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Office of Surveillance and Epidemiology**

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To: M. Dianne Murphy, M.D.
Director, Office of Pediatric Therapeutics (OPT), OIASI
Office of the Commissioner

CDR Lisa L. Mathis, USPHS M.D.,
OND Associate Director
Pediatric and Maternal Health Team

Hari C. Sachs, M.D., FAAP
Medical Officer
Pediatric and Maternal Health Team
Office of New Drugs

Thru: Solomon Iyasu, M.D., M.P.H., Director
Division of Epidemiology
Office of Surveillance and Epidemiology

From: Laura Governale, Pharm.D., MBA, Drug Use Data Analyst,
Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology

Subject: One Year Post-Pediatric Exclusivity Post-marketing Adverse
Event Review: Drug Utilization Analysis
Pediatric Exclusivity Grant Date: August 23, 2006

Drug Name(s): Celebrex[®] (celecoxib) Capsules

Submission Number: S-021

Application Type/Number: NDA 20-998

Applicant/sponsor: Pfizer

OSE RCM #: 2006-837

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EXECUTIVE SUMMARY

This review examines the drug utilization patterns for Celebrex[®] (celecoxib) two years before and one year following the granting of Pediatric Exclusivity on August 23, 2006, with a primary focus on the use in the pediatric population, ages 0 through 18 years. Outpatient drug use patterns for celecoxib, as well as other selected anti-rheumatic products were examined for the three 12-month periods from September 1, 2004 through August 31, 2007, using proprietary drug use databases licensed by FDA.

Total prescriptions dispensed for celecoxib decreased by 21% from 14.1 million prescriptions during the baseline period, September 2004 – August 2005, to 11.1 million during the post-exclusivity period, September 2006 – August 2007. Between the pre-exclusivity period (September 2005 – August 2006) and the post-exclusivity period (September 2006 - August 2007), prescription volume increased slightly from 11 million prescriptions to 11.1 million prescriptions, respectively. During the entire study period, celecoxib was the third most dispensed NSAID drug product in this selected group of anti-rheumatic products.

Adults accounted for over 99% of dispensed prescriptions throughout the study period. In adults (ages 19 years and above), celecoxib ranked 3rd in terms of prescription volume and accounted for approximately 15% of the selected anti-rheumatic market share during the entire study period. In the pediatric population, celecoxib ranked 8th in terms of prescription volume and accounted for approximately 1% of the selected anti-rheumatic market share during the entire study period. Between the baseline period (September 2004 – August 2005) and the post-exclusivity period (September 2006 - August 2007), there was a 28% decrease in prescription volume for celecoxib. Between the pre- (September 2005 – August 2006) and the post-exclusivity period (September 2006 - August 2007), there was a nearly 3% growth in prescription volume for celecoxib. Trends for patient data were similar to that of prescription data.

The General Practice* specialty was the most common prescribing specialty for celecoxib, accounting for approximately 33-35% of the dispensed prescriptions throughout the study period. Prescriptions by Rheumatology specialists accounted for approximately 5-6%, and Pediatricians accounted for less than 1% of all celecoxib prescriptions throughout the study period.

The most common diagnoses associated with the use of celecoxib in the pediatric population was “sprains and strains of ankle and foot” ICD-9 845, “osteochondropathies” ICD-9 732, and “sprains and strains of knee and leg” ICD-9 844. These diagnoses accounted for approximately 21%, 16%, and 12% of use during the post-exclusivity period. Uses related to “rheumatoid arthritis and other inflammatory polyarthropies” ICD-9 714 accounted for only 4% of use during the post-exclusivity period.

According to office-based physician surveys, the majority of drug occurrences in the pediatric population was for 16-30 days of therapy during the pre- and post-exclusivity periods.

1 BACKGROUND

1.1 INTRODUCTION

* GP/FM/DO – General Practice, Family Medicine, Doctors of Osteopathy

On January 4, 2002, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that Act requires the review of adverse events associated with the use of a drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug soon after the one-year anniversary of granting exclusivity. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

1.2 REGULATORY HISTORY

Celebrex[®] (celecoxib; NDA 20-998) Capsules 100 mg, and 200 mg was approved on December 31, 1998, for management of the signs and symptoms of osteoarthritis and rheumatoid arthritis. Pediatric Exclusivity was granted for Celebrex[®] on August 23, 2006, based on studies submitted under NDA 20-998/S-021. On December 15, 2006, Celebrex[®] received marketing approval for use in the pediatric population, ages 2 years and over, for the treatment of Juvenile Rheumatoid Arthritis (JRA).

2 METHODS AND MATERIALS

2.1 INTRODUCTION

Using the currently available data resources, this review describes the drug utilization patterns for Celebrex[®] (celecoxib) in the pediatric population as well as in the adult population in the years prior to and subsequent to the granting of pediatric exclusivity on August 23, 2006. For the remainder of this review, Celebrex[®] will be referred to as celecoxib. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

2.2 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives[™] data were used to determine the settings in which celecoxib is sold. Sales of this product by extended units (number of capsules) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for the year following the granting of pediatric exclusivity on August 23, 2006, from September 2006 through August 2007. During this 12-month time period, approximately 91% of celecoxib capsules were distributed to the outpatient setting.¹ More specifically, nearly 65% of celecoxib capsules were distributed to retail sales channels (Food Stores, Chain Pharmacies, Independent Pharmacies), 26% to mail order channels and 9% to non-retail channels (Long Term Care Facilities, Clinics, Non-Federal Hospitals, Prisons, Federal Facilities, Home Health Care, HMOs, Universities). Thus, we examined celecoxib utilization patterns in the outpatient setting.

2.3 DATA SOURCES USED

Outpatient use and patient demographics were measured with two data sources from Verispan, LLC: Vector One[®]: National (VONA) and Total Patient Tracker (TPT) (see Appendix 2). From these two sources, nationally projected estimates of the number of prescriptions dispensed by retail pharmacies and the number of patients who received a dispensed prescription for celecoxib were obtained. Indications for use were obtained from the Verispan, Physician Drug and

¹ IMS Health, IMS National Sales Perspective[™], September 2006 - August 2007, Data extracted 1-2008. Source File: 0801cele.dvr

Diagnosis Audit database (see Appendix 2). Outpatient drug utilization patterns were examined for three twelve-month periods from September 1, 2004 through August 31, 2007.

