. Tables 1-4 in Appendix A show 'funnel' diagrams of the relative risk of vertebral and non-vetebral fractures for each drug compared to placebo from a recently published meta-analysis. Table 5 in Appendix A shows the results of studies that compared each drug to placebo for hip fractures. In their responses to a PEC survey, 50 out of 57 DoD providers stated that they believe alendronate and risedronate have similar efficacy. The Council concluded that alendronate and risedronate have similar efficacy in reducing fractures.
- *Safety/Tolerability* – Oral bisphosphonates are well tolerated when taken according to manufacturers' recommendations. Clinical trials show adverse event rates that are not statistically different from placebo, but gastrointestinal disturbances (sometimes severe) can occur if patients do not follow dosing instructions. Two head-to-head trials examined the tolerability of alendronate and risedronate. The first head-to-head trial compared 28-day regimens of alendronate 40 mg and risedronate 30 mg. The study failed to find a statistically significant difference in endoscopically diagnosed ulceration or patient-reported GI toxicity. The second study evaluated 14-day regimen of alendronate 10 mg and risedronate 5mg. A significant difference in endoscopically diagnosed ulceration was found for gastric ulcers (13.2% for alendronate group and 4.1% for risedronate group), but not for esophageal or duodenal ulcers. No significant difference in patient-reported upper GI adverse events was seen between each group and no correlation was found between upper GI events and the presence or absence of gastric or esophageal ulcers. An accompanying editorial regarding this study stated, "the clinical relevance of small endoscopic ulceration observed is unclear." The editorial also stated, "it is controversial whether acute endoscopically diagnosed superficial mucosal injury (including gastric ulcers as small as 3mm in diameter) is at all related to subsequent development of serious clinical consequences..." The Council concluded that alendronate and risedronate are similar in regard to safety and tolerability.

Coverage of Clinical Needs: Although alendronate is the only bisphosphonate that has an FDA-approved indication to increase bone mass in men with osteoporosis, an analysis of DoD prescription data showed that the percent of total days of therapy dispensed to men were similar for both alendronate and risedronate. The difference in FDA-approved indications does not

appear to affect usage of the two drugs in clinical practice. The Council concluded that either agent would likely meet the clinical needs for more than 90% of the population requiring treatment.

Provider Acceptance:

- *New Starts*- The majority (48 - 7) of providers responding to a PEC survey were willing to use either agent equally. Some providers preferred alendronate because of its indication for osteoporosis in men and perception of greater efficacy in reducing hip fractures.
- *Patient Switches* – The majority (43 - 16) of providers were also willing to switch current patients to the selected agent if the switch could be done at a regularly scheduled visit rather than incurring an extra visit.

The Council voted unanimously to support any contracting/formulary strategy (to include a closed class contract with patient switches) designed to lower the cost of bisphosphonate drug therapy for DoD.

B. Glaucoma Agents — Primary open-angle glaucoma (POAG) is the most common type of glaucoma. POAG leads to progressive visual field loss followed by central field loss, usually but not always in the presence of elevated intraocular pressure (IOP). Lowering IOP remains the primary modality for therapy for POAG and appears to protect against further damage. The therapy for POAG often is characterized by poor compliance since POAG is entirely asymptomatic.

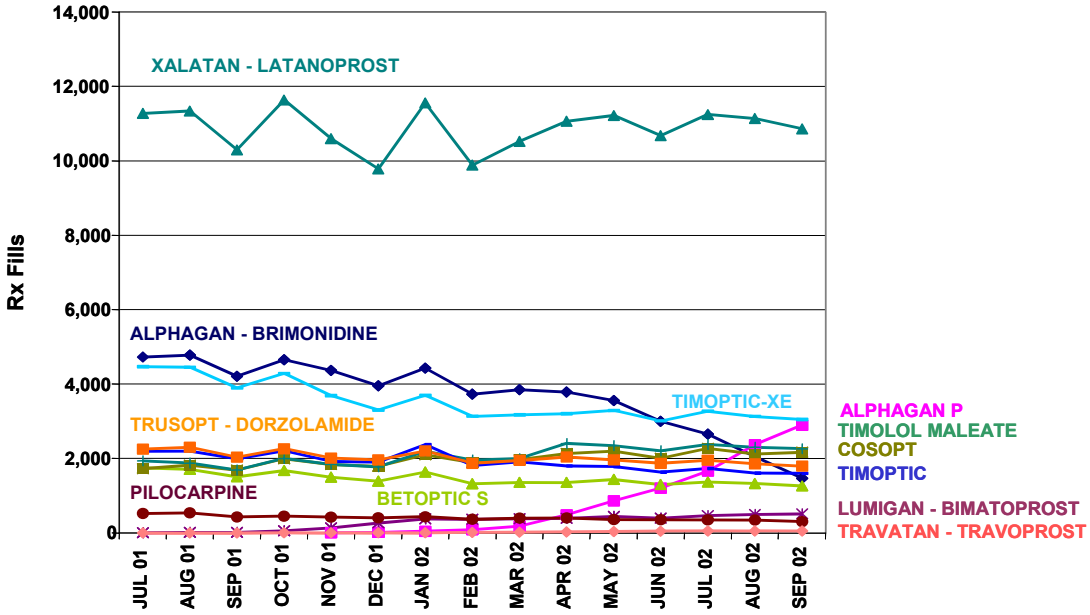
High utilization of latanoprost (Xalatan) and timolol maleate gel (Timoptic XE), which are not currently on the BCF, and new products for the treatment of glaucoma, triggered this class review. The PEC also received a request from the field to delete pilocarpine from the BCF due to low utilization.

Currently the BCF contains the following glaucoma medications:

- *Topical β-blocker* (timolol 0.25%, 0.5% ophth soln – Alcon Labs brand only- DoD mandatory source contract): This drug effectively lowers IOP by 27-35% and is considered initial drug therapy in primary open angle glaucoma (POAG) and ocular hypertension, except in patients with cardiac or pulmonary contraindications. Topical β-blockers have few ocular side effects, however major side effects are similar to those associated with systemic beta-blocker therapy (worsening of heart failure, bradycardia, heart block, and increased airway resistance). The current BCF listing does not include timolol maleate gel (Timoptic XE), which is applied once daily vs. the twice-daily ophthalmic solution.
- *Sympathomimetic agent* (brimonidine 0.15% ophth soln – Alphagan P): Efficacy studies report a decrease in IOP of 20-27%. These agents are indicated for both short-term treatment to prevent intraocular pressure (IOP) spikes after laser trabeculoplasty and for chronic treatment in patients with ocular hypertension or POAG. The Alphagan Purite 0.15% formulation has a 41% lower rate of ocular allergy than brimonidine 0.2% resulting in a reduced rate of discontinuation due to adverse events.
- *Miotic* (pilocarpine ophthalmic solution): Efficacy studies report a decrease in IOP of 20-30%. Pilocarpine's unique place in therapy is in the use for glaucoma emergencies such as acute angle closure glaucoma and glaucoma laser surgery.

