Department of Defense
Pharmacoeconomic Center

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MCCS-GPE **15 August 2001**

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

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

1. The DoD P&T Executive Council met from 0800 to 1600 hours on 15 August 2001 at the Non-Commissioned Officers Club, Ft. Sam Houston, TX. The DoD P&T Executive Council is responsible for performing certain inherently governmental functions relevant to the DoD pharmacy benefits program. The Council focuses primarily on issues related to the Basic Core Formulary (BCF), national pharmaceutical contracts, and blanket purchase agreements. The DoD P&T Executive Council is comprised of federal employees who are members of the DoD P&T Committee.

2. MEMBERS PRESENT

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

MEMBERS ABSENT

COL Rosa Stith, MC	Army
Dick Rooney	Department of Veterans Affairs

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TRICARE Management Activity
COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LtCol Gary Blamire, MSC	Lead Agent Office, Region 6
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LTC Doreen Lounsbery, MC	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, BSC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	DoD Pharmacoeconomic Center
MAJ Cheryl Filby, MS	Defense Supply Center Philadelphia
MAJ Barbara Roach, MC	DoD Pharmacoeconomic Center
SFC Tom Bolinger	DoD Pharmacoeconomic Center
SFC Augustin Serrano	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Carol Scott	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia

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

4. ADVANCES IN MEDICAL PRACTICE (AMP) PROGRAM

TMA recently released AMP funds for FY 2001 to the military services. Based on prime vendor data, MTFs spent $37.3 million on AMP drugs during the first nine months of FY 2001 (see Appendix A). Total AMP expenditures for FY 2001 will likely be close to the projected figure of $50 million.

5. PROGRAM BUDGET DECISION 812

Program Budget Decision (PBD) 812, approved by the Deputy Secretary of Defense on 21 June 2001, increases MTF pharmacy funding by $307.1 million in FY 2002 to recognize the cost growth experienced in FY 2001. PBD 812 also funds MTF pharmacies at a 15% annual growth rate through FY 2007. MTF pharmacy expenditures will be reviewed annually to determine the adequacy of the revised program funding, and it will be adjusted accordingly. The PBD recognizes the fact that inadequate funding of MTF pharmacies can cause beneficiaries to fill their prescriptions in the private sector at much higher cost to the government.

6. COX-2 INHIBITORS

At the last meeting, the Council agreed that management of the COX-2 inhibitors should ideally focus on two issues: accurately and efficiently targeting COX-2 therapy to those patients at greatest risk for gastrointestinal (GI) adverse events, and reducing the unit cost of COX-2 inhibitors.

A. *Formulary status of COX-2 inhibitors and the use of targeting programs at MTFs*

A PEC survey of MTFs in August 2001 found that 54% of the MTFs have no COX-2 inhibitors on formulary and 77% of the MTFs have a program to target COX-2 inhibitor therapy (see Table 1). Most MTFs use the NMOP prior authorization criteria to target therapy.

Table 1: Formulary Status and Targeting Programs for COX-2 Inhibitors at MTFs

Service	MTFs responding	COX-2s on formulary			MTFs with Targeting Program
		None	One*	Both	
Navy	**14**	12	0	2	8
Air Force	**19**	6	7	6	19
Army	**25**	13	4	8	18
Total	**58**	**31 (53%)**	**11 (19%)**	**16 (28%)**	**45 (78%)**

* 10 MTFs had celecoxib and 1 MTF had rofecoxib

B. *Use of COX-2 inhibitors in the Military Health System (MHS)*

Table 2 displays the number of prescriptions filled for COX-2 inhibitors and traditional NSAIDs at the various MHS outpatient pharmacy points of service during July 2001.

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

	MTF prescriptions	MCSC retail network prescriptions	NMOP prescriptions	Total
COX-2 inhibitors	45,345 (13%)	40,094 (37%)	12,826 (43%)	98,265 (20%)
Traditional NSAIDs	298,799 (87%)	67,960 (63%)	17,306 (57%)	384,065 (80%)
Total	344,144	108,054	30,132	482,330

Source: Pharmacy Data Transaction Service Customer Service Support Center

C. *Therapeutic interchangeability of COX-2 inhibitors*

A significant reduction in unit cost would likely be achieved by a closed class contract that selects a single COX-2 inhibitor for the BCF, but a closed class contract is feasible only if the drugs are therapeutically interchangeable. Additional safety data concerning rofecoxib and celecoxib recently became available due to the release of FDA advisory committee briefing documents and reviews of additional data from two large trials—the Vioxx Gastrointestinal Outcomes Research (VIGOR) study and the Celecoxib Long-term Arthritis Safety Study (CLASS). These data were submitted to the FDA Arthritis Advisory Committee to support manufacturers' requests to remove NSAID-class GI warnings from product labeling. (The review documents represent the opinions of reviewers and not final conclusions of the FDA, which has not yet made a final determination.) The Council assessed various concerns about the therapeutic interchangeability of celecoxib and rofecoxib, including two key issues that arose from review of this additional information.

1. *Vioxx Gastrointestinal Outcomes Research study (VIGOR)* – Data from the VIGOR trial showed an increased risk of serious thrombotic cardiovascular events for rofecoxib compared to naproxen. The rate of confirmed thrombotic cardiovascular serious adverse events was 1.67 per 100 patient-years for the rofecoxib group and 0.70 per 100 patient-years for the naproxen group (RR 2.37; 95% CI 1.39 – 4.06; p=0.0016). The difference in the composite measure was primarily due to a difference in the incidence of myocardial infarctions between the rofecoxib and the naproxen group. These results could be explained by either a prothrombotic effect of rofecoxib or an antithrombotic cardioprotective effect of naproxen. See Appendix B for a more detailed discussion of VIGOR results.

2. *Celecoxib Long-term Arthritis Safety Study (CLASS)* – Published results of the CLASS trial were limited to data obtained during the first six months of study participation, although about 35% of patients completed nine months or more of treatment. Published results did not show a significant difference in the primary endpoint of the study [annualized incidence of confirmed complicated UGI events (perforations, obstructions, and GI bleeds)] between celecoxib and the pooled group of comparator non-steroidal anti-inflammatory drugs (NSAIDs) in the overall study population. There was a significant difference in the primary endpoint in the subgroup of patients not taking low dose aspirin.

   Results from the entire study period did not show a significant difference for the primary endpoint in either the overall study population or in the subgroup of patients not taking aspirin. The differences between the six-month and entire study period data appeared to be due to the occurrence of relatively more confirmed complicated UGI events in the celecoxib group than in the NSAID group in the time period subsequent to the first six months of study participation.

   These results raise doubts about the GI protective effects of celecoxib. The additional data also suggest that the statistically significant differences in GI safety endpoints between celecoxib and the pooled NSAID group are primarily due to differences between celecoxib and ibuprofen; celecoxib was not statistically significant from diclofenac for any patient group or endpoint. This finding raises additional doubts about the generalizability of CLASS results to patients receiving "traditional" NSAIDs not tested in the CLASS trial. See Appendix B for a more detailed discussion of CLASS results.