2.4 PRODUCTS INCLUDED

We examined prescriptions dispensed for celecoxib as well as other products in the anti-rheumatic drug market for comparative purposes. Products in the anti-rheumatic market included the following NSAID products: ibuprofen, naproxen, meloxicam, diclofenac, nabumetone, etodolac, indomethacin, piroxicam, oxaprozin, sulindac, ketoprofen, flurbiprofen, mefenamic acid, fenoprofen, tolmetin, meclofenamate, valdecoxib, and rofecoxib. Also included in the analysis was leflunomide, an immunomodulatory agent used for the treatment of active rheumatoid arthritis. These products constituted the anti-rheumatic drug market in this review.

3 RESULTS

3.1 DISPENSED PRESCRIPTIONS

3.1.1 Selected Anti-Rheumatic Products

Overall, the total number of dispensed prescriptions for the selected anti-rheumatic drug products declined by approximately 6% from 90.7 million dispensed prescriptions during the baseline period, September 2004 – August 2005, to 84.9 million dispensed prescriptions during the post-exclusivity period, September 2006 – August 2007 (Appendix 1: Table 1). The pre-exclusivity period, September 2005 – August 2006, accounted for the lowest prescription volume for the entire market among the three 12-month periods (Appendix 1: Figure 1). Of the top 5 dispensed products, prescription ibuprofen products had the largest share of the market at an average of approximately 30%, followed by naproxen at 19%, celecoxib at 14%, meloxicam at 9% and diclofenac at 7%. Dispensed prescriptions for leflunomide accounted for less than 1% of the market share during the entire study period among these selected anti-rheumatic agents.

3.1.2 Celecoxib

Total prescriptions dispensed for celecoxib decreased by 21% from 14.1 million prescriptions during the baseline period, September 2004 – August 2005, to 11.1 million during the post-exclusivity period, September 2006 – August 2007 (Appendix 1: Table 1). Between the pre-exclusivity period (September 2005 – August 2006) and the post-exclusivity period (September 2006 - August 2007), prescription volume increased slightly from 11 million prescriptions to 11.1 million prescriptions, respectively. During the entire study period, celecoxib was the third most dispensed NSAID drug product in this selected group of anti-rheumatic agents.

3.2 PATIENT DEMOGRAPHICS

3.2.1 Prescriptions Dispensed

3.2.1.1 Selected Anti-Rheumatic Products

Examination of the entire market of selected anti-rheumatic drug products by patient age showed that the majority of these products are used in adults who accounted for approximately 94% of dispensed prescriptions throughout the study period prescription (Appendix 1: Table 2, Figure 2). Prescription ibuprofen and naproxen products were the top two dispensed products among pediatric patients (aged 0-18 years) and adults (19 years and above).

In the pediatric population, prescription volume for the entire market of anti-rheumatic drug products increased by 11% and 4%, respectively, between the baseline period (September 2004 – August 2005) and the post-exclusivity period (September 2006 - August 2007), and the pre-exclusivity period (September 2005 – August 2006) and the post-exclusivity period (September 2006 - August 2007) (Appendix 1: Table 2, Figure 3). Prescription ibuprofen and naproxen products accounted for over 70% and nearly 20%, respectively, of the share of dispensed prescriptions in this selected anti-rheumatic drug market during the entire study period. Only prescription ibuprofen, naproxen, diclofenac, meloxicam, nabumetone, piroxicam, and leflunomide (10%) realized positive growth in prescription volume with piroxicam realizing the largest growth (20%) between the baseline period (September 2004 – August 2005) and the post-exclusivity period (September 2006 - August 2007).

In adults, prescription volume for the entire market of anti-rheumatic drug products decreased by approximately 7% between the baseline period (September 2004 – August 2005) and the post-exclusivity period (September 2006 - August 2007), and increased by 3% between the pre-exclusivity period (September 2005 – August 2006) and the post-exclusivity period (September 2006 - August 2007) (Appendix 1: Table 2). Prescription ibuprofen and naproxen products accounted for approximately 30% and 20% of the market share for these selected anti-rheumatic products. The products which realized positive growth in prescription volume between the baseline period (September 2004 – August 2005) and the post-exclusivity period (September 2006 - August 2007) were ibuprofen, naproxen, meloxicam, diclofenac, nabumetone, etodolac, piroxicam, leflunomide (26%), and fenoprofen, with fenoprofen accounting for the largest growth (38%).

3.2.1.2 Celecoxib

In the pediatric population, celecoxib ranked 8th in terms of prescription volume and accounted for approximately 1% of the selected anti-rheumatic market share during the entire study period (Appendix 1: Table 2). Between the baseline period (September 2004 – August 2005) and the post-exclusivity period (September 2006 - August 2007), there was a 28% decrease in prescription volume for celecoxib. Between the pre- (September 2005 – August 2006) and the post-exclusivity period (September 2006 - August 2007), there was a nearly 3% growth in prescription volume for celecoxib.

Analysis of pediatric sub-age groups revealed that the majority of prescriptions are dispensed to the age 12-18 year old population. There was a nearly 8% increase in prescription volume between the pre- and post-exclusivity periods for this age group while prescription volume declined among all other pediatric sub-groups (Appendix 1: Table 3). Between the baseline period and the post-exclusivity period, prescription volume declined for all pediatric sub-age groups as well as in the adults.

In adults (ages 19 years and above), celecoxib ranked 3rd in terms of prescription volume and accounted for approximately 15% of the anti-rheumatic market share during the entire study period (Appendix 1: Table 2). Adults accounted for over 99% of dispensed prescriptions throughout the study period (Appendix 1: Table 3). Prescription volume decreased by 20% between the baseline period (September 2004 – August 2005) and the post-exclusivity period (September 2006 - August 2007), and increased by 2% between the pre-exclusivity period (September 2005 – August 2006) and the post-exclusivity period (September 2006 - August 2007).

3.2.2 Patient Counts for Celecoxib Dispensed Prescriptions

Trends for patient data were similar to that of prescription data. Adults had the greatest proportion of use at approximately 98% while the pediatric subage group 12 – 18 years had the greatest proportion of use among the pediatric population (Appendix 1: Table 4). The number of patients receiving a prescription for celecoxib in the outpatient retail pharmacies decreased for all age groups between the baseline and post-exclusivity period by nearly 28%. However, the number of patients remained relatively constant between the pre- and post-exclusivity periods.