MTF RX Fills for Anti-glaucoma Agents

(July 01-September 02)



Source: PDTS

The BCF does not contain medications in the following classes of glaucoma medications:

- *Carbonic anhydrase inhibitors (CAI):* Acetazolamide is the most commonly used oral CAI. These drugs effectively lower IOP by 20-40% with low ocular adverse effects, however their systemic adverse effects hamper their use in the management of glaucoma. These agents are contraindicated in patients with renal failure, hepatic insufficiency, lowered plasma potassium and sodium levels, and chronic obstructive pulmonary disease. Due to low utilization of these agents and their poor tolerability these agents were not considered for BCF inclusion.
- *Prostaglandins (latanoprost, bimatoprost, travoprost, unoprostone)*: These agents are indicated for the reduction of elevated IOP in patients with open angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.

Despite their "second line" place in therapy, the prostaglandin class has been targeted for a procurement strategy due to increased utilization, increased cost, and potential for price competition due to the number of agents in the market basket. A significant price reduction might be achieved through a procurement initiative that places one or more prostaglandin on the BCF. The following analysis focuses on prostaglandins.

Prostaglandin Clinical Efficacy: Clinical trials have not demonstrated *a priori* that treating to predefined IOP targets preserves vision. Nor have there been clinical trials demonstrating that more aggressive IOP lowering targets result in preservation of vision. Limited observational data suggests that patients achieving lower IOP with combined surgical and medical treatment experience less visual field deterioration. Finally, there are no clinical trials comparing the amount of preservation of visual acuity afforded by the different topical ophthalmic drops. All

comparisons of efficacy rely on the surrogate marker of lowering IOP. A measurement error of 1-2 mmHg may be seen in IOP measurement.

Randomized controlled clinical trials demonstrated that bimatoprost, travoprost, and latanoprost given once daily produced equal or superior efficacy to twice-daily timolol. Appendix B shows the results of prostaglandin head-to-head comparison trials.

Prostaglandin Safety and Tolerability: Both bimatoprost and travoprost have shown to have statistically significant more cases of hyperemia and pruritis than latanoprost. Mean hyperemia scores in all treatment groups, however, were in the trace to mild hyperemia range. Local adverse effects seem to be unassociated with long-term effects or increased discontinuation of medications in the clinical trials. See table 1 for adverse events related to prostaglandin ophthalmic agents found in head-to-head comparison trials.

Table 1: Adverse events related to prostaglandin ophthalmics

Study	Adverse Event	Timolol 0.5%	Latanoprost 0.005%	Bimatoprost 0.03%	Travoprost 0.004%	Unoprostone 0.12%
Tin Aung 2001	Ocular irritation	N/A	12/37 (32%)	N/A	N/A	21/34 (62%)
	Iris pigment changes	N/A	0	N/A	N/A	0
	Eye redness	N/A	13/37 (35%)	N/A	N/A	6/34 (18%)
Netland 2001	Hyperemia*	14%	27.6%	N/A	49.5%	N/A
	Iris pigment changes*	0%	5.2%	N/A	3.1%	N/A
	Eyelash changes*	3.1%	25.8%	N/A	57.1%	N/A
Gandolfi 2001	Hyperemia*	N/A	14.2%	36.1%	N/A	N/A
	Iris pigment changes	N/A	Not reported	Not reported	N/A	N/A
	Eyelash changes*	N/A	4.4%	12.6%	N/A	N/A
DuBiner 2001	Hyperemia	N/A	3/21 (14%)	3/21 (14%)	N/A	N/A
	Iris pigment changes	N/A	Not reported	Not reported	N/A	N/A
	Eyelash changes	N/A	Not reported	Not reported	N/A	N/A

Tin Aung: One patient on latanoprost did not complete the study because of severe swelling of the eyelids.
Netland: No reported discontinuations in article due to adverse events
Gandolfi: Six bimatoprost patients discontinued due to adverse events: 4 due to ocular events, 2 due to systemic and ocular adverse events. Five latanoprost patients discontinued due to adverse events: 2 due to ocular events, 3 due to systemic and ocular adverse events.
DuBiner: One patient discontinued from the latanoprost group because of body aches and stomach cramps. Two patients discontinued from the bimatoprost group because of ocular symptoms (eyelid edema, conjunctival hyperemia, foreign body sensation) or nausea and ocular symptoms (eyelid edema, asthenopia, conjunctival hyperemia).

Therapeutic Interchangeability: Unoprostone is not considered therapeutically equivalent to latanoprost, bimatoprost or travoprost because of its lower efficacy (Appendix B, Table 1) and twice-daily dosage schedule. Latanoprost, bimatoprost, and travoprost have each been demonstrated to provide statistically significantly greater reductions in IOP than timolol. Head-to-head trials did not show statistically significant differences between latanoprost and travoprost 0.004% or between latanoprost and bimatoprost in lowering IOP. Post-hoc subgroup analysis of the data from the clinical trial by Netland et al. showed that travoprost lowered IOP more than latanoprost at specific time points among African American study subjects. However, the IOP differences in the travoprost vs. latanoprost group in African American patients during treatment may have resulted from preexisting differences in baseline IOPs, some of which were statistically significant. If the results were expressed as a change in IOP from baseline measurements, no significant difference in efficacy of the drugs in African American population exists. The effect of travoprost in the African American population requires further analysis and clarification.

Both bimatoprost and travoprost may have more hyperemia and pruritis than latanoprost, but less iris or eyelash pigment changes. Mean hyperemia scores in all treatment groups were in the trace and mild hyperemia score. Local adverse effects seem to be unassociated with long-term effects or increased discontinuation of medication in the clinical trials.

Latanoprost currently requires refrigeration prior to dispensing to maintain a 36-month shelf life, while bimatoprost and travoprost do not. The manufacturer of latanoprost has stated their belief that the FDA will eliminate this requirement in early 2003.

Coverage of Clinical Needs: Latanoprost has 95% of the market share in MTFs and 79% in the MHS (MTF, NMOP, and retail). To date there are no studies to show that if one patient fails to respond to one prostaglandin that they will respond to another.

