Department of Defense
Pharmacoeconomic Center

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MCCS-GPE **7 August 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 1430 hours on 7 August 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 Mike Heath, MS (Representing MAJ Brett Kelly, MS)	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
COL John R. Downs, MC	Air Force
COL Bill Sykora, MC	Air Force
COL Ardis Meier, BSC (Representing LtCol George Jones, BSC)	Air Force Pharmacy Consultant
CAPT Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
CAPT Robert Rist	Coast Guard
Dick Rooney	Department of Veterans Affairs

VOTING MEMBERS ABSENT

COL Rosa Stith, MC	Army
LTC (P) Joel Schmidt, MC	Army

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
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, BSC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC	DoD Pharmacoeconomic Center
HM1 Lisa Drumm, USN	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia
Alexandra Masterson, Pharm.D.	Dewitt Army Hospital, Ft. Belvoir, VA

3. REVIEW MINUTES OF LAST MEETING/ADMINISTRATIVE ISSUES

The minutes from the last meeting were accepted as written.

4. INTERIM DECISIONS – None

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

Contract awards, renewals, and terminations

- New joint DoD/VA contracts were awarded for benztropine, carbidopa/levodopa IR, famotidine, digoxin, indomethacin, metformin, captopril, paclitaxel, trazadone, and chlorhexidine.
- The following joint DoD/VA contracts were not awarded because the bid prices were higher than existing FSS prices: prednisone and cimetidine.
- The following joint DoD/VA contracts are in various stages of solicitation: penicillin, dicloxacillin, tretinoin cream, amoxicillin, and cephalexin.
- The following joint DoD/VA contracts were extended: salsalate and all Geneva generics.

6. EXPIRATION OF LISINOPRIL CONTRACT

LCDR Briski provided information concerning the availability and pricing of lisinopril within the direct care system. The DoD contract with Astra Zeneca that provided the Zestril brand of lisinopril at $0.14 per tablet expired on 31 July 2002. Astra-Zeneca refused a DoD request to extend the Zestril contract. The VA's contract with Merck for the Prinivil brand of lisinopril expires 19 October 2002. Astra-Zeneca and Merck are phasing out production of lisinopril. Although several companies market generic versions of lisinopril, none are listed on the Federal Supply Schedule, and all are priced significantly higher than $0.14 per tablet. The DoD and VA are seeking a joint contract for a generic version of lisinopril, but that contract will not be awarded until after the VA's

Prinivil contract expires. MTFs will probably have to pay higher prices for lisinopril until the contract for a generic version of lisinopril is awarded—hopefully by November 2002.

7. PENDING CONTRACT INITIATIVES

A. *Status of contracting initiatives for Leutinizing Hormone Releasing Hormone (LHRH) agonists, nasal corticosteroids, triptans, and quinolones* – The joint DoD/VA solicitations for these items are still pending.

B. *Status of contracting initiative for Angiotensin Receptor Blockers (ARBs)* – In order for DoD to potentially join the VA in seeking a closed class contract for an ARB, LCDR Briski asked the Council to reconsider its May 2002 decision that the procurement strategy must leave the ARB class "open" on the BCF. The Council's decision not to support a closed class contract centered on concerns about therapeutic interchangeability and clinical coverage for treating congestive heart failure (CHF) and preventing the progression of renal disease in type 2 diabetics.

   The Council considered new information about the extent to which ARBs are prescribed at MTFs for conditions other than hypertension. An analysis of data from the Uniformed Services Prescription Database (USPD) and the M2 (formerly known as the ARS Bridge) database found ICD-9 codes consistent with a diagnosis of CHF or type 2 diabetic renal disease for only 289 (5%) of 5,680 patients who were prescribed two or more daily doses of an ARB (Note: patients with CHF are more likely to be prescribed multiple daily doses of an ARB than patients who are being treated for hypertension). The Council concluded that a closed class contract would be acceptable because the usage of ARBs for these conditions is low enough that MTFs could use the non-formulary request process to provide non-contracted ARBs to patients in the event that the contracted ARB does not meet the clinical needs of patients with CHF or type 2 diabetes. The Council voted unanimously to expand the authorized procurement strategies for the ARB class to include a closed class contract that does not mandate that patients be switched from non-contracted ARBs to the contracted ARB.

C. *Status of contracting initiative for thiazolidinediones (TZDs, "glitazones")* – In order for DoD to potentially join the VA in seeking a closed class contract for a TZD, LCDR Briski asked the Council to reconsider its May 2002 decision that the procurement strategy must leave the TZD class "open" on the BCF. The Council's decision not to support a closed class contract stemmed from concerns that rosiglitazone and pioglitazone may differ significantly in their effects on LDL-cholesterol (LDL-C) levels. The Council considered the results of (1) a more extensive analysis of changes in LDL-C levels reported in clinical trials of TZDs, and (2) an analysis of concomitant statin therapy for DoD patients who were newly started on TZD therapy.

   Comparison of changes in LDL-C levels in clinical trials of TZDs: There are no head-to-head trials that compare the changes in LDL-C levels that are associated with the use of rosiglitazone and pioglitazone. In order to compare the changes in LDL-C levels while attempting to control for known and unknown variations that exist across clinical trials of TZDs, the PEC calculated the percentage change in LDL-C incremental to placebo in nine rosiglitazone trials and five pioglitazone trials. As shown in Tables 1 and 2 below, the incremental percentage increases in LDL-C are consistently larger for rosiglitazone than pioglitazone.

Table 1: Monotherapy trials with TZDs and corresponding LDL changes, incremental to placebo

Rosiglitazone				Pioglitazone			
Dose (N)	**Base-line LDL**	**% change in LDL**	**% change incremental to placebo**	**Dose (N)**	**Base-line LDL**	**% change in LDL**	**% change incremental to placebo**
Patel				Aronoff			
2 mg bid (79)	125	↑ 13.6%	**↑ 12.4%**	30 mg qd (87)	136	↑ 5.2%	**↑ 0.42**
Placebo (74)	130	↑ 1.2%		Placebo (79)	139	↑ 4.8%	
Lebovitz				Study 026			
2 mg bid (166)	121	↑13.7%	**↑ 8.9%**	30 mg qd (100)	126	↓ 7%	**↓ 7%**
Placebo (158)	121	↑ 4.8%		Placebo (93)	133	No change	
Phillips				Study 012			
2 mg bid (186)	130	↑ 9.5%	**↑ 7.8%**	30 mg qd (85)	123	↑ 7%	**↑ 1%**
Placebo (173)	127	↑ 1.7%		Placebo (83)	135	↑ 6%	
Phillips							
4 mg qd (181)	125	↑ 10.6%	**↑ 8.9%**				
Placebo (173)	127	↑ 1.7%					
Lebovitz				Aronoff			
4 mg bid (169)	124	↑ 18.6%	**↑ 13.8%**	45 mg qd (80)	127	↑ 6%	**↑ 1.2%**
Placebo (158)	121	↑ 4.8%		Placebo (79)	139	↑ 4.8%	
Phillips				Study 012			
4 mg bid (187)	135	↑ 14.3	**↑ 12.6%**	45 mg qd (85)	133	↑ 8%	**↑ 2%**
Placebo (173)	127	↑ 1.7%		Placebo (83)	135	↑ 6%	
Phillips							
8 mg qd (181)	129	↑ 18.3%	**↑ 16.6%**				
Placebo (173)	127	↓ 1.7%					