3.3 PRESCRIBER SPECIALTY

The General Practice* specialty was the most common prescribing specialty for celecoxib, accounting for approximately 33-35% of the dispensed prescriptions throughout the study period (Appendix 1: Table 5). Internal Medicine was the second most common prescribing specialty with approximately 25-26% of the dispensed prescriptions, followed by Orthopedic Surgery at 8-10% and Rheumatology at 5-6%. Prescriptions by Pediatricians accounted for less than 1% of all celecoxib prescriptions throughout the study period.

3.4 INDICATIONS FOR USE

According to Verispan's office-based physician practice survey database, the most common diagnoses associated with the use of celecoxib in the pediatric population was "sprains and strains of ankle and foot" ICD-9 845, "osteochondropathies" ICD-9 732, and "sprains and strains of knee and leg" ICD-9 844 (Appendix 1: Table 6). These diagnoses accounted for approximately 21%, 16%, and 12% of use during the post-exclusivity period. Uses related to "rheumatoid arthritis and other inflammatory polyarthropies" ICD-9 714 accounted for only 4% of use during the post-exclusivity period.

In the adult population, the most common diagnoses associated with the use of celecoxib were "osteoarthritis" ICD-9 715, "backdisorders" ICD-9 724, and "peripheral enthesopathies and allied syndromes" ICD-9 726 which accounted for approximately 24%, 12%, and 8% of uses during the post-exclusivity period, respectively. Uses related to "rheumatoid arthritis and other inflammatory polyarthropies" ICD-9 714 accounted for only 2% of use during the post-exclusivity period.

3.5 DURATION OF USE

We also examined the estimated therapy days for celecoxib to determine roughly the duration of use among the pediatric and adult populations. Therapy days are calculated by dividing the prescribed days of therapy given to a patient (calculated based on the extended units which includes both Quantity and Refills) by the Signa (dosing amount and frequency). According to office-based physician surveys, the majority of drug occurrences in the pediatric population was for 16-30 days of therapy during the pre- and post-exclusivity periods (Appendix 1: Table 7). However, during the baseline period the majority of drug occurrences was for 8-15 therapy days followed by greater than 91 days in this population. For adults, the majority of drug occurrences were for greater than 91 days during the baseline and pre-exclusivity period. This shifted to 16-30 therapy days during the post-exclusivity period.

* GP/FM/DO – General Practice, Family Medicine, Doctors of Osteopathy

4 DISCUSSION

Based on the databases employed for this analysis, prescriptions dispensed for celecoxib in the pediatric population accounted for only small proportion of the total prescriptions for celecoxib as well as other selected anti-rheumatic products during the pre- and post-exclusivity periods.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that celecoxib is distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

While we conducted a comprehensive analysis of the use of this product in the outpatient setting, in which the majority of use occurred, a significant proportion of wholesale sales of celecoxib products were to mail order pharmacies. Mail order data was not included in this analysis and likely underestimates the true extent of use of celecoxib as well as other selected anti-rheumatic products.

Verispan's Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. Verispan recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals and trending variability. For instance, the diagnoses associated with the use of celecoxib should be viewed without regard to extent of use. Furthermore, these physician survey data reflect the intent of the prescribing physician, not what actually occurs with the patient.

5 CONCLUSIONS

During the entire study period, celecoxib was the third most dispensed NSAID drug product in this selected group of anti-rheumatic products. Celecoxib is used primarily in adults. In adults (ages 19 years and above), celecoxib ranked 3rd in terms of prescription volume and accounted for approximately 15% of the selected anti-rheumatic market share during the entire study period. In the pediatric population, celecoxib ranked 8th in terms of prescription volume and accounted for approximately 1% of the selected anti-rheumatic market share during the entire study period.

The General Practice* specialty was the most common prescribing specialty for celecoxib. Prescriptions by Rheumatology specialists accounted for approximately 5-6%, and Pediatricians accounted for less than 1% of all celecoxib prescriptions throughout the study period.

The most common diagnoses associated with the use of celecoxib in the pediatric population were for non-arthritic conditions. Uses related to "rheumatoid arthritis and other inflammatory polyarthropies" ICD-9 714 accounted for only 4% of use during the post-exclusivity period. The

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majority of drug occurrences in the pediatric population were for 16-30 days of therapy during the pre- and post-exclusivity periods.

Laura Governale, Pharm.D., MBA
Drug Utilization Analyst, Team Leader

APPENDICES

APPENDIX 1: Tables and Figures

Table 1. Total number of dispensed prescriptions through U.S. outpatient retail pharmacies for the selected anti-rheumatic* drug market, September 1, 2004 - August 31, 2007

| | SEP 2004 - AUG 2005 | | SEP 2005 - AUG 2006 | | SEP 2006 - AUG 2007 | |
|----------------------|---------------------|---------------|---------------------|---------------|---------------------|---------------|
| | Retail TRxs | Share | Retail TRxs | Share | Retail TRxs | Share |
| | N | % | N | % | N | % |
| TOTAL MARKET | 90,712,526 | 100.0% | 82,577,778 | 100.0% | 84,899,373 | 100.0% |
| Ibuprofen | 25,382,608 | 28.0% | 25,420,545 | 30.8% | 25,909,355 | 30.5% |
| Naproxen | 15,432,548 | 17.0% | 15,738,365 | 19.1% | 16,486,999 | 19.4% |
| celecoxib | 14,060,407 | 15.5% | 10,964,651 | 13.3% | 11,126,781 | 13.1% |
| meloxicam | 7,323,023 | 8.1% | 6,741,854 | 8.2% | 8,300,184 | 9.8% |
| diclofenac sodium | 5,210,113 | 5.7% | 5,954,692 | 7.2% | 6,014,505 | 7.1% |
| nabumetone | 4,327,486 | 4.8% | 4,747,041 | 5.7% | 4,637,196 | 5.5% |
| etodolac | 3,046,738 | 3.4% | 3,327,926 | 4.0% | 3,262,164 | 3.8% |
| indomethacin | 3,479,055 | 3.8% | 3,461,436 | 4.2% | 3,243,043 | 3.8% |
| Piroxicam | 2,022,932 | 2.2% | 2,198,657 | 2.7% | 2,118,176 | 2.5% |
| oxaprozin | 1,157,961 | 1.3% | 1,195,375 | 1.4% | 1,128,464 | 1.3% |
| sulindac | 1,258,729 | 1.4% | 1,226,236 | 1.5% | 1,130,130 | 1.3% |
| leflunomide | 427,120 | 0.5% | 462,498 | 0.6% | 534,343 | 0.6% |
| ketoprofen | 560,869 | 0.6% | 530,172 | 0.6% | 483,008 | 0.6% |
| flurbiprofen | 276,142 | 0.3% | 264,076 | 0.3% | 239,266 | 0.3% |
| mefenamic acid | 148,382 | 0.2% | 138,847 | 0.2% | 116,280 | 0.1% |
| fenoprofen calcium | 52,593 | 0.1% | 75,204 | 0.1% | 70,966 | 0.1% |
| tolmetin sodium | 81,961 | 0.1% | 69,407 | 0.1% | 56,297 | 0.1% |
| meclofenamate sodium | 65,567 | 0.1% | 59,938 | 0.1% | 42,120 | 0.0% |
| valdecoxib | 5,304,139 | 5.8% | -- | 0.0% | -- | 0.0% |
| rofecoxib | 1,094,153 | 1.2% | -- | 0.0% | -- | 0.0% |