Provider Acceptance: Responses from ophthalmologists agreed that a prostaglandin should be on the BCF. Currently 75% of MTF formularies contain latanoprost, 9% bimatoprost, 4% travoprost, and 2% unoprostone. Providers stated that they are standard second line therapy in the treatment of glaucoma and first line therapy when beta-blockers are contraindicated. Two of the five ophthalmologists preferred latanoprost to other prostaglandins; the other three had no preference. Latanoprost has been on the market longer than the other prostaglandins, so providers have more confidence in its safety profile. Providers were uniformly opposed to a contract that would require patients to be switched from one prostaglandin to another.

Although pilocarpine has low utilization in the MTFs the Council unanimously voted to maintain its BCF status due to its unique place in therapy in the treatment of acute closed angle glaucoma. Timoptic XE has a utilization rate that is consistently higher than the contracted timolol ophthalmic solution, once daily vs. twice daily dosing that may potentially increase compliance, and a current contract price that makes its cost comparable to the ophthalmic solution. The Council unanimously voted to add Timoptic XE to the BCF. The Council voted unanimously 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.

10. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF ADDITION

A. *Atypical antipsychotics* –In November 2001, the DoD P&T Executive Council removed oral haloperidol from the BCF due to decreasing utilization and the perception that primary care providers in the outpatient setting do not commonly prescribe antipsychotics. The BCF does not currently include any agents approved specifically for the treatment of psychosis.

After considering the following, the Council agreed that one or more atypical antipsychotic agents are needed on the BCF:

- The PEC received two requests from MTF providers to add one or more atypical antipsychotics to the BCF (one for olanzapine and one for olanzapine and risperidone). The requestors argued that: atypicals are first-line agents in treating psychotic manifestations of psychiatric disorders, they are utilized by civilian and military psychiatrists and should be readily available for continuation treatment, and that typical antipsychotics are no longer standard of care for patients who need long-term therapy.
- All eleven MTF providers (10 psychiatrists, 1 internist) who responded to a PEC survey responded “yes” to the following question: “In your opinion, is there a need to make one or more atypical antipsychotic uniformly available across the MHS by adding it or them to the BCF (which would require all MTFs to add them to their formularies)?”

- Utilization of atypical antipsychotics at MTFs is increasing, both in absolute number of prescriptions and relative to prescriptions for typical antipsychotics.
- An analysis of formulary information from 102 MTFs revealed that 69 facilities had at least one atypical antipsychotic on formulary.
- Atypical antipsychotics are termed atypical due to a decreased propensity to induce extrapyramidal side effects (EPS) and decreased risk of tardive dyskinesia relative to typical antipsychotics. Atypical antipsychotics may also be more effective than typical antipsychotics for treating the negative symptoms of schizophrenia and may be effective in patients refractory to typical antipsychotics.
- Atypical antipsychotics are used for multiple conditions besides schizophrenia (e.g., bipolar mania, depression with psychosis, acute agitation in the elderly; symptoms of dementia including agitation, hyperactivity, hallucinations, suspiciousness, hostility and uncooperativeness; bipolar disorder, anxiety disorders, developmental disorders, autism, aggression/self injurious behavior, and Tourette's syndrome), some of which may be treated by primary care providers. In addition, primary care providers may continue medications written by specialists.
- Addition of an atypical antipsychotic to the BCF may foster the recapture of prescriptions from the retail point of service. However, the potential for recapture may be somewhat limited by the fact that civilian providers write about 50% of prescriptions for atypical antipsychotics filled by MTFs. Overall, civilian providers write about 40% of the prescriptions filled by MTFs (based on prescription data from the Uniformed Services Prescription Database).

The Council unanimously approved a recommendation that the PEC complete its review of the atypical antipsychotics and make a specific recommendation to the Council at the next meeting regarding the number of agents that should be added, and which agent(s) represent the most cost-effective choice.

B. *Oral contraceptives* – The BCF does not currently include an oral contraceptive (OC) with low estrogen content (20 mcg ethinyl estradiol [EE]). OCs with low estrogen content have a lower risk of venous thromboembolism and other adverse events. The two monophasic OCs with 20 mcg ethinyl estradiol most commonly used in MTFs are norethindrone/EE/ferrous fumarate 1/0.02 mg and levonorgestrel/EE 0.1/0.02 mg. The brand of norethindrone/EE/ferrous fumarate 1/0.02 mg most commonly used in MTFs is Loestrin FE, which is available at a cost of about $0.21 per cycle. A generic equivalent for Loestrin FE, Microgestin FE, is available but is not currently listed on the FSS. The brand of levonorgestrel/EE 0.1/0.02 mg most commonly used in MTFs is Alesse, which is available at a cost of about $6.03 per cycle. A generic equivalent for Alesse, Aviane, is available but is not currently listed on the FSS. Aviane is the most commonly used product in this category in the retail network and NMOP.

After noting that previous attempts to contract for OCs met with limited success, the Council voted to add norethindrone/EE/ferrous fumarate 1/0.02 mg (Loestrin FE or its generic equivalent) to the BCF.

The Council was also informed that a generic version of ethinyl estradiol 35/norethindrone 0.5/0.75/1 mg oral (Ortho-Novum 7/7/7) is expected to be available early in 2003. The Council has previously discussed the difficulty of obtaining the best price for this product, since lower priced "clinic" packs are available only by direct purchase from the manufacturer, not from Prime Vendor, and the previous depot contract expired at the end of February 2002.

C. *Paroxetine controlled release (Paxil CR)* – Paxil CR is a controlled release formulation of paroxetine that shifts absorption to the small intestine and controls release of paroxetine over 4-5 hours. Because of reduced bioavailability, Paxil CR is formulated as 12.5, 25, and 37.5 mg tablets, which are equivalent to 10, 20, and 30 mg of immediate release paroxetine, respectively. Paxil CR was added to the NMOP formulary in May 2002, but it was not added to the BCF because the information available at that time did not demonstrate that Paxil CR offered any significant advantages compared to Paxil. Paxil CR was to be reviewed again at the November 2002 meeting for potential addition to the BCF.

The clinical trials of Paxil CR for major depressive disorder (MDD) included Paxil treatment arms, but the studies were not designed to compare the efficacy of Paxil CR to the efficacy of Paxil. The clinical trials of Paxil CR for treatment of panic disorder did not include Paxil treatment arms.

Pooled data from MDD trials showed that 23% of Paxil patients and 14% of Paxil CR patients reported nausea during the first week of therapy (a statistically significant difference). Statistically significant differences were not seen in the percentages of patients reporting nausea during weeks 2, 3, 4,or 12 of the trials. According to manufacturer information, the dropout rate in the two adult MDD trials was 6% for placebo, 10% for Paxil CR (non-significant difference), 16% for Paxil (significantly higher than placebo). Paxil CR and Paxil were not directly compared. The percentage of patients dropping out due to nausea was 3.7% in the Paxil CR arm and 0.5% in the placebo arm, but patient dropouts due to nausea were not reported for the Paxil arm.