Table 2: TZD trials in combination with a sulfonylurea or metformin and corresponding LDL changes, incremental to placebo

Rosiglitazone				Pioglitazone			
Dose (N)	**Base-line LDL**	**% change in LDL**	**% change incremental to placebo**	**Dose (N)**	**Base-line LDL**	**% change in LDL**	**% change incremental to placebo**
Wolffen				Kipnes			
2 mg bid +SU (183)	139	↑ 6%	**↑ 6%**	30 mg qd +SU (189)	127	↑ 6.6%	**↓ 0.4%**
Placebo + SU (192)	139	No change		Placebo +SU (187)	124	↑ 7%	
Study 079							
2 mg bid + glyb (98)	125	↑ 10.4%	**↑ 10.2%**				
Glyb (99)	125	↑ 0.24%					
Study 079							
2 mg bid (99)	125	↑ 17.6%	**↑ 17.4**				
Glyb (99)	125	↑ 0.24%					
Study 096							
4 mg qd + glyb (116)	122	↑ 14.8%	**↑ 12.4%**				
Placebo (115) + glyb	122	↑ 2.4%					
Fonesca*				Einhorn*			
4 mg qd + met (119)	115	↑ 15.4%	**↑ 12%**	30 mg qd +met (161)	119	↑ 7.7%	**↓ 4.2%**
Met + placebo (116)	117	↑ 3.4%		Placebo +met (149)	118	↑ 11.9%	
Fonesca*				No combination trials with 45 mg pioglitazone			
8 mg qd + met (113)	112	↑ 18.7%	**↑ 15.3%**				
Met + placebo (116)	116	↑ 3.4%					

SU = sulfonylurea, glyb = glyburide, met = metformin
*Concomitant lipid-lowering drugs were allowed

Analysis of concomitant statin therapy among DoD patients newly started on TZD therapy: Using data from the Pharmacy Data Transaction Service (PDTS), the PEC identified 14,301 patients who began therapy with rosiglitazone or pioglitazone between 1 November 2001 and 28 February 2002 and analyzed their concomitant statin usage through 30 June 2002. The PEC identified patients who had received prescriptions for statins before starting their TZD therapy, patients who initiated statin therapy after starting TZD therapy, and patients who experienced an increase in the dosage of their pre-existing statin therapy. Table 3 shows that the percentages of patients who were on statin therapy at baseline, were started on a statin, or whose statin dose was increased are very similar for rosiglitazone and pioglitazone.

Table 3: Statin use in DoD patients newly started on TZDs

	Rosiglitazone (n=8369)	Pioglitazone (n=5932)
Statin therapy change	**2120 (25.3%)**	**1371 (23.1%)**
Statin started after TZD started	1702 (20.3%)	1103 (18.6%)
Statin dose increased	418 (5%)	268 (4.5%)
No statin therapy change	**6249 (74.7%)**	**4561 (76.9%)**
No statin prescription	3606 (43.1%)	2641 (44.5%)
Statin dose not increased	2643 (31.6%)	1920 (32.4%)

Conclusion: While the data from clinical trials suggest that rosiglitazone is associated with larger increases in LDL-C than pioglitazone, concomitant usage of statins by DoD patients is very similar for both drugs. The Council voted 8-2 to expand the authorized procurement strategies for the TZD class to include a closed class contract that does not mandate that patients be switched from a non-contracted TZD to a contracted TZD.

D. *Status of contracting initiative for statins* – The Council reviewed recent label changes for simvastatin (Zocor) that Merck voluntarily initiated with the FDA as a result of normal post-marketing surveillance and monitoring of ongoing clinical trials. The label changes approved by the FDA on 6 June 2002 further clarify the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin and when used with other drugs. Myopathy and rhabdomyolysis are well-known side effects of all statins. The revised label includes the following:

- *Concomitant use with fibrates and niacin (≥1g/day)* – simvastatin dose should not exceed 10 mg daily unless the benefit outweighs the increased risk.
- *Concomitant use with amiodarone or verapamil* – simvastatin dose should not exceed 20 mg daily unless the benefit outweighs the increased risk. In a clinical trial, 6% of patients taking amiodarone and simvastatin 80 mg daily developed myopathy. Combined clinical trial data showed a 0.6% risk of myopathy with simvastatin (20-80 mg) and verapamil.
- *Dose-related risk of myopathy/rhabdomyolysis* – the incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.02% at 20 mg, 0.07% at 40 mg & 0.3% at 80 mg.

The Council noted that a recent Clinical Advisory on the Use and Safety of Statins from the National Heart, Lung, and Blood Institute, the American College of Cardiology, and the American Heart Association states that a review of data regarding reports of fatal rhabdomyolysis among the different statins strongly suggests that there are no clinically important differences in the rate of

fatal complications among the five statins now available in the U.S., and that clinicians should consider the rates of severe myopathy as equivalent among these statins.

The Council unanimously concluded that the simvastatin label change is not cause to alter its previous decision to support any contracting/formulary strategy (to include a closed class contract) that places at least one high potency statin on the BCF and does not require patients to be switched from one agent to another.