Source: Verispan Vector One[®]: National, Data Extracted 1-2008. File: VONA 2006-837 Celebrex BPCA NSAIDs Arava TRx 1-17-08.qry

* Anti-rheumatic market - selected NSAID's and leflunomide, an immunomodulatory agent

Table 2. Total number of dispensed prescriptions for selected anti-rheumatic* drug market by patient age (0-18, 19+) through U.S. outpatient retail pharmacies, September 1, 2004 - August 31, 2007

| | SEP 2004 - AUG 2005 | | SEP 2005 - AUG 2006 | | SEP 2006 - AUG 2007 | | Baseline to Post- | Pre-Exclusivity to |
|----------------------|---------------------|--------------|---------------------|--------------|---------------------|--------------|-------------------|--------------------|
| | Baseline | | Pre-Exclusivity | | Post-Exclusivity | | Exclusivity | Post-Exclusivity |
| | Retail TRxs | Share | Retail TRxs | Share | Retail TRxs | Share | %change | %change |
| | N | % | N | % | N | % | | |
| TOTAL MARKET | 90,711,972 | 100.0% | 82,577,962 | 100.0% | 84,899,274 | 100.0% | -6% | 3% |
| age 0-18 | 4,392,492 | 4.8% | 4,719,212 | 5.7% | 4,888,696 | 5.8% | 11% | 4% |
| Ibuprofen | 3,058,565 | 69.6% | 3,479,698 | 73.7% | 3,609,844 | 73.8% | 18% | 4% |
| Naproxen | 841,667 | 19.2% | 821,593 | 17.4% | 850,345 | 17.4% | 1% | 3% |
| diclofenac sodium | 61,011 | 1.4% | 64,969 | 1.4% | 66,437 | 1.4% | 9% | 2% |
| etodolac | 62,436 | 1.4% | 63,733 | 1.4% | 59,870 | 1.2% | -4% | -6% |
| meloxicam | 44,297 | 1.0% | 33,066 | 0.7% | 51,710 | 1.1% | 17% | 56% |
| nabumetone | 50,896 | 1.2% | 52,119 | 1.1% | 51,580 | 1.1% | 1% | -1% |
| Piroxicam | 42,347 | 1.0% | 47,230 | 1.0% | 50,775 | 1.0% | 20% | 8% |
| celecoxib | 56,477 | 1.3% | 39,761 | 0.8% | 40,862 | 0.8% | -28% | 3% |
| indomethacin | 33,074 | 0.8% | 32,058 | 0.7% | 29,517 | 0.6% | -11% | -8% |
| mefenamic acid | 28,963 | 0.7% | 25,793 | 0.5% | 22,578 | 0.5% | -22% | -12% |
| ketoprofen | 14,841 | 0.3% | 14,049 | 0.3% | 13,623 | 0.3% | -8% | -3% |
| oxaprozin | 13,647 | 0.3% | 13,021 | 0.3% | 12,886 | 0.3% | -6% | -1% |
| sulindac | 14,557 | 0.3% | 13,154 | 0.3% | 11,411 | 0.2% | -22% | -13% |
| flurbiprofen | 12,284 | 0.3% | 11,067 | 0.2% | 10,356 | 0.2% | -16% | -6% |
| tolmetin sodium | 4,067 | 0.1% | 3,329 | 0.1% | 2,685 | 0.1% | -34% | -19% |
| leflunomide | 1,570 | 0.0% | 1,461 | 0.0% | 1,727 | 0.0% | 10% | 18% |
| meclofenamate sodium | 2,112 | 0.0% | 2,022 | 0.0% | 1,503 | 0.0% | -29% | -26% |
| fenoprofen calcium | 1,012 | 0.0% | 994 | 0.0% | 987 | 0.0% | -2% | -1% |
| rofecoxib | 10,572 | 0.2% | 50 | 0.0% | - | - | | |
| valdecoxib | 38,097 | 0.9% | 45 | 0.0% | - | - | | |
| age 19+ | 85,529,959 | 94.3% | 77,391,590 | 93.7% | 79,742,475 | 93.9% | -7% | 3% |
| Ibuprofen | 22,040,223 | 25.8% | 21,766,304 | 28.1% | 22,205,704 | 27.8% | 1% | 2% |
| Naproxen | 14,460,647 | 16.9% | 14,819,618 | 19.1% | 15,573,590 | 19.5% | 8% | 5% |
| celecoxib | 13,879,505 | 16.2% | 10,871,878 | 14.0% | 11,060,543 | 13.9% | -20% | 2% |
| meloxicam | 7,241,720 | 8.5% | 6,688,470 | 8.6% | 8,232,239 | 10.3% | 14% | 23% |
| diclofenac sodium | 5,117,271 | 6.0% | 5,868,160 | 7.6% | 5,934,934 | 7.4% | 16% | 1% |
| nabumetone | 4,249,307 | 5.0% | 4,675,334 | 6.0% | 4,576,798 | 5.7% | 8% | -2% |
| etodolac | 2,957,844 | 3.5% | 3,245,601 | 4.2% | 3,192,375 | 4.0% | 8% | -2% |
| indomethacin | 3,420,083 | 4.0% | 3,411,341 | 4.4% | 3,202,344 | 4.0% | -6% | -6% |
| Piroxicam | 1,958,731 | 2.3% | 2,131,381 | 2.8% | 2,051,387 | 2.6% | 5% | -4% |
| oxaprozin | 1,134,738 | 1.3% | 1,175,582 | 1.5% | 1,112,870 | 1.4% | -2% | -5% |
| sulindac | 1,233,397 | 1.4% | 1,206,429 | 1.6% | 1,115,917 | 1.4% | -10% | -8% |
| leflunomide | 422,250 | 0.5% | 459,385 | 0.6% | 531,736 | 0.7% | 26% | 16% |
| ketoprofen | 538,883 | 0.6% | 511,658 | 0.7% | 467,292 | 0.6% | -13% | -9% |
| flurbiprofen | 261,411 | 0.3% | 251,141 | 0.3% | 228,085 | 0.3% | -13% | -9% |
| mefenamic acid | 118,976 | 0.1% | 112,711 | 0.1% | 93,494 | 0.1% | -21% | -17% |
| fenoprofen calcium | 50,448 | 0.1% | 73,451 | 0.1% | 69,694 | 0.1% | 38% | -5% |
| tolmetin sodium | 77,320 | 0.1% | 65,695 | 0.1% | 53,222 | 0.1% | -31% | -19% |
| meclofenamate sodium | 62,326 | 0.1% | 56,776 | 0.1% | 40,156 | 0.1% | -36% | -29% |
| valdecoxib | 5,228,884 | 6.1% | 381 | 0.0% | 85 | 0.0% | -100% | -78% |
| rofecoxib | 1,075,995 | 1.3% | 294 | 0.0% | 10 | 0.0% | -100% | -97% |
| age UNSPEC. | 789,521 | 0.9% | 467,160 | 0.6% | 268,103 | 0.3% | -66% | -43% |

