

**Memorandum**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

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**THROUGH:** Gerald Dal Pan, MD, MHS. Director  
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**TO:** Solomon Iyasu, MD, MPH  
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Office of Counter-Terrorism and Pediatric Development

**SUBJECT:** One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data  
Leflunomide (Arava<sup>®</sup>) Tablets: NDA 20-905/SE5-012

**\*\*This document contains proprietary data from IMS Health and Caremark which cannot be shared outside of FDA without clearance from IMS Health and Caremark obtained through the Office of Drug Safety.\*\***

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**EXECUTIVE SUMMARY**

This consult examines drug utilization trends for leflunomide tablets (Arava<sup>®</sup>) in the pediatric population (ages 0-16 years). Sales data were examined for the four-year period from December 1, 2000 – November 30, 2004, with a primary focus on sales patterns 12 months before and 12 months following the granting of Pediatric Exclusivity for Arava<sup>®</sup> on November 10, 2003. Outpatient drug utilization patterns were examined for the 3-year period from December 2001 - November 2004, with a primary focus on utilization patterns during the year before and after the granting of pediatric exclusivity. Because over 94% of Arava<sup>®</sup> sales are into the retail channels, inpatient drug utilization patterns were not addressed.

Total sales of Arava<sup>®</sup> decreased by 13% over the 4 years of this analysis from almost 25 million tablets sold during December 2000 – November 2001 to approximately 21 million tablets sold during December 2003 – November 2004. Outpatient prescriptions of Arava<sup>®</sup> decreased almost 16% during December 2001 – November 2004, dropping from 632,000 prescriptions dispensed

in the 12-month period from December 2001 – November 2002 to 533,000 prescriptions in the 12-month period from December 2003 – November 2004.

The top two prescriber specialties for Arava<sup>®</sup> from October 2003 through November 2004 were rheumatology and internal medicine. Of all specialties, pediatricians were ranked 12<sup>th</sup> in prescribing Arava<sup>®</sup> during this period and accounted for less than 1% of the prescriptions dispensed in each of the 3 one-year periods of this analysis. In general, prescribing patterns for Arava<sup>®</sup> dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month period.

Among a large, insured population whose outpatient pharmacy benefits are managed by Caremark, pediatric participants aged 1-16 years accounted for no more than 0.2% of the claims for Arava<sup>®</sup> in each of the 3 one-year periods from December 2001 - November 2004. Due to the low use of Arava<sup>®</sup> in patients age 1-16 years, we were unable to obtain a reliable national estimate of the number of prescriptions claims for children.

The most common diagnosis associated with a mention of Arava<sup>®</sup> in office based physician-patient encounters was rheumatoid arthritis (ICD-9 714.0) which accounted for 90% of mentions during the pre-exclusivity period (December 2002 - November 2003) as well as 90% during the post-exclusivity period (December 2003 - November 2004). The diagnosis associated with the pediatric population was also rheumatoid arthritis (ICD-9 714.0) which accounted for 0.4% of all mentions during the post-exclusivity period (December 2003 - November 2004). It was the only diagnosis associated with the mention of Arava<sup>®</sup> among pediatric patients.

In conclusion, the use of this product in pediatric patients represents a very small proportion of Arava<sup>®</sup> use and does not appear to have significantly changed over the three-year period examined.

## **INTRODUCTION**

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the reporting of adverse events associated with the use of a drug in children during the one-year period following the date on which the drug received pediatric marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Arava<sup>®</sup> (NDA 20-905) is an oral isoxazole immunomodulatory agent. The product is available in tablet form containing 10mg, 20mg or 100mg of leflunomide. Arava<sup>®</sup> was approved on September 10, 1998 for the treatment of active rheumatoid arthritis to reduce signs and symptoms and to retard structural damage as evidenced by x-ray erosions and joint space narrowing. According to the approved labeling of November 2004, the recommended starting dose for initial therapy in adults is one 100mg tablet once daily for three days, followed by daily maintenance therapy dosing of one 20mg tablet once daily. The Pediatric Exclusivity Board of

the FDA granted pediatric exclusivity for Arava<sup>®</sup> (NDA 20-905/SE5-012) on November 10, 2003.