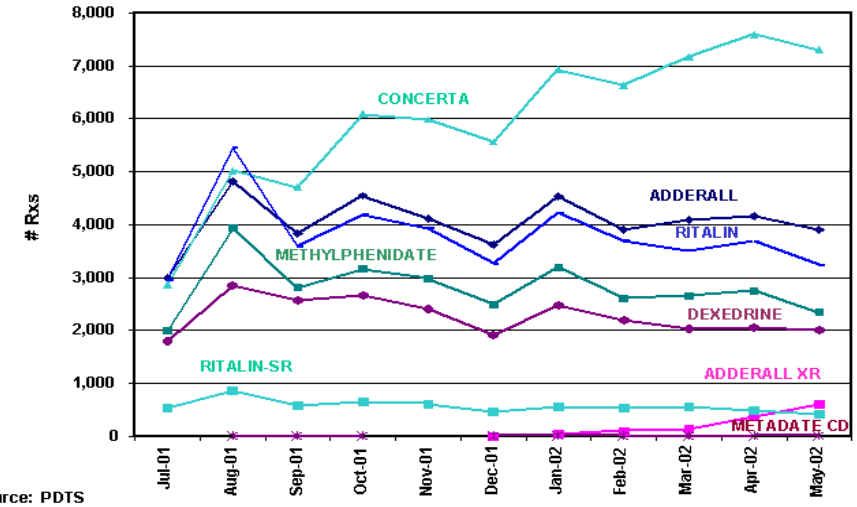
8. DRUG CLASS EVALUATIONS TO DETERMINE CLINICALLY ACCEPTABLE CONTRACTING/FORMULARY STRATEGIES:

A. *Attention Deficit Hyperactivity Disorder (ADHD) stimulant medications* — Based on a recommendation from the PEC, the Council reviewed the list of stimulant medications currently included on the BCF for the treatment of ADHD. The stimulants most widely used for ADHD treatment are methylphenidate, dextroamphetamine, and mixed salts of amphetamine/dextroamphetamine. Methylphenidate is available in immediate-release, sustained-release, and extended release forms. Dextroamphetamine is available in immediate and extended release forms, while the mixed salts of amphetamine/dextroamphetamine are available in sustained release (Adderall and generics) and extended release (Adderall XR) forms. The three agents currently on the BCF are all methylphenidate products: methylphenidate immediate release, methylphenidate sustained release, and Concerta. Pemoline is another stimulant medication used for ADHD, but its side effect profile is not acceptable to most clinicians. Pemoline is reserved as a last-line therapy when all other treatments have failed, and was not considered further in this review.

Therapeutic interchangeability/clinical coverage: There appear to be two subsets of ADHD patients: those who respond to methylphenidate and those who respond to amphetamine products. According to the literature, initial treatment of ADHD with a stimulant medication from a particular class has approximately a 65% likelihood of success. A substantial number of treatment failures can be successfully treated with the alternate drug class. Which class is used first is largely a matter of prescriber preference, as there are no clinical features that predict which class of drugs is more likely to be successful for a given patient. Given these facts, a health system should have products and dosage forms from both the methylphenidate and amphetamine classes available to meet the clinical needs of its ADHD patients. Once a class of drugs is found to be effective, current practice guidelines for the treatment of ADHD recommend that patients be changed to an extended release formulation to enhance compliance, decrease the risk of drug diversion within the school setting, and minimize the stigma associated with school-age children taking midday doses of stimulants. Therefore, optimal management of ADHD requires the availability of both methylphenidate and amphetamine products, and requires that preference be given to dosage forms that minimize the likelihood that patients will need to take additional doses of medication during the school day.

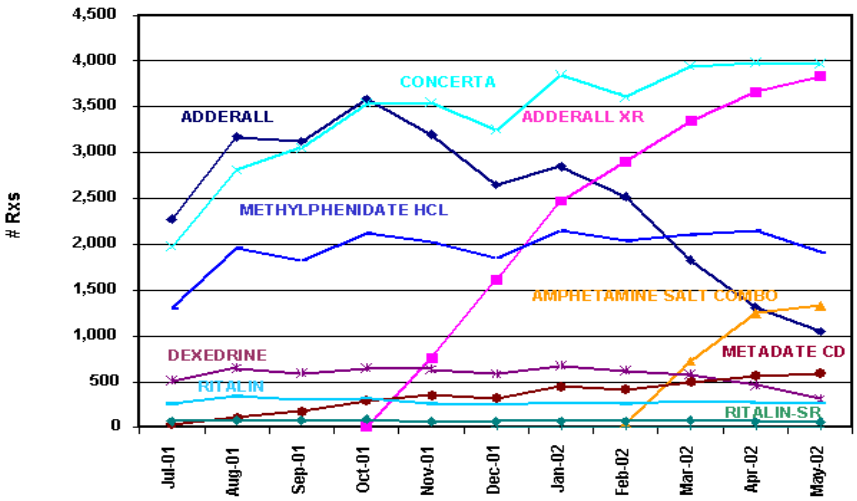
Utilization: The utilization trends within the MTFs and retail network pharmacies are presented in Figures 1 and 2.

Figure 1: MTF Prescriptions for ADHD Stimulant Medications (Jul 01 – May 02)



Source: PDTS

Figure 2: Retail Network Prescriptions for ADHD Stimulant Medications (Jul 01 – May 02)



Source: PDTS

Concerta is the most commonly dispensed stimulant medication at MTFs, with Adderall currently in second place. This is in sharp contrast to the retail network, where Concerta is also the most commonly dispensed drug, but Adderall XR is in second place and rapidly gaining ground. It is also noteworthy that use of Ritalin SR is very low in both points of service, despite its current position on the BCF. The retail network utilization trends (where all products are uniformly available) support the contention that methylphenidate and amphetamine products should both be available for the provision of comprehensive care to patients with ADHD, and also show that providers preferentially select the extended release formulation of these products for long-term therapy.

Provider acceptance: There was strong support among DoD providers who treat children with ADHD for a more robust BCF with broadened clinical coverage for ADHD patients. More than half of the respondents felt that an amphetamine product (Adderall or Adderall XR) should be added to the BCF to improve clinical coverage. Providers indicated that they would not favor any procurement strategy that resulted in a closed class with a single entity or required patients to be switched from one drug class to another. Most physicians felt that parents would be very resistant to medication changes mandated by contract once their child was being effectively treated with a particular medication. All agreed that pemoline is not a candidate for the BCF due to its side effect profile.

Based on this review, the Council approved the following decisions:

- Retain Concerta and methylphenidate IR on the BCF.
- Remove methylphenidate SR from the BCF
- Add Adderall XR 10-, 20- and 30-mg strengths to the BCF. Facilities may add additional strengths if they desire, but they are not mandated to do so.

9. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF ADDITION

A. *Venlafaxine extended release capsules (Effexor XR)* – In February 2002 the Council reviewed the anxiolytic class and concluded that venlafaxine extended release (Effexor XR; Wyeth-Ayerst) was useful in the treatment of several anxiety disorders, particularly in patients with co-morbid depression. A decision to add venlafaxine extended release to the BCF was tabled at that time pending discussions with the company intended to increase the cost-effectiveness of this therapy. Consideration was deferred again in May, as discussions with the company were still ongoing. Subsequently, the company presented a verbal offer of a $0.10 per tablet price reduction on the 150 mg tablet in return for BCF status.