Provider opinion survey results (12 total; 9 from psychiatry) are summarized as follows:

- 1 “add”
- 6 “don’t add”
- 3 “not sure/no opinion”
- 1 “if replaces Paxil at less cost
- 1 “may be some value; slower release may decrease dizziness, vertigo side effects”

Usage of Paxil CR is increasing in the retail network and NMOP, but very few prescriptions for Paxil CR are filled at MTFs. The FSS prices for Paxil CR and all strengths of paroxetine immediate release except the 40 mg tablet are currently the same: $1.31 per tablet ($1.49 for 40 mg). The prices for Paxil and Paxil CR are similar to FSS prices for other SSRIs, with the exception of the $0.04 contract price for generic fluoxetine 20 mg. It is unclear when a generic version of paroxetine will become available; patent litigation has been in progress since 1998.

The Council concluded that Paxil CR has not been shown to offer any significant clinical advantages over Paxil or other SSRIs on the BCF. The four SSRIs currently on the BCF are more than adequate to meet the clinical needs of DoD beneficiaries. The Council also noted that Paxil CR offers no economic advantage over Paxil or other SSRIs on the BCF and that generic fluoxetine is much less expensive than Paxil CR. Inexpensive generic paroxetine will eventually become available. The addition of Paxil CR to the BCF would likely result in higher costs in the long run, because Paxil CR users would be less likely than Paxil users to switch to generic paroxetine when it becomes available. The Council voted unanimously to exclude Paxil CR from the BCF listing for paroxetine. MTFs are not required to add Paxil CR to their formularies.

D. *Escitalopram (Lexapro; Forest Labs)* – Escitalopram is the S-isomer of citalopram (Celexa; Forest Labs). Citalopram is a racemic mixture (equal amounts of S- and R-citalopram). The s-isomer of citalopram appears to be solely responsible for the antidepressant properties of citalopram. The r-isomer exhibits little binding to serotonin receptors and demonstrates no antidepressant properties. Whether or not the r-isomer results in any clinically significant effect is unclear. Comparable efficacy of 10 mg escitalopram and 40 mg citalopram in clinical trials has led to the theory that the r-isomer may impede binding of the s-isomer at the serotonin receptor or impede receptor function in some other way. The r-isomer does demonstrate affinity for histamine receptors, which could theoretically increase side effects (e.g., sedation) with the racemic mixture compared to the s-isomer alone.

The Committee reviewed escitalopram for addition to the NMOP Formulary in May 2002, just prior to FDA approval. Review of escitalopram for the BCF was tabled until after the drug had been approved by the FDA and was on the market. There are currently four SSRIs on the BCF: citalopram (Celexa); generic fluoxetine - excludes Prozac, Sarafem & Prozac Weekly; paroxetine (Paxil); and sertraline (Zoloft). Forest Labs, which manufactures both citalopram and escitalopram, has ceased promoting citalopram (Celexa), although it will continue to be available. Forest has stated that it does not advocate switching patients who are stable on citalopram or other antidepressants to escitalopram.

Escitalopram is indicated for the treatment of major depressive disorder. The manufacturer's dossier of clinical information for escitalopram includes summaries of the following studies of escitalopram in the treatment of depression:

- Two published 8-week, fixed dose trials, one comparing escitalopram 10 mg to placebo and the other comparing escitalopram 10 mg, escitalopram 20 mg, or citalopram 40 mg to placebo.
- Unpublished data from two 8-week flexible-dose trials comparing escitalopram and citalopram to placebo.
- Unpublished data from a long-term (36 week) extension study
- A published analysis of pooled trial data focusing on anxiety symptoms in depressed patients

Unpublished data addressing the use of escitalopram in generalized anxiety disorder, social anxiety disorder, and panic disorder are also available.

The following table summarizes published efficacy data for escitalopram:

Reference	Trial Design	Primary Endpoint	Results
Burke et al. (J Clin Psych 2002; 63:331-6)	Double-blind, RCT in outpatients aged 18-65 years, with MDD for at least 4 weeks 1-week washout, period, then randomized to 8-week treatment with E10 (n=118), E20 (n=123), C40 (n=125), or placebo (n=119)	Change from baseline in MADRS score at Week 8	Placebo: -9.4 E10: -12.8* E20: -13.9* C40: -12.0*
Wade et al (Int Clin Psycopharmacol 2002; 17(3):95-102)	Double-blind, RCT in primary care patients aged 18-65 years, with MDD for at least 4 weeks 1-week washout period, then randomized to 8-week treatment with E10 (n=191) or placebo (n=189)	Change from baseline to final assessment of MADRS score	Placebo: -13.6 E10: -16.3*
Gorman et al (CNS Spectrums 2002: 7 (suppl 1):40-4)	Pooled data from fixed dose study (E10, E20, C40, placebo) & two flexible dose studies (E10-20, C20-40, placebo) combined n = 1321	Mean change in MADRS score at Week 8	Placebo: -11.2 E: -13.8* C: -13.1*

*p<0.05 vs. placebo
RCT = randomized controlled trial; MDD = major depressive disorder; MADRS = Montgomery Asberg Depression Rating Scale ;E10 = escitalopram 10 mg daily; E20 = escitalopram 20 mg daily; C40 = citalopram 20 mg daily

In the pooled data analysis, two different assessments were evaluated, with two additional analyses of one measure: the Montgomery Asberg Depression Rating Scale (MADRS), the MADRS among patients severely depressed at baseline, the MADRS Inner Tension Item Score, & CGI-I. In each case, the mean change from baseline was determined. For each measure, the mean change from baseline appeared to be significantly different than placebo at earlier time points for escitalopram than for citalopram. Given limited data and the *post priori* nature of the analysis, the existence of a real difference between escitalopram and citalopram with respect to onset of therapeutic effect remains unclear, as do the effect size and clinical importance of any such difference.

Escitalopram appears to have the same generally favorable drug interaction profile as citalopram. Based on available clinical trial data, there is little evidence of differences between the two products with respect to side effect profile. In an 8-week, fixed dose trial (Burke et al) comparing placebo, escitalopram 10 mg, escitalopram 20 mg, and citalopram 40 mg, withdrawal rates due to adverse events were 2.5%, 4.2%, 10.4%*, and 8.8%*, respectively (*p<0.05 vs. placebo). Somnolence occurred in less than 10% of patients in either group.

Provider opinion survey results (12 total; 8 from psychiatry):

- 2 “add”
- 7 “don’t add”
- 1 “too early to tell”
- 1 “add if it’s cheaper”
- 1 “don’t know”

Usage of escitalopram is increasing in the retail network, but very few prescriptions are filled at MTFs or in the NMOP. Forest has offered BPA prices for citalopram and escitalopram. Approval of a generic version of citalopram is not likely until 2005; citalopram’s new molecular entity patent expires July 2003 with a pediatric extension until January 2004.