3. *Lack of rheumatoid arthritis indication for rofecoxib* – Rofecoxib is not currently indicated for rheumatoid arthritis (RA). Merck filed an application for a supplemental NDA for an indication for RA in March 2001 and has submitted additional studies to the FDA.

4. *Edema and hypertension* – Like traditional NSAIDs, both celecoxib and rofecoxib have been shown to increase blood pressure and produce edema. It is not clear whether there is a clinically significant difference in the propensity of the two drugs to produce such effects. Studies suggest a small, dose-related increase in edema and hypertension with rofecoxib, especially at 50 mg QD. A dose-response relationship has not been clearly shown for celecoxib.

5. *MTF survey regarding therapeutic interchangeability* - A survey was sent to lead agent pharmacists to ascertain the opinions of MTFs in their regions. The survey focused on the consensus opinions of facility P&T committees, not individual provider opinions. Lead agent pharmacists had the option of reporting individual MTF responses or submitting a single consensus response from their entire region. The survey included a clinical review comparing celecoxib and rofecoxib and a fact sheet outlining possible scenarios for contracting and/or BCF status. Questions about possible contracting and/or BCF status were to be answered under the assumption that the Program Budget Decision 812 would provide MTFs with adequate funding for these agents. Responses to the survey are summarized in Table 3.

Table 3: Responses to the COX-2 Interchangeability Survey

Region			1	2	3	4	5	6	7/8	9	10	11	12	Summary
Number of facilities responding			12	5	4	0	*	6	*	2	4	2	11	
% of patients whose initial clinical needs are met by	Celebrex	>90%	5	2	2			4		0	1	1	5	20
		75-90%	3	1	0			1		0	3	0	4	12
		<75%	3	2	2		X	1	X	2	0	1	2	14
	Vioxx	>90%	6	2	2			3		0	2	1	6	18
		75-90%	1	2	0			1	X	1	2	0	3	10
		<75%	4	1	2		X	2		1	0	1	2	12
Product more likely to fail		Equal	10	4	4		X	1		1	2	1	10	34
		Celebrex	1					1	X		1		1	5
		Vioxx								1	1			2
Relative acceptability of management options – means of individual responses (1 = Most acceptable; 5 = Least acceptable)														
Closed class contract			3.5	4	2.5		2	1	3		5	3	1.5	2.8
Add specific agent in open class			2	2	2.5		3	3	2	1.5	2	2	1.5	2.2
Add requirement for agent but do not specify			1	1	4		5	2	1	1.5	1	4	3.5	2.4
Add both agents to BCF			3.5	3	5		4	5	4		3	5	5	4.1
Add neither agent to BCF			5	5	1		1	4	5		4	1	3.5	3.3

* Consensus response from entire region only

D. *VA/DoD Clinical Review*

The PEC and the VA PBM are collaborating on a clinical review of the COX-2 inhibitors, but the review is not complete yet.

E. *P&T Executive Council Conclusions*

Based on the available safety and efficacy data and the lack of a RA indication for rofecoxib, the Council could not conclude that celecoxib and rofecoxib are therapeutically interchangeable. MTFs vary significantly in their support for a closed class contract. The Council does not support a closed class contract for a COX-2 inhibitor at this time.

The analysis of all the data for the CLASS study raises questions about the GI protective effects of celecoxib. The VIGOR study raises concerns about a potential increase in risk of cardiovascular events with rofecoxib. The COX-2 inhibitors are no more effective than traditional NSAIDs for treating osteoarthritis or rheumatoid arthritis. The COX-2 inhibitors cost much more than traditional NSAIDs. The Council concluded that a COX-2 inhibitor should not be added to the BCF at this time.

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

A. *Contract awards, renewals, and terminations*

- As of 1 August 2001, 47 joint VA/DoD national contracts have been awarded. Information on national pharmaceutical contracts, including NDC numbers and prices, is available on the DSCP website (www.dmmonline.com).
- Since the last meeting, DoD/VA single source contracts were awarded for the following drugs:
  - Carbidopa/levodopa 25 mg/100 mg and 50 mg/200 mg sustained action tablets, to Dupont Pharma
  - Glyburide 1.25mg, 2.5mg and 5mg tablets, to Pharmacia Corporation
  - Ointment Base (Absorbase 50% water-in-oil emulsion) 454- and 120-gram jars, to Carolina Medical Products
- The 21-count, 6-cycle package of ethinyl estradiol/ norethindrone tabs (Norinyl) was removed from the national contract effective 24 July 2001. The item may be purchased off the FSS at the same price. The 28-count packages remain on the contract.
- The albuterol inhaler contract will not be renewed due to continuing availability problems with all the chlorofluorocarbon (CFC) albuterol products.

B. *Financial impact of contracts* – Cost avoidance has been estimated by subtracting the actual expenditures for the "market basket" of products affected by a contract from the expenditures that would have occurred if the contract did not exist (based on the prices that existed before the contract took effect). This method is reasonably accurate for the first year of a contract, but changes in the "market basket" of products (e.g., new indications, generic availability, price changes for non-contracted drugs, introduction of new products, product withdrawals, etc.) make it difficult to accurately estimate "what would have been paid" if the contract did not exist in subsequent years. The Council agreed that the cost per patient-day of therapy or cost per member per month within therapeutic categories would be useful indicators of the financial impact of national pharmaceutical contracts and would avoid the ambiguities of cost avoidance estimates.

C. *Statin Contract* - The withdrawal of cerivastatin (Baycol) from the market leaves simvastatin (Zocor) as the only statin on the Basic Core Formulary (BCF) and the National Mail Order Pharmacy (NMOP) formulary. The P&T Executive Council concluded that simvastatin could meet the clinical needs of the vast majority of patients who previously took cerivastatin, so there is no need to add a second statin to the BCF or NMOP formulary at this time. Patients who previously took cerivastatin should be switched to simvastatin. Other statins should be used only when simvastatin will not meet the clinical needs of an individual patient.

The simvastatin contract requires the statin class to remain "closed" on the BCF and NMOP formulary. The simvastatin contract is in effect until February 2002, and there is an option to renew the contract to February 2003. The DoD P&T Executive Council will evaluate clinical and economic information regarding the statin class and make a

recommendation to the Defense Supply Center Philadelphia (DSCP) regarding the potential renewal of the simvastatin contract. The Council will consider the impact of new NCEP guidelines on statin usage; the potential availability of rosuvastatin (Crestor); and impending patent expirations (lovastatin - expected Dec 2001; pravastatin - expected early 2003).

The P&T Executive Council was informed that Merck would reduce the DoD contract prices for four of the five strengths of simvastatin effective 1 Sep 2001 (see Table 4).