Juvenile rheumatoid arthritis (JRA) is a chronic condition causing joint inflammation for at least six weeks in a child 16 years of age or younger. It is the most common rheumatic condition in children, with an overall prevalence estimated at between 30 and 150 per 100,000 children<sup>1</sup>. JRA is treated with a combination of medication, physical therapy, and exercise, with the aim to relieve pain and inflammation, prevent or retard the destruction of joints, and restore the use and function of affected joints. Although Arava<sup>®</sup> does not have a pediatric indication, it is currently being utilized by children.

This review describes outpatient drug usage of Arava<sup>®</sup> in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

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## **DATA SOURCES**

This review describes the annual sales and drug use patterns of Arava<sup>®</sup> in the pediatric population as compared to the adult population in several years before and one year after the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The data sources for this analysis are described in detail below.

### ***IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS<sup>™</sup> (NPA PLUS<sup>™</sup>)***

NPA Plus<sup>™</sup> measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis included all prescriptions dispensed from December 1, 2001 – November 30, 2004 inclusive.

### ***IMS HEALTH, NATIONAL SALES PERSPECTIVES<sup>™</sup>***

IMS Health National Sales Perspectives<sup>™</sup> measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars, vials, and market share. 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

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<sup>1</sup> Ilowite NT: Current treatment of juvenile rheumatoid arthritis. *Pediatrics* 2002;109(1):109-15.

market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. These data are based on national projections.

For this analysis, the sales trend for Arava<sup>®</sup> was examined from December 1, 2000 – November 30, 2004 inclusive (the most current data available at the time of this analysis).

### ***CAREMARK™***

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 70 million lives, and processing over 545 million prescription claims annually. FDA has access to Caremark's Dimension Rx™ database consisting of a subset of total Caremark paid claims representing 350 million claims per year for prescriptions filled in 57,000 pharmacies across the country. Participants whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark's Dimension Rx™ system represents participants from all 50 states and includes special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in Caremark's Dimension Rx™ system to all persons receiving dispensed prescriptions in the U.S., however, is not known.

For this analysis, prescription claims in the Caremark system were examined from December 1, 2001 – November 30, 2004 inclusive.

### ***IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)***

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practices in the continental U.S. The data are collected from a panel of approximately 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned, and treatment patterns. These data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnoses 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.

For this analysis, we examined annual mentions of Arava<sup>®</sup> during office-based physician visits during the time period from December 1, 2001 – November 30, 2004 inclusive.

## RESULTS

### I. Sales and Distribution Channels

Sales of Arava<sup>®</sup> were examined from December 2000 through November 2004 (Table 1). Retail channels are the largest purchasers of Arava<sup>®</sup>, representing 94% of the total sales of Arava<sup>®</sup> in each of the four one-year periods of this analysis. Total sales of Arava<sup>®</sup> decreased by 13% over the 4 years of this analysis from almost 25 million tablets sold during December 2000 – November 2001 to approximately 21 million tablets sold during December 2003 – November 2004; during the 4-year period, peak sales of over 25 million tablets occurred during December 2001- November 2002. Compared to the pre-exclusivity period (December 2002 – November 2003), sales in the post-exclusivity period (December 2003 – November 2004) declined by almost 7% from 23 million tablets to 21 million tablets sold.