The Council concluded that escitalopram does not offer significant clinical advantages over citalopram or other SSRIs on the BCF. The four SSRIs currently on the BCF are more than adequate to meet the clinical needs of DoD beneficiaries. The Council also noted that escitalopram offers no economic advantage over citalopram or other SSRIs on the BCF and that generic fluoxetine is much less expensive than escitalopram. Inexpensive generic citalopram will eventually become available. The addition of escitalopram to the BCF would likely result in higher costs in the long run, because escitalopram users would be less likely to switch to generic citalopram when it becomes available. The Council voted unanimously to exclude escitalopram from the BCF. MTFs are not required to add escitalopram to their formularies.

E. *Methylphenidate extended release capsules (Metadate CD)* – The Council reviewed Metadate CD for inclusion on the BCF, secondary to new clinical information and a BPA offer from Celltech Pharmaceuticals in exchange for placement on the BCF. The Council voted not to add Metadate CD to the BCF. The reasons for this decision were:

- The new clinical information presented by Celltech did not demonstrate that Metadate CD was clinically superior to Concerta.
  - The information provided was a summary of unpublished data that was not peer-reviewed.
  - There were concerns about the study design, statistical methods, and reporting of the results.
  - The assessment tools used to demonstrate the statistical superiority of Metadate CD are not routinely used in clinical practice, making it difficult to determine the clinical relevance of the research findings.
  - These assessment tools appeared to show that the active comparator Concerta was more efficacious at 12 hours post dose.
- Concerta was added to the BCF to take advantage of its long duration of action, which hopefully would eliminate the need for additional immediate release (IR) methylphenidate later in the school day. A subsequent analysis of PDTS data revealed that 7% of patients receiving Concerta required additional doses of IR methylphenidate later in the school day, compared to 43% receiving Ritalin SR. The data provided to the Council suggested that Metadate CD has a shorter duration of action than Concerta; some members of the Council were therefore concerned that it would be less effective than Concerta in eliminating the need for additional doses of IR methylphenidate later in the day.
- MTF providers responded negatively to the proposal to add Metadate CD to the BCF.
- The offered prices in the BPA proposal would not provide a substantial cost avoidance. While the daily cost of therapy would be lower for Metadate CD at low doses of medication, Metadate CD would actually still be more expensive at higher doses. Also, this price consideration does not take into account the increased likelihood of having to add afternoon or evening doses of immediate release methylphenidate to the regimen. The Council also felt it would be extremely unlikely that Metadate CD would achieve a 35% market share given that most providers surveyed were very pleased with the once-daily stimulant currently on the BCF (Concerta).

F. *Niacin extended release tablets (Niaspan)* – Since the publication of the National Cholesterol Education Program's Adult Treatment Panel III (ATP-III) last year, increasing focus is placed on positively affecting the entire lipid profile by using statin adjuncts for patients with mixed dyslipidemias. The DoD P&T Executive Council evaluated Niaspan (prescription only, extended–release niacin tablets) shortly after its FDA approval. The result was not to add Niaspan to the BCF at that time because sufficient data did not exist to justify its benefit over niacin immediate release therapy. Niacin immediate release oral (OTC) is currently on the BCF.

Since Niaspan's approval, clinical trials using Niaspan in combination with simvastatin and in type 2 diabetics have been published reinforcing niacin's beneficial effects in these populations. The PEC completed a database analysis assessing the tolerability of Niaspan and immediate release niacin treated patients. Niacin-naïve patients beginning Niaspan or other niacins in January and February of 2002 were identified and included for analysis. Patients remaining on therapy at least 6 months later were deemed a success for this analysis. In the Niaspan group, 55% (1676/3044) of the Niaspan group were successful versus 37% (282/769) of the other niacin group were successful in tolerating niacin therapy using continued therapy as the marker.

Niaspan is currently on approximately 40% of MTF formularies and is also on the VA National Formulary. The drug cost for Niaspan remains significantly more than immediate release niacin (~$0.30/tab of Niaspan vs. $0.02/tab of immediate release niacin). Fibrates are the mostly likely alternative to niacin therapy, and the drug costs are comparable ($0.20-$0.85/day) to Niaspan. Fibrates are better tolerated than niacin, but niacin is more effective at raising HDL and is generally considered less likely to cause myopathy than fibrates. Responses from healthcare providers at MTFs were overwhelmingly in favor of adding Niaspan to the BCF.

The Council concluded that niacin therapy remains a recommended treatment in many dyslipidemias. Niaspan significantly improves patient's ability to remain on niacin compared to older formulations, thus reducing the number of patients requiring less effective, and possibly less safe, alternatives.

The Council unanimously voted to replace immediate-release niacin with Niaspan on the BCF. MTFs may continue to have other niacin products on their formularies.

11. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF DELETION

A. *Guaifenesin extended release tablets* – Based on the following information, the Council voted to remove guaifenesin 600 mg extended release from the BCF. MTFs may decide whether or not to remove the product from their formularies.

- As of 12 July 2002, Mucinex (Adams Labs) became the first single ingredient guaifenesin extended release product to be 1) approved as safe and effective under a New Drug Application (NDA) and 2) to be approved as an over-the-counter (OTC) product.
- The FDA has determined that single ingredient guaifenesin extended release drug products are new drugs and require an approved application for marketing. The Durham-Humphrey Amendment of 1951 to the Food, Drug, and Cosmetic Act (FDCA) forbids simultaneous marketing of products of the same strength, dose, and indication for both OTC and prescription use. Manufacturers can no longer market single ingredient guaifenesin extended release products as prescription drugs. In October 2002, the FDA sent warning letters to manufacturers and distributors explaining that currently marketed single ingredient guaifenesin extended release products without an approved application are considered

misbranded and in violation of section 505(a) of the FDCA. The FDA requested action plans to bring their products into legal compliance. At least one affected manufacturer is known to be petitioning this action, but it is not known if any single ingredient guaifenesin extended release product other than Mucinex will continue to be available in the near future.

- The Council reviewed the issue of OTC coverage on the BCF at the May 2002 meeting. Although TRICARE policy (which limits coverage of OTCs to insulin, diabetic supplies, and vitamins when used as a specific treatment of a medical condition) does not govern the availability of OTC products at MTF pharmacies, the Council has historically refrained from adding OTC products to the BCF. In addition, the Uniform Formulary Proposed Rule states, "The Basic Core Formulary (BCF) is a subset of the Uniform Formulary and is a mandatory component of all MTF pharmacy formularies." If the BCF is to be a subset of the Uniform Formulary, the inclusion of OTCs on the BCF will be limited by TRICARE policy. The Council voted not to add any additional OTC products to the BCF beyond those identified in the TRICARE Policy Manual. The Council encouraged MTFs to continue providing OTC medications when they represent cost-effective alternatives to legend drugs.