Table 4: Current FSS pricing of Effexor/Effexor XR:

Drug	Strength	Price/tablet	Cost/30 days
Effexor	25 mg	$0.57	$34.20
	37.5 mg	$0.60	$35.76
	50 mg	$0.61	$36.84
	75 mg	$0.66	$39.30
	100 mg	$0.69	$41.52
Effexor XR	37.5 mg	$1.06	$31.80
	75 mg	$1.19	$35.70
	150 mg	$1.29	$38.70

Given the current rate of growth in utilization of venlafaxine extended release, the MHS would likely realize a cost avoidance of over $200,000 annually by accepting this offer. More savings are possible if BCF addition facilitates MTF recapture of venlafaxine extended release prescriptions from the retail network. The Council voted unanimously to add venlafaxine extended release 37.5, 75, and 150 mg tablets to the BCF, contingent on the signing of a BPA between Wyeth-Ayerst and DSCP establishing the $0.10 price reduction for the 150 mg tablet.

B. *Insulin glargine (Lantus)* – The Council considered a proposal to add insulin glargine (Lantus; Aventis Pharmaceuticals) to the BCF. Insulin glargine is a modified human insulin designed to act as a peakless basal insulin product with a 24-hour duration of action. It was approved by the FDA in April 2000 but was not launched until May 2001. The major advantage of insulin glargine is an approximately 10% lower incidence of symptomatic hypoglycemia, nocturnal

hypoglycemia, and severe hypoglycemia compared to NPH insulin. Initial studies suggested that the efficacy of insulin glargine in reducing HbA_{1c} levels was equivalent to that of NPH. Other brief trials demonstrated a significant decrease in the fasting plasma or whole blood glucose levels compared to NPH. Abstracts presented at the most recent American Diabetes Association meeting suggested that the enhanced safety profile of insulin glargine allows for a more aggressive approach to escalating insulin therapy in both Type 1 and Type 2 diabetics, and that this more aggressive approach in fact leads to a significant decrease in HbA_{1c} levels compared to traditional therapy with NPH insulin.

Even though insulin glargine costs much more than human NPH insulin at MTF pharmacies ($25.38 versus $4.49 per 10 ml vial) and is currently on fewer than half of MTF formularies, the prescription volume for insulin glargine increased 3.5 fold at MTF pharmacies between October 2001 and May 2002. Prescription volume for insulin glargine increased 2.5 fold in the retail network during the same period.

The Council concluded that insulin glargine represents a true advance in the treatment of both Type 1 and Type 2 diabetes and that it should be uniformly available at MTF pharmacies. The Council voted unanimously to add insulin glargine to the BCF.

C. *Gabapentin (Neurontin)* – In February 2002 the Council reviewed gabapentin for potential addition to the BCF, due to high usage rate and high expenditures in the retail network. The Council decided not to add gabapentin at that time due to concern that gabapentin was not FDA approved for pain control and that it may pose a large cost burden to small MTFs. The FDA recently approved gabapentin for treatment of post herpetic neuralgia. A generic version of gabapentin may become available in the near future. In the retail network gabapentin is in the top 20 for expenditures and top 50 for number of prescriptions. Gabapentin is among the top 100 drugs for number of prescriptions in the MTFs and is on 70% of MTF formularies. Gabapentin usage has continued to rise in all three points of service, with the majority of use for neuropathic pain in the over-65 aged population. The Council voted unanimously to add gabapentin to the BCF.

10. CLARIFICATION OF STATUS OF BLOOD GLUCOSE TEST STRIPS ON BCF – Precision (Abbott) blood glucose test strips have been on the BCF since its inception. Precision's status on the BCF is supported by an incentive price agreement that offers a lower price system-wide as market share increases. A medical/surgical product standardization initiative for TRICARE Regions 6, 7 and 8 recently selected the Accucheck (Roche Diagnostics) blood glucose test strip. Some pharmacies were incorrectly told that they had to switch from Precision test strip to the Accucheck test strip. LCDR Briski wrote an article in the May edition of the *PEC Update* and also disseminated information through the service pharmacy consultants/specialty leaders to MTF pharmacies to clarify that Precision test strips remain on the BCF and that regional medical/surgical standardization initiatives do not create "sole source" agreements that force MTFs to switch away from an item listed on the BCF.

The Army serves as the Executive Agent for medical/surgical regional standardization. The Council agreed that COL Remund should meet with COL Kissane, the Army OTSG/MEDCOM Deputy Chief of Staff for Logistics, to work out some rules of engagement that would enable national standardization through the BCF and regional standardization initiatives to productively coexist.

LCDR Briski also briefed the Council about Abbott Diagnostic's plan to phase out the Precision QID strip and meter, while phasing in their newer product, Precision Extra. The Precision Extra

product offers significant advancements over the Precision QID product. The Council voted to reaffirm its intent to keep Precision products as the sole blood glucose strip on the BCF. The Council encourages MTFs to expeditiously transition to the Precision Extra product.

11. CLARIFICATION OF 27- AND 54-MG STRENGTHS OF METHYLPHENIDATE EXTENDED RELEASE (CONCERTA) – When Concerta was first added to the BCF in November 2000, the only strengths available were 18 mg and 36 mg. A 54 mg capsule was marketed in December 2000, and a 27 mg capsule was added in April 2002. Multiple strengths allow more precise titration of dosages. During a recent PEC review of Concerta utilization at MTFs, it was noted that several large MTFs were dispensing a large number of dual prescriptions to patients for both 18 mg and 36 mg Concerta capsules rather than for 54 mg capsules. This results in an inconvenience to the patient, an increase in workload for the pharmacy, and an excess cost of $38.40 per patient per month.

To facilitate dosage titration and to maximize the likelihood that Concerta will be used in as cost-effective a manner as possible, the Council voted to add the 27 mg and 54 mg strengths of Concerta to the BCF. The vote was 8 in favor, one against, and one abstention.

