

**Memorandum**

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

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**TO:** Solomon Iyasu, M.D., M.P.H.  
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**SUBJECT:** One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data  
Ortho Tri-Cyclen<sup>®</sup> tablets (NDA 19-697), Ortho Tri-Cyclen<sup>®</sup> Lo tablets (NDA 21-241)

**\*\*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 Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup> Lo in the pediatric population (ages 1-16 years), with a primary focus on patterns of use one-year before and one-year following the granting of Pediatric Exclusivity on December 18, 2003. Proprietary drug use databases licensed by the Agency were used to determine the various retail and non-retail channels of distribution. Since the majority of use for this product occurs in the outpatient setting, we focused our review of utilization patterns for Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup> Lo on the outpatient setting. Outpatient use was measured by two IMS Health Audits, the National Prescription Audit *Plus*<sup>™</sup> (NPA *Plus*<sup>™</sup>) and the National Disease and Therapeutic Index<sup>™</sup> (NDTI<sup>™</sup>), along with prescription claims for a 36-month period of time from Caremark (Dimension RX<sup>™</sup>).

Several categories of contraceptive products were examined to obtain a comprehensive overview of trends in the contraceptive market, including generic products of Ortho Tri-Cyclen<sup>®</sup>.

Sales data were examined for the three-year period from January 1, 2002 - December 31, 2004 with a primary focus on sales patterns 12 months before and 12 months following the granting of Pediatric Exclusivity for Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup> Lo on December 18, 2003. Outpatient drug utilization patterns were examined for the same period.

Outpatient prescriptions of the selected contraceptive market increased 8%, from over 92 million prescriptions dispensed in 2002 to over 99 million prescriptions dispensed in 2004. Ortho Tri-Cyclen<sup>®</sup> dropped from being the most commonly dispensed contraceptive product in the selected contraceptive market with 23% of dispensed prescriptions in 2002 to being third in 2004, accounting for 6% of dispensed prescriptions in this market. The combined number of prescriptions dispensed for Ortho Tri-Cyclen<sup>®</sup> brand and generic products totaled over 10.1 million prescriptions from January-December 2004. This accounted for approximately 10% of the market share for the selected contraceptive market during the same time period. There was a 47% decline in dispensed prescriptions for Ortho Tri-Cyclen<sup>®</sup> brand and generic products in the first year post-exclusivity (January 2004-December 2004) compared to the prior year (January 2003- December 2003). In addition, there was a 9.6% decline in dispensed prescriptions in the one-year pre-exclusivity period (January 2003- December 2003) relative to the previous year (January 2002- December 2002). Dispensed prescriptions of Ortho Tri-Cyclen<sup>®</sup> alone decreased a total of 68% from 2002 to 2004.

Obstetrics/gynecology and family practice were the most frequent prescriber specialties of Ortho Tri-Cyclen<sup>®</sup> from 2002-2004. Of all specialties, pediatricians ranked 8<sup>th</sup> in prescribing Ortho Tri-Cyclen<sup>®</sup> during this period, accounting for less than 5% (or 303,000) dispensed prescriptions in each of the three years surveyed in this analysis. Prescribing patterns for Ortho Tri-Cyclen<sup>®</sup> Lo compared to Ortho Tri-Cyclen<sup>®</sup> were similar across provider specialties during the period surveyed.

Female pediatric participants aged 1-16 years in the Caremark System accounted for no more than 4.3% of the claims for Ortho Tri-Cyclen<sup>®</sup> and 6.6% of the claims for Ortho Tri-Cyclen<sup>®</sup> Lo from January 2002-December 2004. We estimate that approximately 171,000 prescriptions of Ortho Tri-Cyclen<sup>®</sup> and 348,000 prescriptions of Ortho Tri-Cyclen<sup>®</sup> Lo were dispensed for females aged 1-16 years in the U.S. during 2004 from retail pharmacies.

The most common diagnosis associated with a mention of Ortho Tri-Cyclen<sup>®</sup> in office based physician patient encounters was “general counseling/advice” (ICD-9 code V25.0), which accounted for an average 43-48% of mentions during the pre-exclusivity period (January 2002 - December 2003) and 50% during the post-exclusivity period (January - December 2004). Mentions for pediatric patients accounted for 6% of all mentions associated with Ortho Tri-Cyclen<sup>®</sup> in 2004, while mentions for pediatric patients accounted for 3% of all mentions associated with Ortho Tri-Cyclen<sup>®</sup> Lo.