As an OTC product, Mucinex will not be available from the retail network or NMOP.

12. MTF REQUESTS FOR BCF CHANGES

A. Requests to add zonisamide (Zonegran) to the BCF – A MTF provider requested the addition of zonisamide to the BCF. The rationale for the request was that zonisamide is a useful and safe drug to use for diabetic peripheral neuropathy, chronic headache syndromes, restless leg syndrome, and chronic back pain. No supporting literature was presented along with the request. CAPT Torkildson performed the analysis and presented the findings to the Council for consideration.

The FDA approved zonisamide in March 2000 as "adjunctive therapy in the treatment of partial seizures in adults with epilepsy". This approval was based on three registration trials that demonstrated statistical and clinical superiority over placebo in treating patients with partial seizures who were inadequately controlled on at least one other antiepileptic drug (AED). There are no data at present supporting its use as monotherapy for partial seizures. Also, despite the statement in the BCF request that zonisamide was useful for the off label indications listed, there are no published data supporting its utility in treating any of the listed conditions. One open-label study was identified that suggested that zonisamide might be of some benefit in treating patients with Parkinson's disease, but this had not yet been confirmed.

Analysis of available safety data raised some concerns. Zonisamide is a sulfonamide derivative, and is contraindicated in patients with an allergy to sulfonamides. Three cases of severe hematologic adverse events (2 cases of aplastic anemia, 1 case of agranulocytosis) have been reported in Japan, where the drug has been on the market for approximately 10 years. Based on the number of patient-years of exposure, the frequency of this adverse event is higher than that observed in the general population. Several cases of oligohydrosis and hyperthermia have been reported in pediatric patients treated with this agent; the FDA added a bolded warning to the package insert in June 2002 notifying prescribers of this concern. Additionally, 4% of 991 patients treated with the drug during its development phase developed renal stones, and in several studies it was noted that patients treated with zonisamide had a mean increase in their BUN and creatinine of 8%, compared to essentially no change in the placebo group. Of particular concern was the fact that these values did not return to baseline following discontinuation of the drug.

Regarding tolerability, it was noted that in several controlled trials the discontinuation rate due to adverse events in the zonisamide group was twice that of the placebo group (12% vs. 6%), while a separate analysis of several trials with a total of 1,336 treated patients revealed that 21% of patients discontinued therapy due to adverse events.

Finally, a utilization analysis revealed that only 61 MTFs filled prescriptions for zonisamide in FY02, only 23 MTFs filled more than 6 zonisamide prescriptions in that year, while 26 sites filled 3 or fewer. During that same period a total of 3,800 prescriptions for zonisamide were filled in the retail network.

Based on this review, the PEC concluded that there was insufficient evidence to support the use of zonisamide for the conditions outlined in the BCF request. Additionally, the level of concern regarding safety is higher for zonisamide than for other products, such as gabapentin, used for the treatment of these conditions. Gabapentin was added to the BCF in August 2002, providing uniform availability of a similar product with a more acceptable safety and efficacy profile. Finally, the overall utilization of this product across the MHS appears insufficient to require all facilities to make this product available. The PEC recommended that zonisamide not be added to the BCF. The Council unanimously approved this recommendation.

B. *Request to add pimecrolimus (Elidel) to the BCF–* A MTF provider requested that pimecrolimus, a topical immunomodulator (TIM), be added to the BCF. This is a new class of topical, nonsteroidal medications indicated for the treatment of atopic dermatitis (AD). Tacrolimus (Protopic) has been available since December 2000, and is FDA approved for treatment of moderate to severe atopic dermatitis. Pimecrolimus (Elidel) has been available since early 2002, and is FDA approved for the treatment of mild to moderate atopic dermatitis. Atopic dermatitis starts in early childhood and causes significant quality of life issues related to the pruritis and appearance of the rash. Ninety percent of AD patients have mild to moderate severity of disease and the rest are moderate to severe.

   Efficacy: Randomized-controlled trials demonstrate that both agents are more efficacious than placebo in the treatment of AD. Tacrolimus appears to be as efficacious as a medium potency topical corticosteroid, where pimecrolimus is as efficacious as a low potency topical corticosteroid.

   Safety/tolerability: Neither drug has clinically significant adverse effects, which cause the patients to discontinue use. The drugs are not systemically absorbed, so can be used long term without the worries associated with long-term topical corticosteroids (CS) use. They can also be used in sensitive body areas such as the face and intertriginous regions where one would not want to use topical CS.

   Other: Provider response was markedly positive regarding the potential of having an alternative to topical steroids for patients that require one. At the same time, providers noted that these will not take the place of the low potency topical CS and the usual initial therapies for mild AD. Pimecrolimus prescription fills in all points of service (MTF, NMOP, and retail) are increasing, with the majority of its use in the very young (ages 0 - 4) and elderly (ages 65+) population. Providers feel that usage will continue to increase significantly in this class.

   The Council agreed that topical immunomodulators (TIMS) are a unique class and have a substantial place in therapy for the treatment of AD, however there is concern regarding the cost of these agents and the potential for misuse. The Council agreed to consider one or both of these medications for addition to the BCF at their next meeting. They asked the PEC to explore procurement options and report back in three months.

13. DEPLOYMENT FORMULARY AND SUPPORTING HOMELAND SECURITY (JRCAB) – LTC Marc Caouette presented information and a short brief on homeland security and deployment formulary to the DoD P&T Executive Council.

14. ADJOURNMENT

The meeting adjourned at 1530 hours on 20 November 2002. The next meeting will be held at Fort Sam Houston, TX at 0800 on Wednesday, 6 March 2003. All agenda items should be submitted to the co-chairs no later than 14 February 2003.