12. MTF REQUESTS FOR BCF CHANGES

A. Requests to delete particular strengths or dosage forms of BCF items – The Health Affairs Policy for Basic Core Formulary and Committed Use Requirements Contracts (Policy #98-034) states, "In the case of multiple strength BCF drugs, all strengths need not be stocked but all prescriptions for that agent will be filled regardless of strength." The BCF page on the PEC website explains that a listing for an oral medication "indicates all oral dosage forms and strengths will be provided unless otherwise noted." The DoD P&T Executive Council has deleted or excluded some dosage forms/strengths from the BCF for one or more of the following reasons:

- Substantially higher cost than other dosage forms/strengths
- Excessive administrative burden associated with maintaining multiple strengths (e.g., controlled substances)
- The BCF listing is intended to cover an indication that is limited to a specific dosage form/strength (e.g., fluconazole 150 mg for vaginal yeast infections)
- New dosage form/strength offers no significant clinical advantage and is apparently designed to avert competition from generic versions of the drug
- Low usage combined with one or more of the factors above

Some MTF requests to delete a particular strength or dosage form of a BCF drug appear to be based primarily on objections to stocking an item that has a low usage rate. The Council reiterates that if an MTF has little or no demand for a particular BCF item, the MTF is not required to physically stock the item in the pharmacy. However, the MTF must provide the item if it is prescribed.

B. *Request to remove cimetidine from the BCF* – A MTF pharmacist requested the deletion of cimetidine from the BCF due to low usage. Cimetidine and ranitidine are the two H2 blockers currently on the BCF. Ranitidine prescriptions outnumber cimetidine prescriptions 9 to 1 at MTF pharmacies. Indications and efficacy are similar for both drugs, but cimetidine has more side effects and drug interactions than ranitidine. Ranitidine costs $0.06 - $0.07 per day; cimetidine costs $0.10 to $0.13 per day. The Council voted unanimously to delete cimetidine from the BCF. MTFs may decide to retain cimetidine on their local formularies if so desired.

C. *Request to remove cyproheptadine from the BCF* –An MTF pharmacist requested deletion of cyproheptadine from the BCF because there are better alternatives on the BCF to treat allergies and headache and because cyproheptadine had been dispensed fewer than 20 times in the past 6 months at the requestor's MTF. More than 90 responses were received from providers and pharmacists in the field, overwhelmingly and convincingly offering reasons why this drug should be maintained on the BCF in spite of low usage. Cyproheptadine has a unique place in therapy with no good alternative treatments for pregnant patients and young children with migraine headaches, in addition to other uses. The 4 mg tablet is priced as low as $0.03 per tablet, and the 2 mg per 5 ml syrup costs $0.15 per 5 ml. The Council voted unanimously to retain cyproheptadine on the BCF.

D. *Request to remove theophylline elixir from the BCF* –An MTF pharmacist requested deletion of theophylline oral liquid from the BCF because it has been dispensed less than 20 times in the past 6 months at the requestor's MTF. Children and elderly patients who cannot swallow solid dosage forms or are unable to use a metered-dose-inhaler effectively account for almost all of the theophylline oral liquid use. Theophylline remains on asthma and COPD treatment guidelines, and the oral liquid form is the only dosage form that is suitable for some patients. Theophylline oral liquid is inexpensive ($0.003 to $0.045 per ml). The Council voted unanimously to retain theophylline oral liquid on the BCF.

E. *Request to add budesonide inhalation suspension (Pulmicort Respules) to the BCF* – A pediatrician requested addition of budesonide inhalation suspension to the BCF for the following reasons: 1) it is the only FDA-approved, nebulized steroid available and can be used for patients as young as 12 months of age; 2) prior to the availability of budesonide inhalation suspension, steroid metered dose inhalers (MDIs) were used for persistent asthmatics—young children could not always cooperate effectively with these; 3) parents appreciate the convenience of nebulized medications in children and studies have shown them to be efficacious; and 4) one in nine children has asthma—addition would enhance primary care options for treatment.

   The safety and tolerability of nebulized budesonide are no different than other inhaled steroids. Both inpatient and outpatient studies have shown efficacy in respect to symptom relief. As expected, use of this medication is low and almost exclusively for patients in the 0 to 4 age group, which is consistent with appropriate use of the product. MDIs are still the inhaled steroid formulation of choice in the treatment of asthma. Budesonide inhalation suspension is intended for those who cannot yet use MDIs appropriately. The Council voted unanimously to add budesonide inhalation suspension (Pulmicort Respules) to the BCF.

F. *Request to add meloxicam (Mobic) to the BCF* – The PEC received two requests to add meloxicam to the BCF, one from an Air Force physician and one from an Army pharmacist. Both requestors represent facilities currently using meloxicam as an alternative to "COX-2 inhibitors" (rofecoxib, celecoxib, or valdecoxib).

The Council considered the following points:

- *Background* - Meloxicam is FDA-approved only for osteoarthritis (OA). Because patent protection/exclusivity for meloxicam is expected to expire within the next three years, the manufacturer has stated that they do not plan to pursue additional indications. The drug is approved in various European countries for rheumatoid arthritis (RA). Despite its relatively recent introduction in the U.S. in April 2000, meloxicam has been available in other countries since 1995. The manufacturer estimates that more than 45 million patients have been exposed to meloxicam worldwide.
- *Efficacy* - There are published clinical trials showing efficacy of meloxicam for the treatment of OA, RA, and other chronic painful conditions, including ankylosing spondylitis and low back pain. Publication of the IMPROVE trial, a 6-month naturalistic (effectiveness) trial in OA patients (meloxicam vs. "usual care" NSAIDs) is expected shortly; summary results are available in abstract.
- *Safety –NSAID-associated GI adverse events*
  - *COX-2 selectivity* - The most extensive analysis of COX-2/COX-1 selectivity of NSAIDs to date (Warner et al. Proc Nat Acad Sci 1999; 96:7563-8) constructed the following ranking based on a whole blood assay (from most COX-2 selective to least COX-2 selective): rofecoxib (>50-fold COX-2 selective); etodolac, meloxicam, and celecoxib (grouped together as 5-to 50-fold COX-2 selective); diclofenac, sulindac, piroxicam, ibuprofen, tolmetin, naproxen, aspirin, indomethacin, ketoprofen, ketorolac. According to other researchers, the COX-2 selectivity of meloxicam appears to be dose-related, with greater COX-2 selectivity at a daily dose of 7.5 mg than at 15 mg.
  - *Association of COX-2 selectivity with reduced incidence of serious upper GI events* - The major potential advantage of COX-2 selective NSAIDs relative to non-selective NSAIDs is a reduction in the incidence of complicated upper GI events (GI bleed, perforation, and obstruction) and symptomatic but uncomplicated ulcers. Evidence of a reduced incidence of complicated upper GI events compared to nonselective NSAIDs is most conclusive with rofecoxib, less conclusive with celecoxib and meloxicam, and not yet available for valdecoxib. Because no head-to-head trials of sufficient size and duration to discern a clinically significant difference in complicated upper GI events are available, it is difficult to compare the incidence rate of complicated upper GI events with meloxicam and celecoxib, rofecoxib, or valdecoxib. See Appendix A for a discussion of clinical studies involving meloxicam, celecoxib, and rofecoxib.
- *Safety: Cardiorenal and cardiovascular adverse events* - NSAIDs, including celecoxib, rofecoxib, and valdecoxib, are known to cause fluid retention, edema, blood pressure (BP) elevation, and loss of BP control in patients treated with antihypertensive medications. In addition, the VIGOR trial with rofecoxib showed a statistically significantly higher incidence of adjudicated serious cardiovascular thrombotic events (primarily acute myocardial infarctions) in patients treated with rofecoxib 50 mg QD compared to patients treated with naproxen 500 mg BID [1.1% vs. 0.5%, NNH=167].