Table 4: DoD Contract Prices for Simvastatin

Strength	Old Price	New Price (effective 1 Sep 01)
5 mg	$0.41	$0.38
10 mg	$0.62	$0.50
20 mg	$0.65	$0.60
40 mg	$0.94	$0.85
80 mg	$0.98	$0.98

D. *Proton pump inhibitor contract*

The contract for omeprazole (Prilosec) will expire on 30 September 2001 and will not be renewed because the omeprazole contract price would be much higher than the prices for other proton pump inhibitors. As a consequence, the proton pump inhibitor class will revert to an "open class" on the BCF as of 1 October 2001. The Council reviewed the safety, tolerability, efficacy, price/cost, and other factors associated with proton pump inhibitors.

Safety/Tolerability – The PPIs appear to have similar safety profiles. Early concerns about gastric enterochromaffin-cell hyperplasia and gastric cancer caused by chronic hypergastrinemia have not materialized in clinical practice.

Omeprazole may be the most likely to cause cytochrome P450 drug interactions as it interacts preferentially with CYP2C19, inhibiting the metabolism of diazepam, phenytoin, and warfarin. Rabeprazole, pantoprazole and lansoprazole do not appear to cause clinically significant P450 drug interactions. Experience with esomeprazole is limited. Omeprazole is Pregnancy Category C; the other 4 PPIs are Category B.

Efficacy – When used at appropriate doses, all the PPIs are efficacious for the treatment of a variety of acid-related disorders, including gastroesophageal reflux disease (GERD) and erosive esophagitis. More than 20 published, double-blind, randomized, head-to-head trials used omeprazole as the comparator drug. These studies showed that, in most patients, omeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day, esomeprazole 40 mg/day, and rabeprazole 20 mg/day relieve GERD symptoms within several days and heal esophageal erosions within 4 - 8 weeks of initiating therapy. Reported differences in the duration of antisecretory effect vary between patients and do not necessarily translate into improved clinical efficacy. Lansoprazole 30 mg/day and rabeprazole 20 mg/day may provide more rapid relief of GERD symptoms when compared with omeprazole 20

mg./day, but the differences are usually observed only in the first few days of treatment. Esomeprazole may have a faster onset of healing of esophageal erosions, but healing rates at 12 weeks are similar to those reported with omeprazole.

Price/Cost

Table 5: DoD Prices for Proton Pump Inhibitors

Generic	Brand	Dose	Current Price	After 1 Oct
Rabeprazole	Aciphex	20 mg	$0.22 (FSS)	$0.22 (FSS)
Lansoprazole	Prevacid	30 mg	$2.06 (FSS)	$2.06 (FSS)
Pantoprazole	Protonix	40 mg	$1.27 (FSS)	$1.27 (FSS)
Omeprazole	Prilosec	20 mg	$1.09 (contract)	$2.02 (FSS)
Esomeprazole	Nexium	20 mg	$2.35 (FSS)	$2.35 (FSS)
FSS = Federal Supply Schedule; BPA = Blanket Purchase Agreement				

Other Factors

- *Availability of generic omeprazole* – AstraZeneca has received pediatric exclusivity for Prilosec through 5 Oct 2001. The FDA has granted tentative approval for generic versions of Prilosec to two generic companies: Andrx for 10-, 20- and 40-mg delayed release capsules and GenPharm for 10- and 20-mg delayed release capsules. Due to an agreement between the two companies, Andrx would be considered the "first-to-file" and thus should be the only generic available for the most commonly used 20-mg strength of omeprazole for up to 180 days following approval. It is unknown when generic omeprazole will be available, as lawsuits involving at least 4 generic companies are underway or pending.
- *VA usage* - The VA is currently converting the majority of their patients from lansoprazole, which was previously their contract agent, to rabeprazole. Lansoprazole continues to be available to VA facilities at a BPA price of $0.55 per capsule.
- *Direct-to-consumer (DTC) advertising* - AstraZeneca is currently running an intensive DTC advertising campaign attempting to convince patients to switch from omeprazole to esomeprazole.
- *Provider survey results* – A survey was sent to GI specialists and primary care providers in all three services, who were also asked to forward the survey to other clinicians. The VA PPI class review and a supplemental fact sheet from the PEC were sent along with survey questions. A total of 28 responses were received from 15 Army, 11 Air Force, and 2 Navy providers. The majority of responses were from family medicine (10), followed by GI specialists (6); general surgery (3); internal medicine, primary care, flight medicine, unknown specialty (2 each); and pulmonary/critical care (1). Summary results are shown in Table 6 following.

  Comments from providers generally supported the therapeutic interchangeability of PPIs. Most agreed that using the least costly PPI would be appropriate to treat the majority of patients.

Several providers mentioned the need for alternate PPIs for patients with swallowing difficulties. Only lansoprazole has an oral suspension. Labeling for lansoprazole, omeprazole, and esomeprazole capsules indicates they can be opened and sprinkled on applesauce; rabeprazole and pantoprazole have no alternative dosage forms, but are relatively small tablets. Providers also mentioned the desire to have an intravenous PPI available. Only pantoprazole is available in an intravenous formulation.

Two providers commented negatively on the DTC campaign for esomeprazole. Two Air Force providers mentioned the fact that omeprazole is the only PPI specifically approved for Air Force aircrew waiver.

Table 6: PPI Provider Survey

	Strongly Agree	Agree	Neither Agree or Disagree	Disagree	Strongly Disagree
All the PPIs currently available are likely to be effective for treating the conditions for which I typically prescribe PPIs.	14	13	0	1	0
The differences in FDA-approved indications between these products have little clinical relevance when treating most patients.	8	17	0	3	0
The faster time to relief of symptoms reported by AstraZeneca for esomeprazole has little to no clinical significance.	5	16	4	2	0
The faster time to relief of symptoms reported for rabeprazole has little to no clinical significance.	4	16	5	2	0
Price should be a consideration when providers decide which of these agents to prescribe.	13	14	1	0	0
I have sufficient concerns regarding the safety, efficacy, or patient acceptability of the other available PPIs that I will continue to prescribe Prilosec after October 1st regardless of price.	0	2	0	13	12

After considering safety, tolerability, efficacy, price, and patient acceptability, which of the following PPIs, if available on formulary after October 1, would I feel comfortable using.

Drug	Definitely Use	Consider Use	Use with reservations	Never Use
Omeprazole	14	7	3	1
Rabeprazole	18	8	1	0
Lansoprazole	13	13	0	0
Pantoprazole	7	16	2	1
Esomeprazole	8	8	5	3

The Council concluded that there are no clinical or economic reasons to pursue another closed class contract in this drug class. The Council voted to remove Prilosec from the BCF and add rabeprazole (Aciphex) to the BCF. These BCF changes take effect on 1 Oct 2001. MTFs may have other PPIs on their formularies in addition to rabeprazole as of 1 Oct 2001.