**Table 1. Total Number of Tablets (in thousands) of Arava<sup>®</sup> Sold to U.S. Distribution Channels During December 2000 - November 2004**

	December 2000 - November 2001		December 2001 - November 2002		December 2002 - November 2003		December 2003 - November 2004		Percent Change December 2000 - November 2004
	N (000)	(%)	%						
<b>Arava<sup>®</sup></b>	24,727	(100)	25,167	(100)	23,028	(100)	21,463	(100)	-13
<b>Retail*</b>	23,193	(94)	23,653	(94)	21,709	(94)	20,193	(94)	-13
<b>Non-Retail**</b>	1,533	(6)	1,514	(6)	1,319	(6)	1,269	(6)	-17

\* Retail includes chain, independent, mail order, long term care and food store pharmacies

\*\*Non-retail includes Non-federal hospitals, federal facilities, clinics, HMOs, home health care, prisons, universities, and other

IMS Health, National Sales Perspectives<sup>TM</sup> Combined, Data Extracted 01-2005  
(File:BPCA NSPC Arava<sup>®</sup> 01-05 Sales Channels 0501arsp.xls)

### II. Dispensed Prescriptions

Outpatient prescriptions for Arava<sup>®</sup> decreased almost 16% during December 2001 – November 2004, dropping from 632,000 prescriptions dispensed in the 12-month period from December 2001 – November 2002 to 533,000 prescriptions in the 12-month period from December 2003 – November 2004 (Table 2). The proportion of usage for each strength of Arava<sup>®</sup> remained consistent throughout the three year period.

**Table 2: Total Number of Prescriptions Dispensed (in thousands) in Retail Pharmacies Nationwide for Disease-Modifying Antirheumatic Drugs (DMARD) during December 2001 – November 2004**

	December 2001 - November 2002		December 2002 - November 2003		December 2003 - November 2004	
	N (000)	(%)	N (000)	(%)	N (000)	(%)
<b>Arava®</b>	632	(100)	572	(100)	533	(100)
20mg	537	(85)	482	(84)	450	(84)
10mg	93	(15)	90	(16)	83	(16)
100mg	2	(<1)	00	(0)	00	(0)

IMS Health, NPA Plus™ data extracted 11-2004 (File: BPCA NPA 01-14-05 USC Arava® 0501arus.xls)

The top two prescriber specialties prescribing Arava® from December 2003 through November 2004 were rheumatology and internal medicine (Table 3). Of all specialties, pediatricians were ranked 12<sup>th</sup> in prescribing Arava® during this period and accounted for less than 1% of the prescriptions dispensed in each of the 3 one-year periods of this analysis. In general, prescribing patterns for Arava® dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period.

**Table 3: Total Number of Prescriptions Dispensed (in thousands) for Arava® Nationwide by Physician Specialty (excludes Mail Order and Long Term Care) During December 2001 – November 2004**

Prescriber specialty	December 2001 - November 2002		December 2002 - November 2003		December 2003 - November 2004	
	N (000)	(%)	N (000)	(%)	N (000)	(%)
<b>All prescribers</b>	547	(100)	487	(100)	446	(100)
<b>Rheumatology</b>	377	(69)	331	(68)	301	(67)
<b>Internal Medicine</b>	77	(14)	70	(14)	66	(15)
<b>Osteopathic Medicine</b>	25	(5)	22	(4)	20	(4)
<b>Family Practice</b>	18	(3)	18	(4)	16	(4)
<b>Other Specialties (65)</b>	50	(9)	46	(9)	43	(10)

IMS Health NPA Plus™ Data extracted 1-14-2005 (file: BPCA NPA 01-14-05 MDSpec Arava® 0501arph.xls)

### III. Patient Demographics

Among a large, insured population whose outpatient pharmacy benefits are managed by Caremark, pediatric participants aged 1-16 years accounted for no more than 0.2% of the claims for Arava® in each of the 3 one-year periods from December 2001 – November 2004 (Table 4). Due to the low use of Arava® in patients aged 1-16 years, we were unable to obtain a reliable national estimate of the number of prescriptions dispensed to children.