Pooled data from the Meloxicam Serious GI Event Analysis, which includes clinical trial data involving 27,039 patients who received meloxicam, comparator NSAIDs, or placebo in 35 clinical trials, provides comparative information on the incidence of these adverse events in patients treated with meloxicam or comparator NSAIDs (see Table 5). Placebo data included in this analysis are very limited (736 patients, 113 patient-years of therapy) and are not included in the table because they are unlikely to accurately reflect background rates.

Table 5: Rates of cardiovascular/cardiorenal adverse events

	Meloxicam	NSAIDs
Patients	15,071	11,078
Patient-years of therapy	3129	1202
Myocardial Infarctions (incidence/100 pt-yrs)	18 (0.58%)	8 (0.67%)
Cardiac Failure (incidence/100 pt-yrs)	15 (0.48%)	7 (0.58%)
Peripheral Edema (incidence/100 pt-yrs)	98 (3.13%)	79 (6.57%)
Hypertension (incidence/100 pt-yrs)	82 (2.62%)	32 (2.66%)
Aggravated HTN (incidence/100 pt-yrs)	25 (0.80%)	15 (1.25%)

- *Tolerability* - Meloxicam appears to be as well or better tolerated than the NSAIDs to which it was compared in clinical trials. In the MELISSA study, fewer patients treated with meloxicam withdrew from the study due to GI adverse effects (e.g., dyspepsia, nausea, abdominal pain) compared with diclofenac (3.0% vs. 6.1%); similar results were observed in the SELECT trial (3.8% vs. 5.3% with piroxicam). Preliminary results from the IMPROVE study show significantly fewer discontinuations of therapy due to adverse effects compared to "usual care" NSAIDs.
- *Other Factors*
  - *Frequency of Dosing* - Meloxicam is dosed once daily.
  - *Provider Input* - The PEC requested provider (physician and pharmacist) input on this issue. Because the VA has selected etodolac for their COX-2 criteria as an alternative to salsalate for patients at significant GI risk, and because etodolac, like meloxicam, has at least some evidence of a lower incidence of GI adverse events than other NSAIDs, providers were asked about etodolac as well as meloxicam. Providers were asked: 1) if their MTF would use meloxicam or etodolac if added to the BCF, 2) the place of the drug(s) in therapy, 3) should meloxicam or etodolac be added to the BCF, and 4) how addition would affect their facility. The responses were mixed. Key points included:
    - One responder pointed out that while BCF addition would probably have a significant budgetary impact on facilities that currently have no COX-2s on formulary, the overall cost to DoD should drop significantly if these facilities would call civilian providers and switch COX-2 prescriptions to meloxicam, preventing a significant number of COX-2 prescriptions from being filled in the network at a higher overall cost to DoD. MTFs that currently do not have COX-2 inhibitors on formulary may incur increased costs.
    - Some responders were concerned that if meloxicam were added to formularies without restrictions, providers may shift from prescribing lower cost generic NSAIDs to prescribing meloxicam, even in patients at low risk for GI adverse events.

- Some responders doubted that providers would use meloxicam or etodolac in place of rofecoxib or commented that these are low use items at their facilities.
- Some responders commented that there was insufficient clinical trial evidence to conclude that meloxicam is COX-2 sparing.
- With regard to etodolac, responders commented that while it is generically available and less costly than meloxicam and there is some evidence that it is COX-2 sparing; it must be dosed 2-3 times per day and is not actively marketed to providers. Comments about the effectiveness of etodolac ranged from "good success" to "useless" (and must, in any case, be regarded as anecdotal).

- *Status on MTF formularies* - Facilities that currently have meloxicam on formulary (either unrestricted or as part of a step therapy program that requires failure of one or more nonselective NSAIDs prior to meloxicam) include: Tripler Army Regional Medical Center (ARMC); Madigan ARMC; Brooke Army Medical Center, Wilford Hall Medical Center, Randolph Air Force Base (AFB); Ft. Polk; Luke AFB; Ft. Hood; Ft. Leonard Wood; William Beaumont ARMC; and Nellis AFB.
- *Dose distribution - MTFs vs. retail network* - Since the COX-2 selectivity of meloxicam appears to be dose-related, the percentage of patients receiving 7.5- vs. 15-mg daily doses is of interest. As of July 2002, about 80% of meloxicam prescriptions filled in the NMOP and retail network were for the 7.5-mg strength of meloxicam, which is consistent with the 80-85% reported by the manufacturer as typical in the civilian marketplace. Only about 35% of meloxicam prescriptions filled at MTFs were for the 7.5 mg strength; however, the true percentage of MTF meloxicam prescriptions written for a 7.5-mg daily dose is likely to be closer to 65% due to splitting of the 15-mg tablet (see following analysis).
- *Cost*
  - *Dose distribution and MTF cost per day* - The PEC analyzed signatura (directions for use) for all MTF prescriptions for meloxicam, celecoxib, rofecoxib, and etodolac with valid signatura in the Uniformed Services Prescription Database from Jan – April 2002 (134,883 Rxs). This analysis served two purposes: to analyze the dose distribution of meloxicam and to compare the weighted average cost per day of meloxicam to the COX-2 inhibitors and to etodolac. Valdecoxib was not included due to the limited number of MTF prescriptions during this time period.