E. *Status of contracting initiative for nasal corticosteroid inhalers* – The DoD P&T Executive Council concluded at the November 2000 meeting that a closed class contract could be sought for a high-potency aqueous nasal corticosteroid. The Council identified five products that could compete for the contract: budesonide 32 mcg/spray, fluticasone 50 mcg/spray, triamcinolone 55 mcg/spray, mometasone 50 mcg/spray, and beclomethasone 84 mcg/spray. The VA recently completed its class review of nasal corticosteroid inhalers. The VA wants to include flunisolide (Nasarel) in the solicitation for a closed class contract. The Council asked the PEC to update its analysis of the nasal steroid class and recommend to the Council whether or not flunisolide should be included in the solicitation.

F. *Status of potential contracting initiative for leukotriene antagonists* – The VA is currently evaluating montelukast (Singulair) and zafirlukast (Accolate) for potential contracting. The 5-lipoxygenase inhibitor Zileuton (Zyflo) is not being considered due to several clinical disadvantages, including four times daily dosing and an increased risk of drug interactions and hepatotoxicity compared to the other two agents. This drug class has been proposed as a potential joint DoD/VA contracting initiative. The BCF currently states that each MTF must have a leukotriene antagonist on formulary, but the selection of the specific product is left to the MTF.

Safety/Tolerability – Placebo-controlled trials with both agents have shown a low incidence of adverse effects. GI symptoms and headache are reported most commonly. In trials comparing leukotriene antagonists with inhaled corticosteroids, both montelukast and zafirlukast were associated with higher discontinuation rates due to adverse events than inhaled corticosteroids.

Both products have been associated with elevations in liver function tests, although confounding factors make causality difficult to assess. One serious adverse reaction, Churg Strauss syndrome, has occurred during steroid tapers with both montelukast and zafirlukast, but may have been associated with "unmasking" of a pre-existing condition. Zafirlukast has clinically significant drug interactions with theophylline and warfarin. Clinically significant drug interactions have not been reported for montelukast.

Efficacy

Adult patients

- *Comparative trials with inhaled ß-agonists*: Studies have shown that adding a leukotriene antagonist to a short acting ß-agonist reduces the occurrence of asthma symptoms and the use of ß-agonists more than placebo.
- *Comparative trials vs. inhaled corticosteroids*: Although similar asthma exacerbation rates have been reported, inhaled corticosteroids significantly improve quality of life, lung function, and symptom control compared with the leukotriene antagonists.
- *Asthma monotherapy trials*: There are no published head-to-head trials with zafirlukast and montelukast. When two individual studies with similar trial design are compared, montelukast was slightly superior to zafirlukast in terms of FEV1 (forced expiratory volume in one second), PEFR (peak expiratory flow rate), and

prn albuterol use at 12 weeks. However, low-dose fluticasone was superior to either leukotriene inhibitor.

- *Combination of leukotriene antagonists with inhaled corticosteroids*: There are no head to head comparisons, and the trial designs of the available studies are too dissimilar to make comparisons

Pediatric patients

- Head to head comparisons between montelukast and zafirlukast are not available. The trial that was the basis for montelukast's pediatric labeling is only available in the package insert and has not been published in a peer-reviewed journal. A pediatric study comparing zafirlukast with low-dose fluticasone has been published. Both montelukast and zafirlukast improve symptoms and lung function compared with placebo. Inhaled steroids show similar exacerbation rates compared to leukotriene antagonists, but result in better improvements in lung function and symptoms.

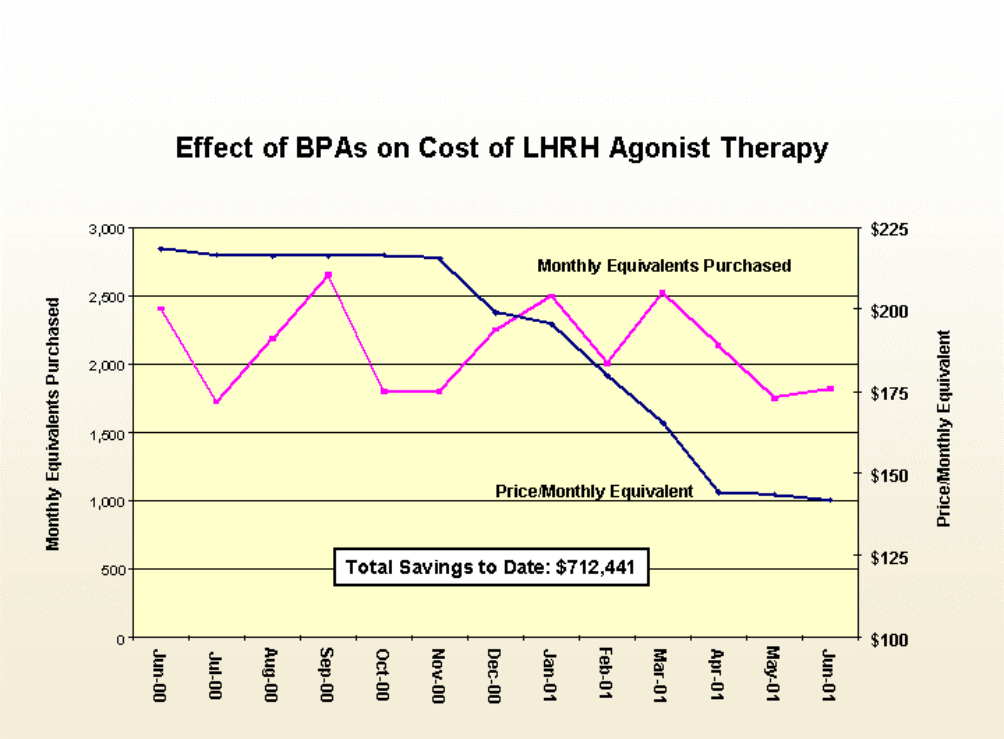
Other Factors

- Based on total tablets purchased, market shares for montelukast and zafirlukast in DoD MTFs are approximately 93% and 7%, respectively. Purchases by VA facilities are more evenly split between the two drugs—43% of leukotriene antagonist tablets purchased are montelukast; 56% are zafirlukast. Zafirlukast is typically dosed twice daily.
- Montelukast is dosed once daily and has FDA approval for patients as young as 2 years of age. A 4-mg chewable tablet formulation is available for children 2-5 years of age. Zafirlukast is dosed twice daily. It is FDA-approved for patients 7 years of age and older.

The Council concluded that montelukast and zafirlukast are not therapeutically interchangeable and that a closed class contract for a leukotriene inhibitor is not feasible for DoD. After considering the safety, tolerability, efficacy, and other factors associated with the leukotriene antagonists, the Council voted to add montelukast to the BCF.

G. *Non-sedating antihistamine contract* – Increases in prescription market share for fexofenadine (Allegra) and decreases in market share for loratadine (Claritin) indicate that MTFs are successfully implementing the non-sedating antihistamine contract. By the end of July 2001, the market share for fexofenadine (as a percent of all prescriptions for non-sedating antihistamines dispensed at MTF pharmacies) increased from 50% prior to the contract to nearly 80%. The prescription market shares for fexofenadine and loratadine remained stable in the retail pharmacy networks and the NMOP, indicating that MTFs are maximizing the use of fexofenadine without shifting loratadine prescriptions into the retail pharmacy network or NMOP. Since the contract took effect, the average cost per non-sedating antihistamine tablet/capsule purchased by MTFs has dropped by 33%, from $0.87 to $0.58. Appendix C contains market share and cost graphs for the non-sedating antihistamines.