Source: Verispan, Vector One[®]: National, Data Extracted 1-2008. File: VQNA.2006-837 Celebrex BPCANSAIDs Arava AgTRx 1-17-08.qry

* Anti-rheumatic market - selected NSAIDs and leflunomide, an immunomodulatory agent

Table 3. Total number of dispensed prescriptions for celecoxib by patient age (0-1, 2-5, 6-11, 12-18, 19+) through U.S. outpatient retail pharmacies, September 1, 2004 - August 31, 2007

| | SEP 2004 - AUG 2005 | | SEP 2005 - AUG 2006 | | SEP 2006 - AUG 2007 | | Baseline to Post-Exclusivity | Pre-Exclusivity to Post-Exclusivity |
|--------------------|---------------------|---------------|---------------------|---------------|---------------------|---------------|------------------------------|-------------------------------------|
| | Baseline | | Pre-Exclusivity | | Post-Exclusivity | | | |
| | Retail TRxs | Share | Retail TRxs | Share | Retail TRxs | Share | % change | % change |
| | N | % | N | % | N | % | | |
| celecoxib | 14,060,411 | 100.0% | 10,964,640 | 100.0% | 11,126,826 | 100.0% | -21% | 1% |
| age 0-18 | 56,477 | 0.4% | 39,761 | 0.4% | 40,862 | 0.4% | -28% | 3% |
| age 0-1 | 1,809 | 3.2% | 670 | 1.7% | 559 | 1.4% | -69% | -17% |
| age 2-5 | 4,789 | 8.5% | 2,200 | 5.5% | 1,257 | 3.1% | -74% | -43% |
| age 6-11 | 6,457 | 11.4% | 4,942 | 12.4% | 4,532 | 11.1% | -30% | -8% |
| age 12-18 | 43,422 | 76.9% | 31,949 | 80.4% | 34,514 | 84.5% | -21% | 8% |
| age 19+ | 13,879,505 | 98.7% | 10,871,878 | 99.2% | 11,060,543 | 99.4% | -20% | 2% |
| age Unspec. | 124,429 | 0.9% | 53,001 | 0.5% | 25,421 | 0.2% | -80% | -52% |

Source: Verispan Vector One®: National, Data Extracted 1-2008. File: VONA 2006-837 Celebrex BPCA Celebrex AgTRx 1-17-08.qry

Table 4. Total number of unique patients receiving a prescription for celecoxib in U.S. outpatient retail pharmacies, September 1, 2004 - August 30, 2007

| | SEP 2004 - AUG 2005 | | SEP 2005 - AUG 2006 | | SEP 2006 - AUG 2007 | | Baseline to Post-Exclusivity | Pre-Exclusivity to Post-Exclusivity |
|--------------------|-------------------------|---------------|---------------------|---------------|---------------------|---------------|------------------------------|-------------------------------------|
| | Baseline | | Pre-Exclusivity | | Post-Exclusivity | | | |
| | Projected Patient Count | | | | | | % change | % change |
| | N | % | N | % | N | % | | |
| Total | 4,650,491 | 100.0% | 3,338,227 | 100.0% | 3,356,857 | 100.0% | -28% | 0.0% |
| Ages 0 - 18 | 33,888 | 0.7% | 23,127 | 0.7% | 24,411 | 0.7% | -28% | 0.0% |
| 0 - 1 | 1,137 | 0.02% | 472 | 0.01% | 301 | 0.01% | -73% | 0.1% |
| 2 - 5 | 1,891 | 0.04% | 906 | 0.03% | 482 | 0.01% | -75% | 0.1% |
| 6 - 11 | 2,311 | 0.05% | 1,530 | 0.05% | 1,577 | 0.05% | -32% | 0.1% |
| 12 - 18 | 28,648 | 0.62% | 20,274 | 0.61% | 22,143 | 0.66% | -23% | 0.0% |
| Ages 19+ | 4,540,767 | 97.6% | 3,286,239 | 98.4% | 3,315,134 | 98.8% | -27% | 0.0% |
| Unknown Age | 150,190 | 3.2% | 73,328 | 2.2% | 57,144 | 1.7% | -62% | 0.0% |

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.