**Table 4: Total Number of Paid Prescription Claims for Arava® From Caremark Pharmacy Benefit Manager Database.**

	Dec 2001-Nov 2002		Dec 2002-Nov 2003		Dec 2003-Nov 2004	
	N	(%)	N	(%)	N	(%)
<b>All Arava® (Total)</b>	92,752	(100)	82,608	(100)	74,574	(100)
<b>Peds (1-16 yrs)</b>	189	(0.2%)	154	(0.2%)	105	(0.1%)
<b>Adults (17+ yrs)</b>	92,563	(99.8%)	82,454	(99.8%)	74,469	(99.9%)

Caremark Dimension Rx: Extracted January 24, 2005.

The most common diagnosis associated with a mention of Arava® in office based physician-patient encounters was rheumatoid arthritis (ICD-9 714.0) which accounted for 90% of mentions during the 2 years surrounding the exclusivity date (Table 5). The same diagnosis is associated with all Arava® mentions for patients under age 17.

**Table 5. Top Diagnoses Associated with Projected Mentions of Arava® (absolute) for Pediatric and Adult Patients during December 2001 - November 2004**

ICD-9 Code	December 2001 - November 2002		December 2002 - November 2003		December 2003 - November 2004	
	N	(%)	N	(%)	N	(%)
<b>Arava® Total Uses</b>	307,834	(100.0)	310,774	(100.0)	224,558	(100.0)
<b>Patient age 17+ Years</b>	307,834	(100.0)	310,774	(100.0)	223,627	(99.60)
<b>714.0 Rheumatoid Arthritis</b>	277,351	(90.1)	278,548	(89.6)	200,834	(89.4)
<b>696.0 Psoriatic Arthropathy</b>	12,466	(4.0)	5,732	(1.8)	10,275	(4.6)
<b>V67.0 Post-Op Surgical Exam</b>	705	(0.2)	---	---	2,520	(1.1)
<b>714.9 Unspecified Inflammatory Arthropathy</b>	1,831	(0.6)	4,718	(1.5)	1,984	(0.9)
<b>Other Diagnoses (22)</b>	15,481	(5.0)	21,776	(7.0)	8,014	(3.6)
<b>Patient age 1-16 Years</b>	---	---	---	---	931	(0.4)
<b>714.0 Rheumatoid Arthritis</b>	---	---	---	---	931	(0.4)

IMS National Disease and Therapeutic Index™, December 2001 - November 2004. CD ROM NDTI 3 Year 12/01 – 11/04. Data extracted 1-24-2005 (File BPCA NDTI 1-24-2005 Arava 0501aravaicd9.dvf)

Among medications mentioned with the diagnosis of Rheumatoid Arthritis, Arava® is ranked 8<sup>th</sup> (Table 6). Arava® mentions decreased from 4.8% for the 12-month period of December 2002 – November 2003 to 3.4% for the 12-month period of December 2003-November 2004. It is also noted that during the same time period, mentions for Enbrel® increased from 3.9% to 5.1%. The most common medication mentioned with Rheumatoid Arthritis during the entire study period is Methotrexate.

**Table 6. Top Products with Projected Mentions (thousands) Associated with Rheumatoid Arthritis (ICD-9 714.0) for Pediatric and Adult Patients during December 2001 - November 2004**