H. *Status of BPAs and potential contracting action for Leutinizing Hormone Releasing Hormone (LHRH) agonists* – The AstraZeneca Federal Account Director has stated that the Blanket Purchase Agreement (BPA) for goserelin (Zoladex) will stay in effect even if the 80% market share requirement is not met by 1 Sep 2001. The Zoladex and leuprolide (Lupron) BPAs have reduced the weighted average cost per monthly equivalent of LHRH agonist therapy for prostate cancer by 35%, from $215 in November 2000 to $140 in June 2001. The BPAs yielded $712,000 in cost avoidance for MTFs from November 2000 to June 2001.



Lupron and Zoladex are generally considered equivalent in safety and efficacy for treatment of prostate cancer. The therapeutic interchangeability of these products hinges on tolerability and other factors that affect patient or provider acceptance of either product. CAPT Torkildson (PEC) obtained input from Urology specialty leaders and other providers:

- Several providers reported that patients had been switched from one product to the other without problems.
- Zoladex must be implanted rather than simply injected, so administration of Zoladex consumes more physician time. Some MTFs improve the efficiency of Zoladex administration by training non-physicians to administer the product.
- Lupron has a 4-month dosage form; Zoladex does not.
- Some providers expressed concern regarding lack of experience with one or the other products.
- There was general agreement that the potential for decreased cost is sufficient reason to seek a contract.

The dosage forms of Lupron and Zoladex that would compete for this contract are not used exclusively for prostate cancer. The PEC estimates that 10% of the Lupron usage and 2% of the Zoladex usage are for conditions other than prostate cancer. However, the age and sex specificity of prostate cancer allows contract compliance to be monitored relatively easily.

The Council voted to support a joint VA/DoD contract for an LHRH agonist for the treatment of prostate cancer.

8. THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS (CURE) TRIAL

The Council reviewed preliminary summary information from the CURE trial. (Complete results of the trial were subsequently published in the 16 Aug 2001 issue of the New England Journal of Medicine.) The CURE trial enrolled approximately 12,500 patients with unstable angina and non-ST elevation MI presenting within 24 hours of the onset of symptoms. Patients were randomized into two groups: aspirin alone (75 to 325 mg QD) or aspirin plus clopidogrel (300 mg immediately, then 75 mg QD). Follow-up was for an average of 9 months. A 20% reduction in the composite endpoint of cardiovascular death, nonfatal MI, or stroke was reported for the combination of clopidogrel plus aspirin compared to aspirin alone. The combination reportedly had both an early (within 2 hours) and sustained benefit relative to aspirin alone. A significant increase in major (but not life-threatening) bleeds was reported in patients receiving both aspirin and clopidogrel, but there was insufficient information to adequately assess the severity of the incremental risk of bleeding.

Clopidogrel is currently indicated for prevention of stroke and/or MI in patients with aspirin allergy and for short-term use following cardiac stent placement. Clopidogrel is not on the BCF. The Council agreed that it would be premature to consider clopidogrel for the BCF on the basis of preliminary data, but asked the PEC to review results of the published study and make recommendations.

9. MTF REQUESTS FOR BCF CHANGES

A. *Request to remove quinidine from the BCF* – A pharmacist from an Army medical center requested removal of quinidine products from the BCF due to infrequent usage.

Meta-analyses have shown increased mortality rates in patients given quinidine during or after acute myocardial infarction and patients given quinidine after cardioversion for atrial fibrillation. Mortality rates in patients with ventricular arrhythmias were three times higher with quinidine than other Class I antiarrhythmics. In addition, the risk of torsade de pointes, a potentially fatal arrhythmia, is estimated to be 1.5% to 8% in patients treated with quinidine. (Some clinicians feel this may underestimate the true occurrence.) Current therapy recommendations relegate quinidine to second or third-line status for either atrial or ventricular arrhythmia. According to data from the Uniformed Services Prescription Database, MTF prescriptions for quinidine products have consistently decreased over the past 3 years to fewer than 200 prescriptions per month for quinidine sulfate and fewer than 1300 prescriptions per month for quinidine gluconate.

The Council voted to remove both quinidine sulfate and quinidine gluconate from the BCF. MTFs may choose to remove or retain these products on their formularies.

B. *Request to remove primidone from the BCF* – A pharmacist from an Army medical center requested removal of primidone from the BCF due to infrequent usage.

Primidone is FDA approved for treatment of partial complex seizures but is rarely used for that indication. Its primary use is off-label for the treatment of essential tremor. Safer, more tolerable alternatives are available for both seizure disorder and essential tremor. The DoD P&T Council voted to remove primidone from the BCF because it has no clinical benefit over agents already on the formulary. MTFs may choose to remove or retain primidone on their formularies.

C. *Request to add amiodarone to the BCF* – A primary care provider and a cardiologist from an Air Force teaching facility requested addition of amiodarone to the BCF based on current use of this drug in clinical practice.

Safety/Tolerability - Amiodarone carries a black box warning that lists potentially fatal toxicities, including proarrhythmic effects, pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis), and overt liver disease (in a few cases). Proarrhythmic effects appear to occur in less than 1% of patients, mostly in conjunction with electrolyte abnormalities or when used concurrently with other antiarrhythmics. This is a less frequent occurrence than seen in other antiarrhythmics. Pulmonary toxicity can be seen in 5% to 15% of patients, but has a good prognosis when the drug is discontinued.

The most common adverse effect of amiodarone is thyroid dysfunction; discontinuation of the drug is usually not necessary. Most other adverse effects are dose dependent. In general, smaller doses of amiodarone are required to treat atrial arrhythmias than ventricular arrhythmias. No other Class III antiarrhythmics are currently available.

Efficacy – Amiodarone is only FDA-indicated for the management of life-threatening recurrent ventricular fibrillation or hemodynamically unstable ventricular tachycardia, but use of the drug in clinical practice has changed significantly since its introduction in 1985. Amiodarone is now widely used to treat both atrial and ventricular arrhythmias. .

Other Factors – The VA developed a form to assist in monitoring amiodarone patients with regard to drug-drug interactions and timing of labs and other ancillary services (available at: www.vapbm.org/monitoring/amiodaron.htm). Guidelines intended for the use of primary care providers who follow patients on amiodarone have been issued by the North American Society of Pacing and Electrophysiology [Arch Intern Med 2000 (26 June); 160(12):1741-8]. Publication of guidelines for the treatment of atrial fibrillation by the American College of Cardiology and the American Heart Association are anticipated by the end of Aug 2001.

The Council added amiodarone to the BCF.