Source: Verispan, Vector One®: Total Patient Tracker. File: TPT 2006-837 Celebrex custom age display.xls

Table 5. Total number of dispensed prescriptions for celecoxib in outpatient retail pharmacies by prescribing specialty, September 1, 2004 - August 30, 2007

| | SEP 2004 - AUG 2005 | | SEP 2005 - AUG 2006 | | SEP 2006 - AUG 2007 | |
|---------------------------|------------------------|---------------|------------------------|---------------|------------------------|---------------|
| | Baseline | | Pre-Exclusivity | | Post-Exclusivity | |
| | N | % | N | % | N | % |
| celecoxib | 14,060,422 | 100.0% | 10,964,669 | 100.0% | 11,126,755 | 100.0% |
| GP/FM/DO* | 4,640,731 | 33.0% | 3,789,123 | 34.6% | 3,791,542 | 34.1% |
| INTERNAL MEDICINE | 3,611,278 | 25.7% | 2,785,562 | 25.4% | 2,777,795 | 25.0% |
| ORTHOPEDIC SURGERY | 1,147,948 | 8.2% | 1,009,061 | 9.2% | 1,098,250 | 9.9% |
| RHEUMATOLOGY | 688,243 | 4.9% | 618,143 | 5.6% | 621,874 | 5.6% |
| UNSPECIFIED | 1,288,976 | 9.2% | 561,005 | 5.1% | 426,013 | 3.8% |
| NURSE PRACTITIONER | 229,754 | 1.6% | 208,875 | 1.9% | 247,032 | 2.2% |
| PHYSICIAN ASSISTANT | 206,810 | 1.5% | 199,953 | 1.8% | 244,865 | 2.2% |
| ANESTHESIOLOGY | 173,568 | 1.2% | 179,286 | 1.6% | 209,779 | 1.9% |
| PHYSICAL MEDICINE & REHAB | 182,560 | 1.3% | 178,561 | 1.6% | 207,888 | 1.9% |
| PODIATRIST | 151,319 | 1.1% | 148,474 | 1.4% | 181,973 | 1.6% |
| CARDIOVASCULAR DISEASES | 179,174 | 1.3% | 125,908 | 1.1% | 121,678 | 1.1% |
| NEUROLOGY | 130,158 | 0.9% | 110,176 | 1.0% | 123,349 | 1.1% |
| PEDIATRICS | 122,404 | 0.9% | 94,228 | 0.9% | 101,542 | 0.9% |
| All others | 2,614,457 | 18.6% | 1,911,850 | 17.4% | 1,945,656 | 17.5% |

Source: Verispan Vector One®: National, Data Extracted 1-2008. File: VONA 2006-837 Celebrex BPCA Celebrex MD 1-17-08.qry

*GP/FM/DO – General Practice, Family Medicine, Doctors of Osteopathy

Table 6. Diagnoses associated with the use* of celecoxib by patient age (0-18, 19+) as reported by office-based physician practices, September 1, 2004 - August 30, 2007

| | SEP 2004 – AUG 2005 | | SEP 2005 – AUG 2006 | | SEP 2006 – AUG 2007 | |
|------------------------------|------------------------|---------------|------------------------|---------------|------------------------|---------------|
| | Baseline | | Pre-Exclusivity | | Post-Exclusivity | |
| | Uses N | Share % | Uses N | Share % | Uses N | Share % |
| TOTAL MARKET | 11,980,954 | 100.0% | 11,072,834 | 100.0% | 10,720,640 | 100.0% |
| 0-18 | 216,090 | 1.8% | 199,194 | 1.8% | 164,807 | 1.5% |
| 845 SPRAIN OF ANKLE & FOOT | 49,132 | 22.7% | 56,758 | 28.5% | 34,281 | 20.8% |
| 732 OSTEOCHONDROPATHIES | 21,314 | 9.9% | 38,812 | 19.5% | 26,419 | 16.0% |
| 844 SPRAIN OF KNEE & LEG | 33,980 | 15.7% | 15,397 | 7.7% | 20,027 | 12.2% |
| 716 ARTHROPATHIES NEC/NOS | 14,910 | 6.9% | 3,204 | 1.6% | 16,091 | 9.8% |
| 840 SPRAIN SHOULDER & ARM | -- | -- | -- | -- | 14,964 | 9.1% |
| 719 JOINT DISORDER NEC & NOS | 6,594 | 3.1% | 14,502 | 7.3% | 14,389 | 8.7% |
| 726 PERIPH ENTHESOPATHIES | 8,360 | 3.9% | 21,744 | 10.9% | 12,827 | 7.8% |
| 717 INTERNAL DERANGEMNT KNEE | -- | -- | 7,632 | 3.8% | 7,821 | 4.7% |
| 847 SPRAIN OF BACK NEC/NOS | -- | -- | -- | -- | 7,094 | 4.3% |
| 714 OTH INFLAMM POLYARTHROP | 5,670 | 2.6% | -- | -- | 6,764 | 4.1% |
| 825 FX OF TARSAL/METATARSAL | -- | -- | -- | -- | 4,129 | 2.5% |
| All Others | 76,130 | 35.2% | 41,147 | 20.7% | -- | -- |
| 19+ | 11,441,280 | 95.5% | 10,392,642 | 93.9% | 10,220,960 | 95.3% |
| 715 OSTEOARTHRISIS ET AL | 2,784,759 | 24.3% | 2,300,164 | 22.1% | 2,482,873 | 24.3% |
| 724 BACK DISORDER NEC & NOS | 1,136,906 | 9.9% | 1,255,535 | 12.1% | 1,185,594 | 11.6% |
| 726 PERIPH ENTHESOPATHIES | 863,513 | 7.5% | 765,213 | 7.4% | 831,351 | 8.1% |
| 716 ARTHROPATHIES NEC/NOS | 1,013,334 | 8.9% | 782,098 | 7.5% | 782,856 | 7.7% |
| 719 JOINT DISORDER NEC & NOS | 802,462 | 7.0% | 695,296 | 6.7% | 470,528 | 4.6% |
| 722 INTERVERTEBRAL DISC DIS | 165,451 | 1.4% | 177,497 | 1.7% | 356,304 | 3.5% |
| 847 SPRAIN OF BACK NEC/NOS | 320,640 | 2.8% | 211,447 | 2.0% | 320,701 | 3.1% |
| 728 DIS OF MUSCLE/LIG/FASCIA | 322,882 | 2.8% | 322,996 | 3.1% | 295,520 | 2.9% |
| 729 OTHER SOFT TISSUE DIS | 266,780 | 2.3% | 285,192 | 2.7% | 291,142 | 2.8% |
| 836 DISLOCATION OF KNEE | 127,308 | 1.1% | 256,764 | 2.5% | 273,801 | 2.7% |
| 727 OTH DIS SYNOV/TEND/BURSA | 225,219 | 2.0% | 321,280 | 3.1% | 262,593 | 2.6% |
| 714 OTH INFLAMM POLYARTHROP | 376,266 | 3.3% | 384,084 | 3.7% | 239,615 | 2.3% |
| 844 SPRAIN OF KNEE & LEG | 149,959 | 1.3% | 215,643 | 2.1% | 231,139 | 2.3% |
| 723 OTHER CERVICAL SPINE DIS | 191,988 | 1.7% | 228,790 | 2.2% | 221,286 | 2.2% |
| 840 SPRAIN SHOULDER & ARM | 200,248 | 1.8% | 193,804 | 1.9% | 187,901 | 1.8% |
| 845 SPRAIN OF ANKLE & FOOT | 122,501 | 1.1% | 218,194 | 2.1% | 137,657 | 1.3% |
| All Others | 2,371,063 | 20.7% | 1,778,645 | 17.1% | 1,650,100 | 16.1% |
| UNSPEC. | 323,584 | 2.7% | 480,997 | 4.3% | 334,873 | 3.1% |