In summary, with the recent introduction of several new products to the contraceptive market, Ortho Tri-Cyclen<sup>®</sup> usage has been decreasing over the past three years. Ortho Tri-Cyclen<sup>®</sup> Lo use has increased since being approved in 2002. Pediatric prescription claims account for 3% of Ortho Tri-Cyclen<sup>®</sup> prescriptions and 6% of Ortho Tri-Cyclen<sup>®</sup> Lo prescriptions. During 2004, the number of pediatric prescriptions for Ortho Tri-Cyclen<sup>®</sup> Lo was more than double the number of pediatric prescriptions for Ortho Tri-Cyclen<sup>®</sup>.

## 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.

Ortho Tri-Cyclen<sup>®</sup> 28 Tablets (NDA 19-697) and Ortho Tri-Cyclen<sup>®</sup> Lo Tablets (NDA 21-241) are oral contraceptives. Each product is available in a DIALPAK<sup>®</sup> Tablet Dispenser containing a total of 28 tablets in three different combinations of norgestimate and ethinyl estradiol<sup>1</sup>. Each DIALPAK<sup>®</sup> contains 7 each of white, light blue, and dark blue active tablets, and 7 green inactive tablets. The active ingredients for each product are shown in the table below.

<b>Active Ingredients for Ortho Tri-Cyclen<sup>®</sup> 28 (NDA 19-697) and Ortho Tri-Cyclen<sup>®</sup> Lo Tablets (NDA 21-241)</b>		
<b>Ortho Tri-Cyclen<sup>®</sup> 28 Tablets (NDA 19-697)</b>		
Tablet Color	Norgestimate	Ethinyl Estradiol
white	0.180 mg	0.035 mg
light blue	0.215 mg	0.035 mg
dark blue	0.250 mg	0.035 mg
green	-	-
<b>Ortho Tri-Cyclen<sup>®</sup> Lo Tablets (NDA 21-241)</b>		
Tablet Color	Norgestimate	Ethinyl Estradiol
white	0.180 mg	0.025 mg
light blue	0.215 mg	0.025 mg
blue	0.250 mg	0.025 mg
green	-	-

<sup>1</sup> PDR<sup>®</sup> Electronic Library<sup>™</sup>. Ortho Tri-Cyclen Tablets.

<sup>1</sup> PDR<sup>®</sup> Electronic Library<sup>™</sup>. Ortho Tri-Cyclen Tablets.

Ortho Tri-Cyclen<sup>®</sup> was approved on July 3, 1992, and Ortho Tri-Cyclen<sup>®</sup> Lo was approved on August 22, 2002, for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. The safety and efficacy of both Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup> Lo have been established in women of reproductive age. According to the labeling of both products, safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of both products before menarche is not indicated.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Ortho Tri-Cyclen<sup>®</sup> (NDA 19-697) and Ortho Tri-Cyclen<sup>®</sup> Lo (NDA 21-241) on December 18, 2003.

This review describes outpatient drug usage of Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup> Lo Tablets 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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## **METHODS**

Several categories of contraceptive products were used to define the market that was used to analyze Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup> Lo Tablets to obtain a comprehensive overview of trends in the contraceptive market. Selected contraceptives that included oral, parenteral, vaginal, and topical formulations were used in this analysis, as well as Ortho Tri-Cyclen<sup>®</sup> generics (Tri-Sprintec<sup>®</sup> and Tri-Previfem<sup>®</sup>). These products were included based on high usage data; 98% of the 140 products not included in this analysis each held less than 3% of the contraceptive market share.

IMS Health, IMS National Sales Perspectives<sup>™</sup> data were used to determine the setting in which the product was sold. Sales of Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup> Lo by number of tablets sold from the manufacturer to various retail and non-retail channels of distribution were analyzed (Table 1). Since these products are used largely in the outpatient setting, this examination focuses solely on outpatient utilization.

## **DATA SOURCES**

This review describes the annual sales and drug use patterns of Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup> Lo in the pediatric population as compared to the adult population two 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 and are described below in detail.