10. REVIEW OF ACNE MEDICATIONS FOR THE BCF

MAJ Barbara Roach reported on the PEC review of acne medications. The BCF currently lacks topical treatment choices for patients with acne who do not respond to over-the-counter benzoyl peroxide. The PEC evaluated the safety, tolerability, efficacy, cost, and historical MTF usage of topical acne medications and recommended the addition of clindamycin phosphate 1% solution and tretinoin cream 0.025% and 0.05% to the BCF. The PEC also recommended the removal of age restrictions for tretinoin cream in the NMOP and retail

pharmacies because it is commonly used for seborrheic keratoses (which occur in older adults).

The Council added clindamycin phosphate 1% solution to the BCF. Council members were concerned that the removal of age restrictions would allow tretinoin to be used for cosmetic treatment of photoaged skin (wrinkles and liver spots). The Council was uncertain as to whether the age restriction was specified in the Code of Federal Regulations, TRICARE policy, or the NMOP Statement of Work. Military service policies might also have age limits on tretinoin availability. The Council voted to table the decision on tretinoin until these issues are clarified.

11. OBTAINING INPUT FROM PROVIDERS

The PEC has substantially increased efforts to obtain input from physicians and pharmacists on formulary and contracting issues. A BCF request form is available for MTF personnel to recommend changes in the BCF. Teleconferences are conducted with the pharmacy consultants/specialty leaders and pharmacists representing each TRICARE region. The PEC has surveyed specialty consultants and MTF providers to obtain input on important drug classes such as COX-2 inhibitors, proton pump inhibitors, LHRH agonists, and low molecular weight heparins, but these are informal surveys instituted on a case-by-case basis. There is no formal, recognized, systematic method for MTF providers to routinely have input on formulary and contracting issues.

The Council appointed a subcommittee to explore ways to systematically obtain input from providers on formulary and contracting issues. Subcommittee member are COL Downs, LCDR Briski, and COL Davies or his designee.

12. The meeting adjourned at 1600 hours on 15 August 2001. The next meeting will be held in the Washington DC area (specific location to be determined) and is scheduled for 14 Nov 2001 at 0800. All agenda items should be submitted to the co-chairs no later than 19 October 2001.

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

LIST OF APPENDICES

Appendix A: MTF Expenditures for Drugs Included in the Advances in Medical Practice (AMP) Program

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Appendix A: MTF Expenditures for Drugs Included in the Advances in Medical Practice (AMP) Program

MTF Expenditures On Amp Drugs, First Nine Months Of FY 01

Drug Name*	Air Force	Army	Navy	Grand Total
Abciximab	$254,828	$216,886	$75,396	$547,110
Alpha-1-Proteinase Inhibitor			$18,228	$18,228
Becaplermin	$62,291	$94,926	$43,818	$201,035
Cyclosporine	$322,159	$235,474	$178,033	$735,666
Cyclosporine Microemulsion	$662,783	$632,102	$628,818	$1,923,703
Dornase Alfa	$238,605	$136,393	$154,692	$529,690
Epoetin Alfa	$3,074,457	$3,640,225	$1,957,694	$8,672,375
Eptifibatide	$66,227	$299,967	$179,640	$545,834
Etanercept	$1,165,366	$825,910	$499,619	$2,490,896
Factor VIIa,Recomb		$4,218		$4,218
Filgrastim	$1,071,525	$1,379,019	$809,235	$3,259,779
Gemcitabine Hcl	$168,885	$296,224	$225,954	$691,062
Glatiramer Acetate	$368,394	$180,715	$100,230	$649,339
Infliximab	$251,723	$258,436	$332,440	$842,598
Interferon Beta-1a	$1,211,255	$979,842	$496,651	$2,687,748
Interferon Beta-1b	$374,021	$512,901	$332,929	$1,219,851
Interferon Gamma-1b,Recomb.	$41,678	$65,455	$35,905	$143,037
Irinotecan Hcl	$183,078	$427,646	$232,438	$843,162
Leflunomide	$152,077	$285,243	$171,167	$608,488
Mycophenolate Mofetil	$412,354	$518,043	$219,776	$1,150,173
Mycophenolate Mofetil HCl	$919	$2,082		$3,002
Palivizumab	$1,316,843	$1,401,470	$943,150	$3,661,463
Ribavirin/Interferon A-2b	$539,000	$1,168,805	$423,249	$2,131,054
Rituximab	$284,989	$956,443	$407,289	$1,648,721
Sargramostim	$17,853	$105,341	$8,348	$131,542
Sirolimus	$33,545	$75,817	$31,191	$140,554
Tacrolimus Anhydrous	$409,332	$367,998	$226,014	$1,003,344
Temozolomide	$122,356	$95,662	$67,134	$285,152
Tirofib Hc M-Hyd/Na Chlor 0.9%	$2,745	$21,087		$23,832
Tirofiban HCl M-Hydrate	$87,199	$55,477	$19,159	$161,835
Trastuzumab	$121,671	$269,967	$26,662	$418,300
Grand Total	$13,018,156	$15,509,775	$8,844,859	$37,372,790

* Celecoxib and rofecoxib were removed from the AMP list for FY 01

Appendix B: COX-2 Inhibitor Trials (VIGOR and CLASS)

1. Cardiovascular Safety Data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) Study

The 8076-patient VIGOR trial (NEJM 2000;343:1520-8) included patients with rheumatoid arthritis (RA) who were 50 years old (or 40 years old and receiving long-term glucocorticoids) and excluded patients on low-dose aspirin for cardiovascular prevention. Patients were randomized to rofecoxib 50 mg QD or naproxen 500 mg BID. The median follow-up was 9 months (range 0.5 – 13). Use of aspirin or non-study NSAIDs was not allowed.

A detailed analysis of VIGOR data concerning the occurrence of cardiovascular events is available from FDA briefing documents, available at *www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2.htm*. Overall, the rate of adjudicated thrombotic cardiovascular serious adverse events per 100 patient-years was 1.67 for rofecoxib vs. 0.70 for naproxen [relative risk (RR) 2.37; 95% confidence interval (CI) 1.39-4.06; p=0.0016]. The difference in the composite measure was primarily due to a difference in the incidence of myocardial infarctions between the rofecoxib and the naproxen group. For patients identified as potential candidates for low-dose aspirin, the difference in event rates was marked: 14.29 for rofecoxib vs. 2.94 for naproxen (RR 4.89; 95% CI 1.41-16.88; p=0.0122). For patients not considered candidates for low dose aspirin, the difference in events was less marked but still statistically significant: 1.16 for rofecoxib vs. 0.62 for naproxen (relative risk 1.88; 95% CI 1.03-3.45; p=0.041).

It has been suggested that naproxen, which is relatively COX-1 selective, may have antiplatelet effects similar to aspirin. This may explain the relatively lower incidence of thrombotic events with naproxen compared to rofecoxib, but, as stated by the FDA Advisory Committee review, a direct prothrombotic effect of rofecoxib cannot be ruled out. Whether the putative effect of naproxen in reducing cardiovascular thrombotic effects in the VIGOR trial is reasonable compared to expected results with aspirin is subject to debate. There are no trials assessing the ability of naproxen to reduce cardiovascular events.