Source: Verispan Physician Drug and Diagnosis Audit, Extracted 1-2008. File: PDDA 2006-837 Celebrex Ag 0-18, 19+ Dx3 1-30-08.qry
 * Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

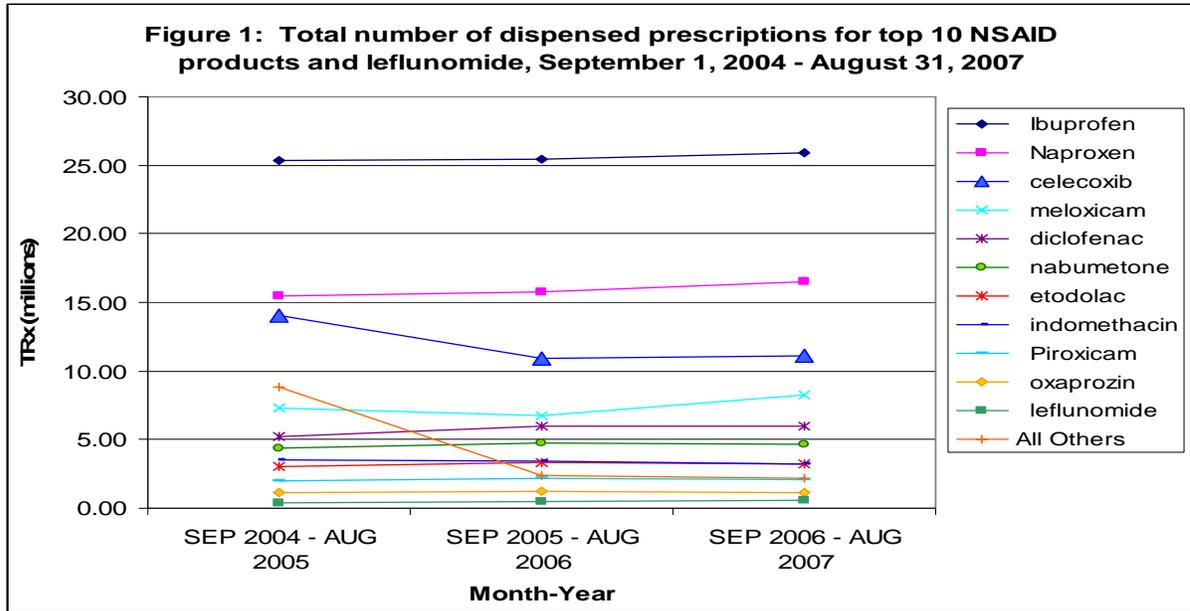
Table 7. Estimated number of therapy days* for celecoxib by patient age (0-18, 19+) as reported by office-based physician practices in the U.S., September 1, 2004 - August 30, 2007

| | SEP 2004 - AUG 2005 | | SEP 2005 - AUG 2006 | | SEP 2006 - AUG 2007 | |
|--------------------|--------------------------|---------------|--------------------------|---------------|--------------------------|---------------|
| | Baseline | | Pre-Exclusivity | | Post-Exclusivity | |
| | Occurrences [†] | Share | Occurrences [†] | Share | Occurrences [†] | Share |
| | N | % | N | % | N | % |
| celecoxib | 11,225,868 | 100.0% | 10,364,539 | 100.0% | 9,990,168 | 100.0% |
| age 0-18 | 216,090 | 1.9% | 199,194 | 1.9% | 164,807 | 1.6% |
| 8-15 days | 59,692 | 27.6% | 18,275 | 9.2% | 12,827 | 7.8% |
| 16-30 days | 33,034 | 15.3% | 72,119 | 36.2% | 109,532 | 66.5% |
| 31-45 days | -- | -- | 7,604 | 3.8% | 16,132 | 9.8% |
| 46-60 days | 12,137 | 5.6% | 15,540 | 7.8% | -- | -- |
| 61-75 days | 6,784 | 3.1% | 12,827 | 6.4% | -- | -- |
| 76-90 days | 18,313 | 8.5% | 25,252 | 12.7% | 4,129 | 2.5% |
| 91+ days | 36,662 | 17.0% | 10,808 | 5.4% | 3,446 | 2.1% |
| Unspec days | 49,469 | 22.9% | 36,770 | 18.5% | 18,741 | 11.4% |
| age 19+ | 10,691,890 | 95.2% | 9,704,629 | 93.6% | 9,522,643 | 95.3% |
| 0-7 days | 236,671 | 2.2% | 254,632 | 2.6% | 257,395 | 2.7% |
| 8-15 days | 684,366 | 6.4% | 652,444 | 6.7% | 595,550 | 6.3% |
| 16-30 days | 1,629,045 | 15.2% | 1,498,512 | 15.4% | 1,864,607 | 19.6% |
| 31-45 days | 177,058 | 1.7% | 141,229 | 1.5% | 119,515 | 1.3% |
| 46-60 days | 1,018,092 | 9.5% | 982,634 | 10.1% | 1,117,851 | 11.7% |
| 61-75 days | 20,039 | 0.2% | 33,385 | 0.3% | 34,541 | 0.4% |
| 76-90 days | 915,680 | 8.6% | 957,015 | 9.9% | 842,991 | 8.9% |
| 91+ days | 2,100,700 | 19.6% | 1,697,824 | 17.5% | 1,434,027 | 15.1% |
| Unspec days | 3,910,239 | 36.6% | 3,486,953 | 35.9% | 3,256,165 | 34.2% |
| age UNSPEC. | 317,888 | 2.8% | 460,716 | 4.4% | 302,719 | 3.0% |