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Table 6: Dose distribution and weighted average daily cost

Generic	Strength / dosage form	Daily dose (# tabs/caps per day)	% of Rxs	Average cost per tab/cap purchased by MTFs	Weighted average daily cost
Meloxicam	15 mg tab	0.5 1	39.6% 34.6%	$0.97	$0.80*
	7.5 mg tab	1 2	19.5% 5.9%	$0.88	
Celecoxib	100 mg cap	1 2	5.9% 15.8%	$0.80	$1.76
	200 mg cap	1 2	54.2% 23.2%	$1.45	
Rofecoxib	12.5 mg tab	1	7.6%	$1.35	$1.43
	25 mg tab	1 2	71.5% 5.9%	$1.37	
	50 mg tab	0.5 1	6.5% 5.7%	$2.13	
Etodolac	200 mg cap	2	2.0%	$0.15	$0.52
	300 mg cap	2 3	8.4% 2.3%	$0.20	
	400 mg tab	1 2 3 4	2.6% 70.4% 6.8% 2.2%	$0.27	

Based on all prescriptions with valid signatura (directions for use) in the Uniformed Services Prescription Database Jan – April 2002 and the average price per tab/cap purchased by MTFs, based on prime vendor data for Apr – May 02. Rows representing less than 2% of all prescriptions for a specific medication are omitted; percentages may not add to 100% for this reason. Usage of extended release etodolac was extremely low and is not reflected in these results.
* Results for meloxicam reflect a high percentage of prescriptions for meloxicam 15 mg tabs as 0.5 tabs per day, most likely due to tablet-splitting. In the absence of tablet-splitting strategies (i.e., substitution of 7.5 tabs for all 15 mg half-tabs), the weighted average cost per day would be about $0.96.

- The manufacturer has offered DoD a blanket purchase agreement for meloxicam. The BPA provides a price reduction from $0.89 to $0.79 for the 7.5 mg tab and from $0.98 to $0.88 for the 15 mg tab, a reduction of about 11%, in return for placing meloxicam on the BCF. The BPA would be effective no later than Oct 2002 and run through 31 Dec 2003. The BPA does not prevent later addition of a COX-2 inhibitor or any other NSAID to the BCF. Using the same method described above, these price decreases would reduce the weighted average daily cost of meloxicam from $0.80 to $0.73 per day.

The Council agreed that the evidence for a GI-sparing effect with meloxicam is not as certain as that for rofecoxib, but that there is sufficient evidence to conclude that meloxicam is associated with fewer serious GI events than the less COX-2 selective NSAIDs with which it has been compared in clinical trials. The Council emphasized that because meloxicam is still substantially more costly than generic NSAIDs (e.g., naproxen, ibuprofen, diclofenac), it does not make sense to use meloxicam in patients at low risk of GI events.

It is difficult to accurately predict whether addition of meloxicam to the BCF will result in greater cost (if meloxicam is used in place of generic NSAIDs) or cost avoidance (if meloxicam is used in place of celecoxib, rofecoxib, or valdecoxib). One large Army MTF that previously had celecoxib and rofecoxib on formulary with a criteria-based prospective medication use evaluation form deleted celecoxib and rofecoxib from their formulary and added meloxicam after discovering that a majority of the patients receiving celecoxib or rofecoxib did not meet criteria. After 4 months, they reported substantial cost avoidance, no adverse drug reactions, no new drug requests for celecoxib or rofecoxib as a result of treatment failures, and a 100% conversion rate when outside providers were contacted requesting a change to meloxicam.

The Council voted to add meloxicam (Mobic) to the BCF. The Council agreed that facility-level guidelines or programs to ensure appropriate use of meloxicam, as well as celecoxib, rofecoxib, or valdecoxib, are consistent with BCF policy as long as the guidelines are applied uniformly and consistently (e.g., to both military and civilian providers).

The Council also considered addition of etodolac to the BCF, but decided that it did not have sufficient data concerning the clinical utility and GI-sparing effect of etodolac and tabled the issue to a later date.

G. *Request to add aspirin/extended release dipyridamole (Aggrenox) to the BCF* – Two providers, a neurologist and a neuro-ophthalmologist, requested that Aggrenox (aspirin 50 mg/extended release dipyridamole 200 mg) be added to the BCF. Aggrenox is indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis. Aggrenox does not have approval for coronary heart disease. The 1999 AHA guidelines for the Management of TIA identify Aggrenox as an acceptable option for initial therapy following a TIA, along with aspirin, clopidogrel and ticlopidine. All have been shown to reduce the risk of recurrent stroke in patients who have had a TIA. Clopidogrel is indicated for reduction of thrombotic events in patients with recent stroke or established peripheral arterial disease, and is also indicated for use in unstable angina or myocardial infarction. Clopidogrel was added to the BCF in February 2002

Safety and tolerability of Aggrenox are similar to the two separate ingredients used in combination, with headache as the major limitation. The European Stroke Prevention Study-2 (ESPS-2) was the major efficacy trial for Aggrenox. Dropout rates in the Aggrenox and dipyridamole groups of the ESPS-2 were significantly higher than those reported in the aspirin and placebo groups. The high overall dropout rate (26%) raises the question of poor patient compliance.

There is no conclusive evidence that Aggrenox offers a significant advantage over the concomitant use of aspirin and dipyridamole to reduce the risk of stroke. The relative risk reduction for aspirin and dipyridamole versus placebo in the ESPS-1 study (38.1%) was similar to the relative risk reduction for Aggrenox versus placebo in the ESPS-2 study (37.2%).

Aggrenox is significantly more expensive than using separate tablets of aspirin or dipyridamole together. Aggrenox costs $1.76/day, which is similar to clopidogrel at $1.80/day. PDTS usage data from July 2001 – June 2002 showed there were only 2000 Aggrenox prescriptions vs. 20,000 clopidogrel prescriptions in the entire DoD.

Only 25 responses were obtained from providers regarding potential BCF addition of Aggrenox, of whom 20 were against BCF addition. Aggrenox has minimal usage in DoD, is not supported by the primary care providers, and does not offer clear benefit over clopidogrel. The Council voted not to add Aggrenox to the BCF. Individual MTFs may add Aggrenox to their local formulary if desired.

13. ADJOURNMENT

The meeting adjourned at 1430 hours on 7 August 2002. The next meeting will be held at the Uniformed Services University of the Health Sciences, Bethesda, Maryland starting at 0800 on Wednesday, 20 November 2002. All agenda items should be submitted to the co-chairs no later than 18 October 2002.