Since RA patients appear to have a higher baseline risk for cardiovascular disease than patients with osteoarthritis (OA), the RA population in VIGOR may have been more sensitive to any potential thrombogenic effect of selective COX-2 inhibition than a population predominated by OA patients. In addition, the effect may be dose-related; the 50-mg daily dose used in VIGOR is at least two times higher than doses recommended for chronic use.

The proposed prothrombotic mechanism is related to cyclooxygenase inhibition. COX-1 mediates production of thromboxane A2, which promotes vasoconstriction, platelet activation and aggregation. COX-2 mediates production of prostaglandins at inflammatory sites as well as prostacyclin (PGI2), a vasodilator and inhibitor of platelet aggregation. If COX-2 is selectively inhibited, unopposed production of thromboxane could result in an increase in CV thrombotic effects. Compensatory mechanisms are known to exist. Whether this theoretical effect applies to celecoxib is unknown, but appears plausible based on the proposed mechanism.

2. Additional Results Concerning GI Protective Effects of Celecoxib from the Celecoxib Long-term Arthritis Safety Study (CLASS)

The Celecoxib Long-term Arthritis Safety Study (CLASS) was an 8059-patient trial that compared celecoxib (400 mg BID) to diclofenac (75 mg BID) or ibuprofen (800 mg TID). Approximately 73% of patients had osteoarthritis; 27% had rheumatoid arthritis. Use of low-dose aspirin for cardiovascular prophylaxis was permitted.

The published report of the trial (JAMA 2000;284:1247-55) was limited to data obtained during the first six months of study participation, although about 35% of patients received nine months or more of treatment. According to published six-month data, the annualized absolute risk (AR) for the primary endpoint of confirmed complicated UGI events (GI bleeds, perforation, or gastric outlet obstruction) was 0.76% for celecoxib vs. 1.45% for the pooled NSAID group (RR 0.53; 95% CI 0.26-1.11; p=0.09), a non-significant difference. The difference in AR was significant when the subgroup of patients not taking aspirin was considered [0.44% for celecoxib vs. 1.27% for the pooled NSAID group (RR 0.35; 95% CI 0.14-0.98; p=0.04)]. However, there was neither a significant difference nor a discernible trend in patients taking aspirin [2.01% for celecoxib vs. 2.12% for the pooled NSAID group (RR 0.95; 95% CI not calculated; p=0.49)], a result that raises the possibility that COX-2 inhibitors may not provide a clinically relevant GI protective effect for patients on low dose aspirin.

When the entire 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 below).

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

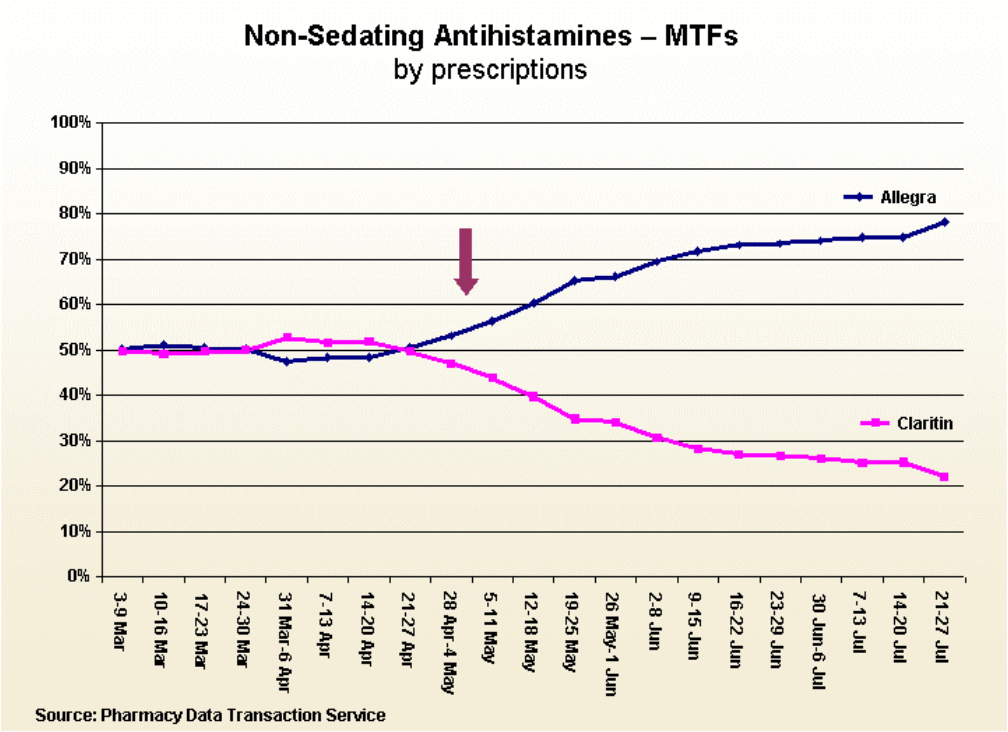
Adapted from Tables 13 and 14, Medical Officer Review for Celebrex®, available at:
www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.doc

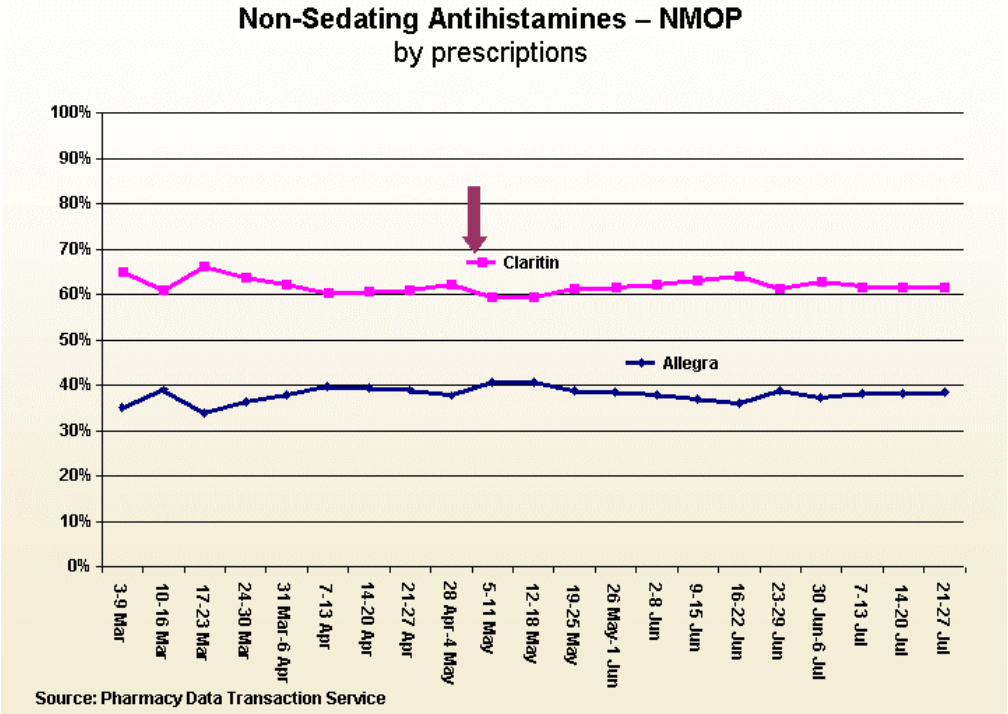
The manufacturer has suggested that this is primarily due to disproportionate dropouts secondary to GI symptoms (e.g., dyspepsia) among patients receiving comparator NSAIDs, artificially decreasing the number of patients in the NSAID group susceptible to GI adverse events. FDA reviewers raise a number of questions concerning the validity of this explanation.