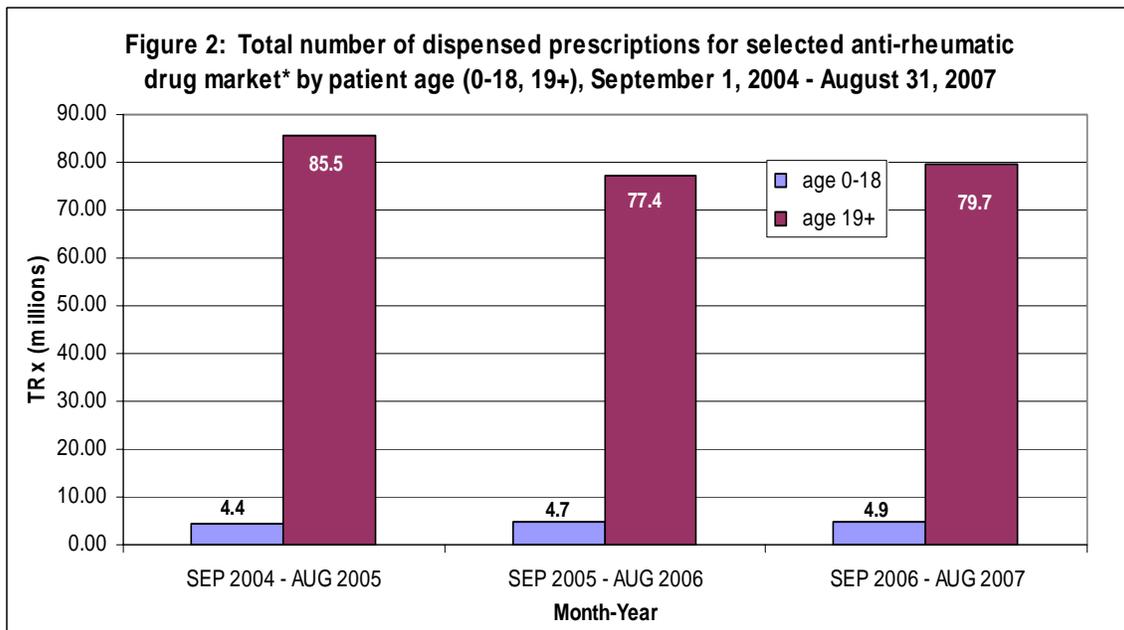
Source: Verispan Physician Drug and Diagnosis Audit, Extracted 1-2008. File: PDDA 2006-837 Celebrex AgeDuration 1-30-08.qry

*Occurrences - The projected number of times a product is mentioned during a patient-physician encounter regardless of diagnosis.

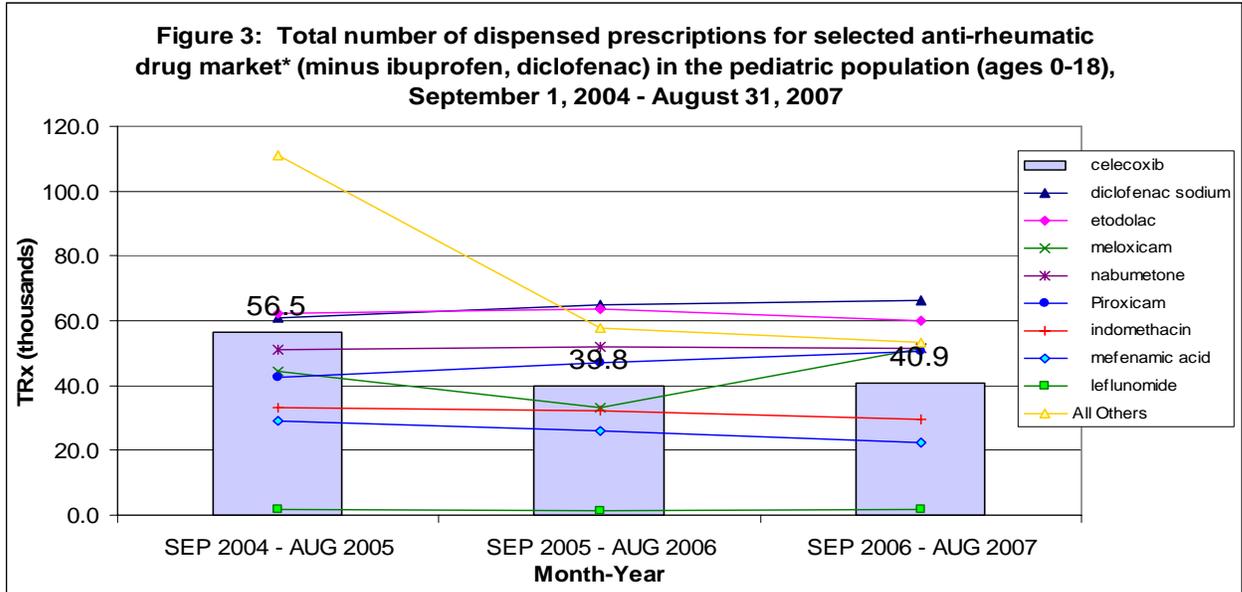
[†]Therapy Days - The number of prescribed days of therapy given to a patient calculated based on the extended units (which includes both Quantity and Refills) divided by Signa (dosing amount and frequency).



Source: Verispan Vector One®: National, Data Extracted 1-2008.
 File: VONA 2006-837 Celebrex BPCA NSAIDs Arava TRx 1-17-08.qry



Source: Verispan, Vector One®: National, Data Extracted 1-2008.
 File: VONA 2006-837 Celebrex BPCA NSAIDs Arava AgTRx 1-17-08.qry
 * Anti-rheumatic market - selected NSAID's and leflunomide, an immunomodulatory agent



Source: Verispan, Vector One®: National, Data Extracted 1-2008.

File: VONA 2006-837 Celebrex BPCA NSAIDs Arava AgTRx 1-17-08.qry

* Anti-rheumatic market - selected NSAID's and leflunomide, an immunomodulatory agent

APPENDIX II: Database Descriptions

Verispan, LLC: Vector One[®]: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One[®] database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One[®] receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One[®] has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One[®]: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One[®] database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One[®] receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

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/s/

Laura Governale
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DRUG SAFETY OFFICE REVIEWER

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MEDICAL OFFICER