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

APPENDIX A: BISPHOSPHONATE CLINICAL EFFICACY: CLINICAL TRIAL RESULTS

Table 1

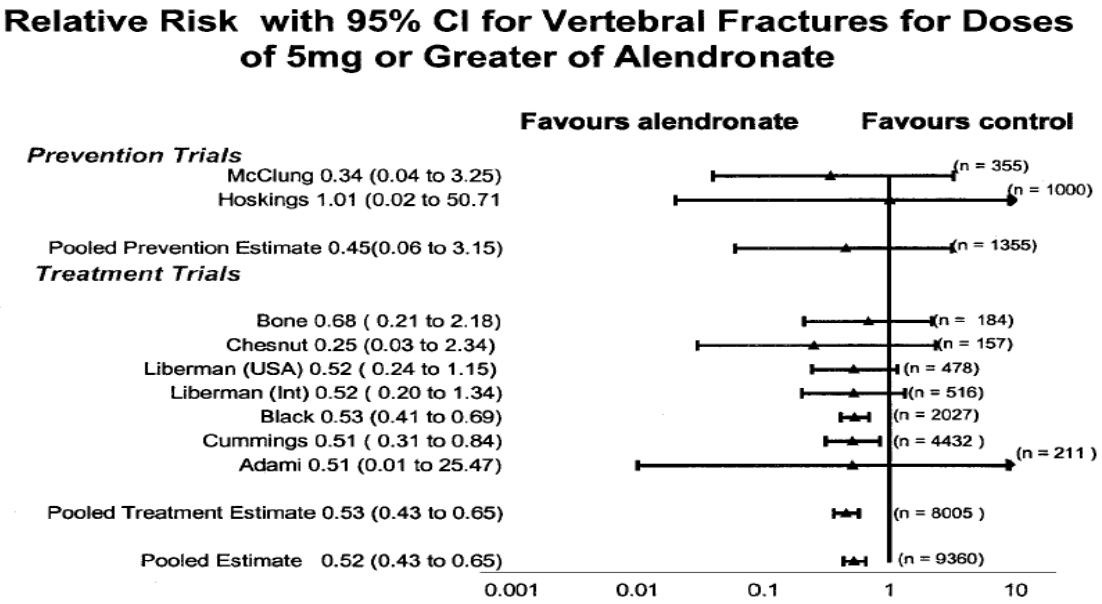


FIG. 2. RR for vertebral fractures with alendronate (5 mg and greater).

From Cranney et al; Endocrine Reviews 2002; 23(4):508-516

Table 2

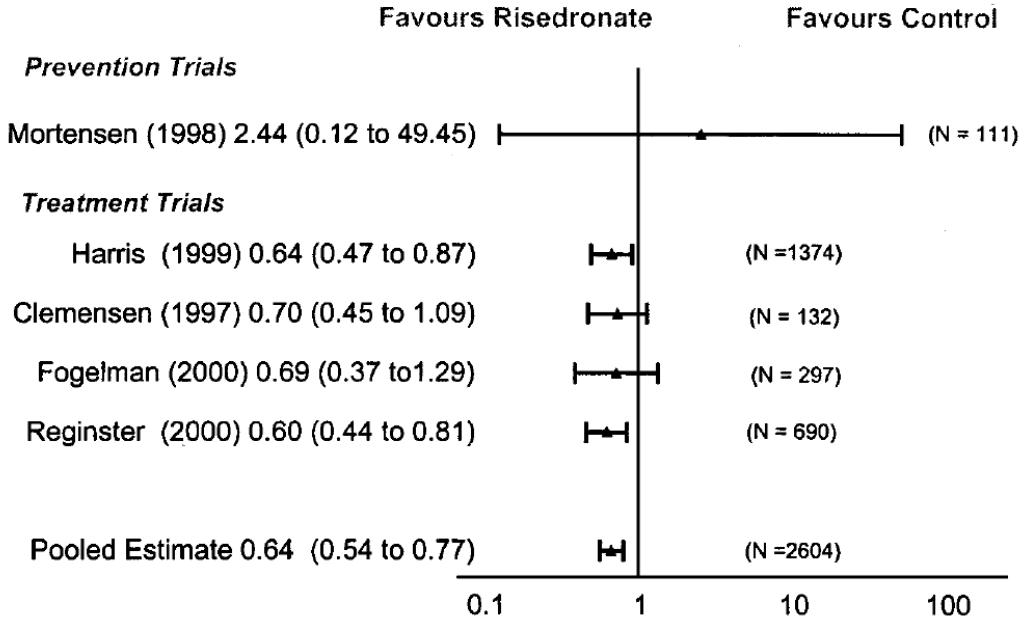


FIG. 2. Relative risk with 95% CI for vertebral fractures after treatment with risedronate.

From: Cranney et al; Endocrine Reviews 2002; 23(4):517-523

Table 3

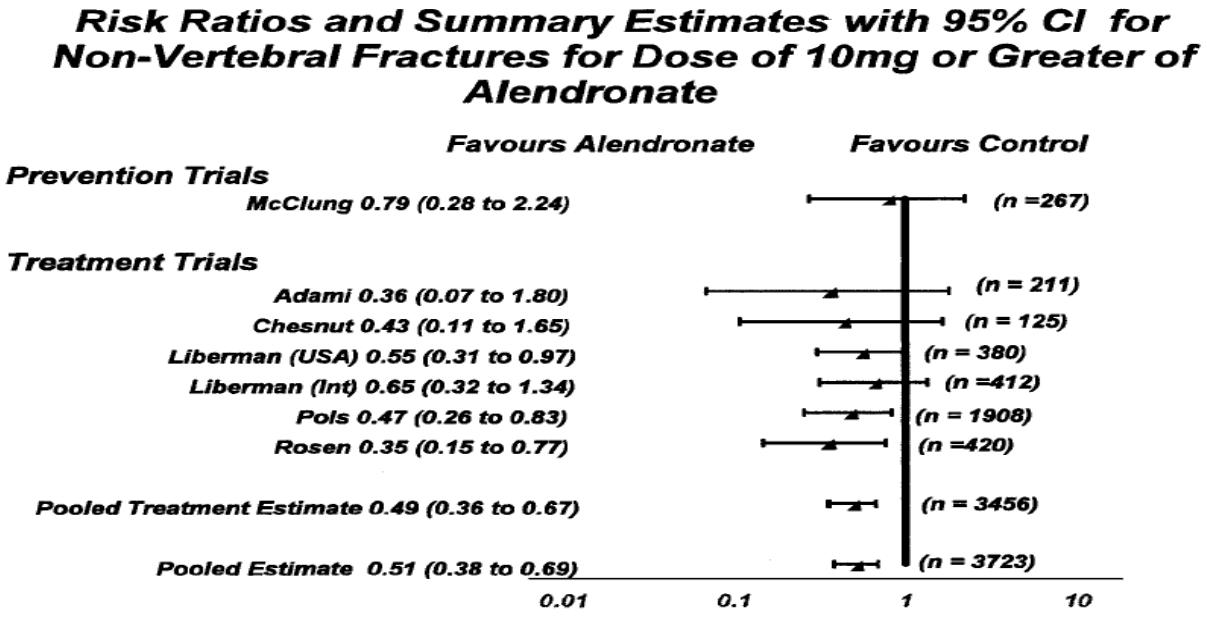


FIG. 3. Risk ratios for nonvertebral fractures with alendronate (10 mg and greater).