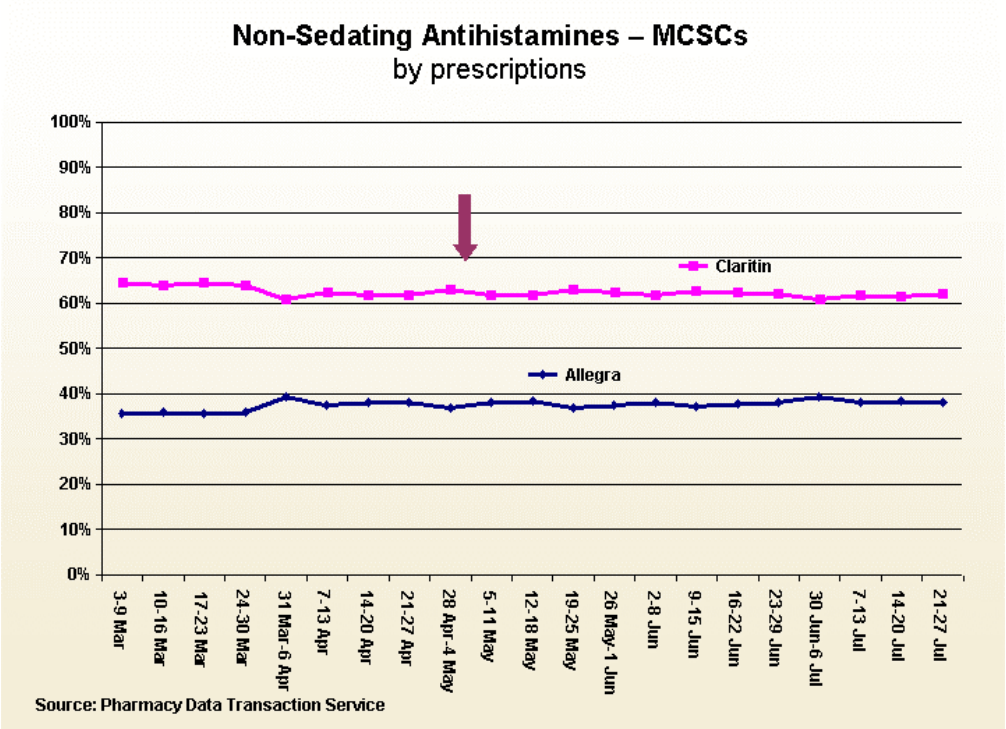
FDA briefing documents and reviews also provide separate data for the two comparator NSAIDs. All differences that were statistically significant between celecoxib and pooled NSAIDs were significant for celecoxib versus ibuprofen. The differences between celecoxib and diclofenac were not statistically significant for any of the endpoints.

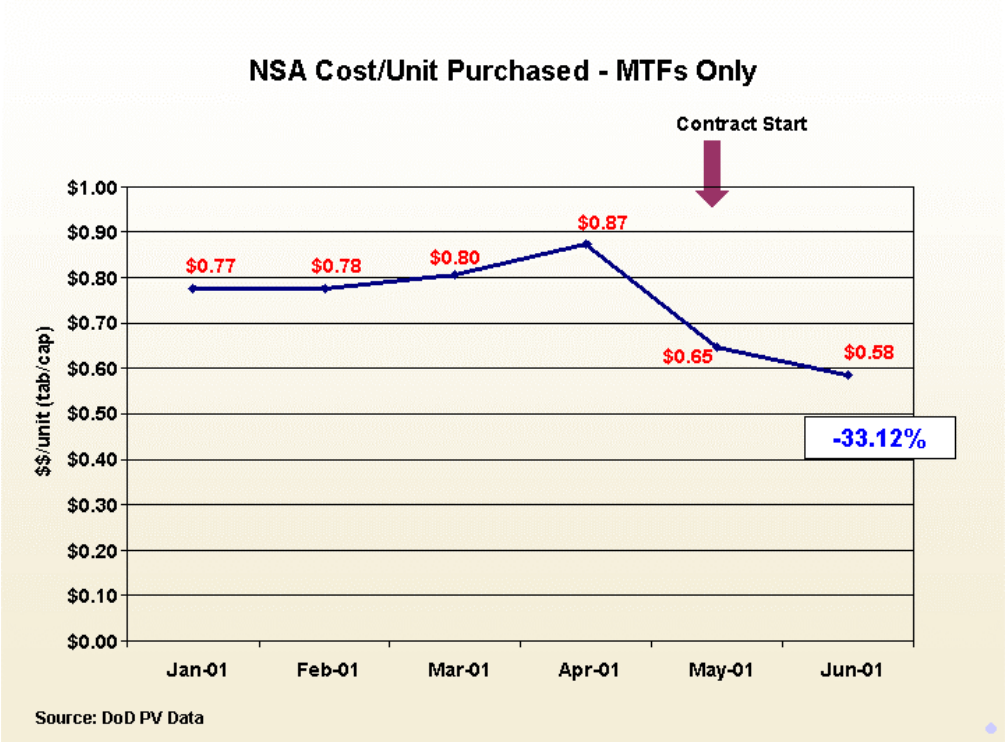
FDA briefing documents and reviews are available at *www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1.htm*.

Appendix C: Market Share and Cost Graphs for the Non-Sedating Antihistamines






Non-Sedating Antihistamines – MCSCs
by prescriptions
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Claritin
Allegra
3-9 Mar
10-16 Mar
17-23 Mar
24-30 Mar
31 Mar-6 Apr
7-13 Apr
14-20 Apr
21-27 Apr
28 Apr-4 May
5-11 May
12-18 May
19-25 May
26 May-1 Jun
2-8 Jun
9-15 Jun
16-22 Jun
23-29 Jun
30 Jun-6 Jul
7-13 Jul
14-20 Jul
21-27 Jul
Source: Pharmacy Data Transaction Service


NSA Cost/Unit Purchased - MTFs Only
Contract Start
$$/unit (tab/cap)
$1.00
$0.90
$0.80
$0.70
$0.60
$0.50
$0.40
$0.30
$0.20
$0.10
$0.00
$0.77
$0.78
$0.80
$0.87
$0.65
$0.58
-33.12%
Jan-01
Feb-01
Mar-01
Apr-01
May-01
Jun-01
Source: DoD PV Data