Product	December 2001 - November 2002		December 2002 - November 2003		December 2003 - November 2004	
	N (000)	(%)	N (000)	(%)	N (000)	(%)
<b>Rheumatoid Arthritis (ICD-9 714.0) Total Mentions</b>	<b>6,368</b>	<b>(100.0)</b>	<b>6,088</b>	<b>(100.0)</b>	<b>6,197</b>	<b>(100.0)</b>
Methotrexate	1,389	(21.8)	1,409	(23.1)	1,394	(22.5)
Prednisone	927	(14.6)	812	(13.3)	752	(12.1)
Folic Acid	407	(6.4)	391	(6.4)	420	(6.5)
Plaquenil®	408	(6.4)	377	(6.2)	405	(6.5)
Celebrex®	476	(7.5)	442	(7.3)	389	(6.2)
Enbrel®	206	(5.0)	238	(3.9)	322	(5.1)
Remicade®	213	(3.2)	198	(3.3)	226	(3.6)
Arava®	286	(4.5)	291	(4.8)	213	(3.4)
Bextra®	90	(1.4)	164	(2.7)	194	(3.1)
Vioxx®	293	(4.6)	227	(3.7)	185	(3.0)
Humira®	---	---	68	(1.1)	173	(2.8)
Sulfasalazine®	81	(1.3)	74	(1.2)	72	(1.2)
<b>Other Products (268)</b>	<b>1,594</b>	<b>(25.0)</b>	<b>1,396</b>	<b>(22.9)</b>	<b>1,452</b>	<b>(23.4)</b>

IMS National Disease and Therapeutic Index™, December 2001 - November 2004. CD ROM NDTI 3 Year 12/01 – 11/04. Data extracted 2-08-2005 (File 0502aravdiagprod.dvf)

## DISCUSSION

Based on the databases used for this consult, the sales of Arava® to retail and non-retail channels combined decreased by 13% over the 4 years from December 2000 through November 2004. Dispensed prescriptions for Arava® decreased almost 16% from December 2001 through November 2004. Pediatric patients accounted for less than 1% of patient claims for Arava® in the Caremark insured patient population.

The two major prescriber specialties for Arava® were rheumatology and internal medicine. Pediatricians accounted for less than 1% of the prescriptions dispensed during the study period. In general, prescribing patterns for Arava® dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period. The use of this product appears to be almost exclusively in the adult population. Arava® represents an average of 4.2% of all medications mentioned with the diagnosis Rheumatoid Arthritis.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. However, NPA Plus™ does not include complete historical demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include mail order and long-term care channels.

NDTI™ 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 when use is not prevalent in the pediatric population, as in the case of Arava®.

Caremark data cannot be projected to provide national estimates, but its large sample size can be helpful for replicating demographic findings in IMS Health's NDTI™, where sample sizes are often small. Although the data from Caremark may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. Estimates of the number of prescriptions dispensed nationally to pediatric populations were not possible based on the small proportion of children receiving prescriptions in the Caremark database. In addition, reliable information for patients less than the age of 1 year is not available from this data source.

## CONCLUSION

Sales of Arava® to retail and non-retail channels combined decreased by 13% over the 4 years from December 2000 through November 2004. Dispensed prescriptions of Arava® decreased almost 16% from December 2001 through November 2004.

The two major prescriber specialties for Arava® were rheumatology and internal medicine. Pediatricians accounted for less than 1% of the prescriptions dispensed during the study period. The use of this product appears to be almost exclusively in the adult population.

Among a large, insured patient population whose outpatient pharmacy benefits are managed by Caremark, pediatric participants aged 1-16 years accounted for no more than 0.2% of the claims for Arava® in each of the 3 one-year periods from December 2001 – November 2004. Due to the low use of Arava® in patients age 1-16 years, we were unable to obtain a reliable national estimate of the number of prescriptions dispensed to children.

The most common diagnosis associated with a mention of Arava® in office based physician-patient encounters was rheumatoid arthritis (ICD-9 714.0) which accounted for 90% of mentions during the pre-exclusivity period (December 2002 - November 2003) and during the post-exclusivity period (December 2003 - November 2004). It was the only diagnosis associated with the mention of Arava® among pediatric patients.

The most common medication associated with a mention of Rheumatoid Arthritis (ICD-9 714.0) is Methotrexate. Arava® is ranked 8<sup>th</sup> among all mentions, accounting for 4.8% of mentions during the pre-exclusivity period (December 2002 - November 2003) and 3.4% during the post-exclusivity period (December 2003 - November 2004).

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