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

Appendix A: Studies Indicating a Reduced Incidence of Complicated Upper GI Events with Rofecoxib, Celecoxib, or Meloxicam

Abbreviations used in this appendix: absolute risk reduction (ARR); confidence intervals (CI); relative risk (RR), number-needed-to-treat (NNT); number-needed-to-harm (NNH)

Rofecoxib

- The VIGOR trial (Bombardier et al. N Engl J Med 2000; 343:1520-8) compared rofecoxib and naproxen in 8000+ RA & OA patients. The median duration of the trial was 9 months; patients on aspirin were excluded. This trial provides the best evidence to date that a COX-2 selective NSAID results in fewer complicated upper GI events (perforations, obstructions, or upper GI bleeds) and symptomatic ulcers. The incidence of confirmed complicated upper GI events was 0.6% in the rofecoxib group vs. 1.4% with naproxen [absolute risk reduction (ARR) = 0.8%, relative risk (RR) = 0.43 (95% CI 0.24-0.78), p=0.005, number needed to treat (NNT) = 125], while the incidence of the combined endpoint of confirmed complicated upper GI events **or** symptomatic ulcers was 2.1% with rofecoxib vs. 4.5% with naproxen [ARR=2.4%, RR=0.46 (95% CI 0.33-0.64), p<0.001, NNT=41].

Celecoxib

- The CLASS trial (Silverstein et al. JAMA 2000; 284:1247-55) compared celecoxib vs. a pooled NSAID group (ibuprofen or diclofenac) in 8000+ OA patients. The duration of the trial was approximately 13 months (6-month results published); patients on prophylactic aspirin were included. Published (6-month) data from the CLASS trial reported fewer confirmed complicated upper GI events with celecoxib vs. pooled NSAIDs, but the difference was not statistically significant [0.76% celecoxib vs. 1.45% NSAIDs; ARR 0.69%; RR=0.53 (95% CI 0.26-1.11), p=0.09]. A statistically significant difference was found for the combined endpoint of complicated upper GI events **or** symptomatic ulcers [2.08% celecoxib vs. 3.54% NSAIDs; ARR 1.46%; RR=0.59 (95% CI 0.38-0.94), p=0.02]. About 22% of patients were receiving low-dose aspirin. A subgroup analysis of patients not receiving aspirin resulted in significant results for celecoxib vs. pooled NSAIDs for both endpoints; there were no differences between celecoxib and pooled NSAIDs in patients receiving low-dose aspirin.

  Subsequent to initial publication, FDA briefing documents and reviews (available at www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1.htm) were made available addressing the entire duration of the trial. When the entire 13-month study period was considered, there was no significant difference between celecoxib and the pooled NSAID group for the primary endpoint of confirmed complicated UGI events in the overall study population, the subgroup of patients not receiving aspirin, or the subgroup of patients receiving aspirin. The differences in statistical significance between six-month data and data from the entire study period appeared to be due to the occurrence of relatively more confirmed complicated UGI events in the celecoxib group than in NSAID groups subsequent to the first six months (see Table 7).

Table 7: Number of confirmed complicated UGI events in the CLASS trial
(uncensored intent-to-treat data)

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
First 6 months	11	9	11
Entire Study Period	17	10	11

Adapted from Tables 13 and 14, Medical Officer Review for Celebrex®, available at: www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.doc

FDA briefing documents and reviews also provide separate data for the two comparator NSAIDs, which was not available in the published report. All differences that were statistically significant between celecoxib and the pooled NSAID group were significant for celecoxib versus ibuprofen. Regardless of aspirin use, there was no difference between diclofenac and celecoxib in any endpoint.

Meloxicam

- Two large (8000+ patient) meloxicam safety trials have been published, SELECT (Dequeker et al. Brit J Rheumatol 1998; 37:946-51) and MELISSA (Hawkey et al. Brit J Rheumatol 1998; 37:937-45). Each of the two 28-day trials randomized patients with OA to meloxicam or a comparator NSAID (piroxicam in SELECT and diclofenac in MELISSA); the trials were otherwise of identical design. The choice of NSAID comparators facilitated comparison of results with meloxicam vs. both a relatively COX-1 selective NSAID (piroxicam) and a relatively COX-2 selective NSAID (diclofenac). In SELECT, 7 patients treated with meloxicam had complicated upper GI events or ulcerations compared to 16 patients treated with piroxicam. All four cases involving perforations or bleeding occurred with piroxicam. In MELISSA, 5 patients treated with meloxicam had complicated upper GI events or ulcerations compared to 7 patients treated with diclofenac. Although both comparisons were statistically nonsignificant, the numerical results are consistent with the known COX-2 selectivity of the comparators.
- While meloxicam lacks a GI safety study comparable in size and duration to VIGOR or CLASS, summary results of large pooled analyses of clinical trial data are becoming available. Summary results of a pooled analysis of meloxicam clinical trial data involving 27,039 patients who received meloxicam, comparator NSAIDs, or placebo in 35 clinical trials have been published in abstract by Dr. Singh and colleagues, and are available from the manufacturer as the "Meloxicam Serious GI Event Analysis." (Note: multiple abstracts concerning this analysis are available at www.eular.org; search 2001 & 2002 abstracts for "meloxicam.")
- An analysis of complicated upper GI events (perforations, obstructions, or clinically serious upper GI bleeds) per 100 patient-years in patients who received placebo, various doses of meloxicam, diclofenac, or piroxicam during meloxicam clinical trials is shown in the table below (Singh G, Triadafilopoulos G. European Congress of Rheumatology, June 2001. Abstract SAT0085). The rate of complicated upper GI events with meloxicam appeared to be dose-related and lower than rates with diclofenac or piroxicam.

Table 8: Rate of complicated UGI events & NNH

Drug	N	Cumulative pt-yrs	Events	Events per 100 pt-yrs	NNH*
Placebo	736	113	0	0	-
Mel 7.5 mg	10158	918	3	0.3	333
Mel 15 mg	2960	1451	9	0.6	167
Mel 22.5	910	600	6	1.0	100
Diclofenac	5464	524	9	1.7	59
Piroxicam	5371	603	16	2.7	37

NNH = number-needed-to-harm to cause 1 additional event compared to placebo

- Preliminary results from an even larger pooled analysis are available in abstract (Furst et al, European League Against Rheumatism 2002, Stockholm, Sweden. Abstract THU0264, available online at www.eular.org). The analysis included data from 48 clinical trials including 117,755 patients with rheumatic diseases who received meloxicam, comparator NSAIDs, or placebo during meloxicam clinical trials. Cumulative hazards (95% CI) after 3 months for complicated upper GI events (perforations, obstructions, or GI bleeds) was: 0.05% (0-0.12%) for meloxicam 7.5 mg; 0.42% (0.12-0.71%) for meloxicam 15 mg; estimate for diclofenac 0.51% (0.16-0.86%); estimate for piroxicam 1.11% (0.35-1.88%).