From: Cranney et al; Endocrine Reviews 2002; 23(4):508-516

Table 4

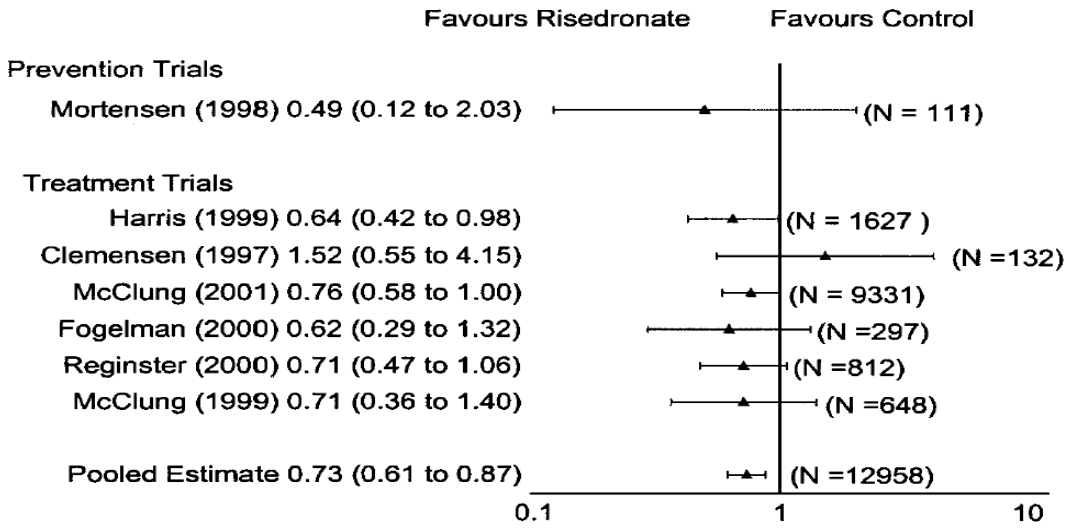


FIG. 3. Relative risk with 95% CI for nonvertebral fractures after treatment with risedronate.

From: Cranney et al; Endocrine Reviews 2002; 23(4):517-523

Table 5 – Summary of Reviewed Bisphosphonate Clinical Trials for Hip Fracture Outcomes

Study*	N	Incidence**	% Risk Reduction	Absolute Risk Reduction	NNT	Significance
Cummings [A] - 4yrs	4,432	A: 0.9% P: 1.1%	18%	0.002	500	No (P=0.44)
Liberman [A] – 3yrs	994	A: 0.2% P: 0.8%	75%	0.006	200	Not powered
Black [A] – 3yrs	2,027	A: 1.1% P: 2.2%	50%	0.011	91	Yes (P=0.047)
McClung [R] – 3 yrs	9,331	R: 2.8% P: 3.9%	28%	0.011	91 (29-333)	Yes (all) (P=0.003)
Harris [R] – 3yrs	1,628	R: 1.5% P: 1.8%	17%	0.003	333	Not powered
Reginster [R] – 3 yrs	814	R: 2.2.% P: 2.7%	19%	0.005	200	Not powered

* Lead author's last name, active component ([A]=alendronate and [R]=risedronate) and study duration
** A=Alendronate, R=Risedronate, P=Placebo

Adapted from Bolognese; The Endocrinologist 2002; 12:29-37

APPENDIX B: PROSTAGLANDIN CLINICAL EFFICACY - HEAD-TO-HEAD COMPARISON TRIALS

Table 1: Latanoprost vs. Unoprostone

Trial	Study Design	Latanoprost	Unoprostone	Duration	N	Baseline IOP (SEM)		End point IOP Reduction1 (SEM)	
						L	U	L	U
Tin Aung 2001	Randomized double-masked crossover	0.005% once daily	0.12% twice daily	2 tx periods of 1 month separated by a 3 week washout period	56	22.3 (0.5)	23.2 (0.4)	6.1 (0.5) p<.001	4.2 (0.4) p<.001

L = latanoprost, U = unoprostone, IOP = intraocular pressure
The difference of 1.9 mmHg between treatments was statistically significant in favor of latanoprost (p = .003, ANCOVA)

Table 2: Latanoprost vs. Travoprost

Trial	Study Design	L	TR	T	Duration	N	Mean Baseline IOP			Mean End point IOP		
							L	TR	T	L	TR	T
Netland 2001	Randomized multicenter, double-masked active-controlled, parallel	0.005% once daily n = 194	0.0015% n = 201 and 0.004% n = 196 once daily	O.5% Twice daily N = 196	12 months	787	25.7	25.1 (0.0015%) 25.5 (0.004%)	25.7	18.7	18.6 (0.0015%) 18.6 (0.004%)	20.2

L = Latanoprost, TR = Travoprost, T = timolol, IOP = intraocular pressure
Baseline and end point IOP difference between timolol and travoprost was statistically significant for both strengths (p<0.001, ANOVA)
Baseline and end point IOP difference between travoprost (both strengths) and latanoprost were statistically insignificant at alpha = 0.05

Table 3: Latanoprost vs. Bimatoprost

Trial	Study Design	L	B	Duration	N	Mean Baseline IOP Range		Mean End point IOP	
						L	B	L	B
Gandolfi 2001	Randomized multicenter, investigator-masked, parallel group trial	0.005% n = 113 once daily	0.03% n = 119 once daily	Three month	232	22.4 to 25.7	22.6 to 25.7	17.4 to 18	17 to 17.5
Trial	**Study Design**	**L**	**B**	**Duration**	**N**	**8 AM Mean Baseline IOP (SEM)**		**Reduction in IOP from baseline at day 29**	
						L	**B**	**L**	**B**
DuBiner 2001	Multicenter, double-masked, randomized, clinical trial	0.005% n = 21 once daily	0.03% n = 21 once daily	30-days	63	25.2 (0.6)	25.6 (0.5)	4.4 – 7.6 20-30%	5.9 – 8.0 25.4–30.9%
		Vehicle n = 21				Vehicle 25.8 (0.6)		Vehicle -0.3 – 1.7 -2 – 6.5%	

L = latanoprost, B = bimatoprost, IOP = intraocular pressure
Gandolfi: Mean IOP was lower with bimatoprost than with latanoprost at all time points (8AM, 12, 4PM, 8PM) during the three month follow-up, although the between group difference was not always statistically significant.
DuBiner: Bimatoprost and latanoprost significantly lowered IOP from baseline (p<0.001). Bimatoprost lowered IOP more than latanoprost at every time point measured, although the between group differences did not reach statistical significance.