### ***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 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 covers all prescriptions dispensed from January 1, 2002 – December 31, 2004 inclusive.

***IMS HEALTH, IMS NATIONAL SALES PERSPECTIVES™***

IMS Health National Sales Perspectives™ 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 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 Ortho Tri-Cyclen® and Ortho Tri-Cyclen® Lo were examined from January 1, 2002 – December 31, 2004 inclusive.

***CAREMARK™***

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 75 million participant lives, and processing over 450 million prescription claims annually. FDA has access to Caremark's database of paid claims for prescriptions filled in approximately 55,000 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 data includes 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 to all persons receiving dispensed prescriptions in the U.S., however, is not known.

For this analysis, prescription claims for female participants in the Caremark system were examined from January 1, 2002 – December 31, 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 Ortho Tri-Cyclen® and Ortho Tri-Cyclen® Lo during office-based physician visits during the time period from January 1, 2002 – December 31, 2004 inclusive.

## RESULTS

### I. Sales and Distribution Channels

Sales of Ortho Tri-Cyclen® were examined from January 2002 through December 2004, and Ortho Tri-Cyclen® Lo from September 2002 through December 2004. Retail channels are the largest purchasers of both medications, representing at least 95% of the total sales in each of the three one-year periods of this analysis, with the exception of 2004 in which Ortho Tri-Cyclen® retail sales accounted for 85% of total sales (Table 1). This decline appeared to have been the result of decreasing overall and retail sales, rather than increasing non-retail sales. Total sales of Ortho Tri-Cyclen® decreased by 68% over the 3 years of this analysis from 716 million tablets sold in 2002 to 230 million tablets sold in 2004. Since Ortho Tri-Cyclen® Lo was approved in September 2002; total sales have increased from 11 million tablets sold in 2002 to over 204 million tablets sold in 2004.

**Table 1. Total Number of Tablets (in thousands) of Ortho Tri-Cyclen® and Ortho Tri-Cyclen® Lo Sold to U.S. Distribution Channels During January 2002 - December 2004**

	January - December 2002		January - December 2003		January - December 2004		Percent Change 2002-2004 %
	N (000)	(%)	N (000)	(%)	N (000)	(%)	
<b>Ortho Tri-Cyclen®</b>	<b>716,111</b>	<b>(100)</b>	<b>658,040</b>	<b>(100)</b>	<b>229,691</b>	<b>(100)</b>	<b>-68</b>
<b>Retail*</b>	683,106	(95)	622,976	(95)	195,376	(85)	-71
<b>Non-Retail**</b>	33,006	(5)	35,065	(5)	34,314	(15)	4
<b>Ortho Tri-Cyclen® Lo</b>	<b>11,281</b>	<b>(100)</b>	<b>91,578</b>	<b>(100)</b>	<b>204,097</b>	<b>(100)</b>	<b>1,709</b>
<b>Retail*</b>	11,070	(98)	89,434	(98)	198,232	(97)	1,691
<b>Non-Retail**</b>	211	(2)	2,144	(2)	5,865	(3)	2,680
<b>Ortho Tri-Cyclen® Generic Equiv. (Tri-Sprintec® &amp; Tri-Previfem®)</b>	---	---	<b>165</b>	<b>(100)</b>	<b>135,914</b>	<b>(100)</b>	<b>82,272</b>
<b>Retail*</b>	---	---	159	(96.4)	130,908	(96.3)	82,232
<b>Non-Retail**</b>	---	---	6	(3.6)	5,006	(3.7)	83,333

\* 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, IMS National Sales Perspectives™ Combined, January 2002 to December 2004, Data Extracted 03-2005 (Original files: NSPC 0503otsp.xls and 0503otge.xls)

The decrease in Ortho Tri-Cyclen<sup>®</sup> sales was likely due to the introduction of several products within the last few years, including Yasmin<sup>®</sup> in June 2001. In 2002, there were three new contraceptive products: Ortho-Evra<sup>®</sup> in March, NuvaRing<sup>®</sup> in June, and Ortho Tri-Cyclen<sup>®</sup> Lo in September. Two generic equivalents to Ortho Tri-Cyclen<sup>®</sup>, Tri-Sprintec<sup>®</sup> and Tri-Previfem<sup>®</sup>, were introduced to the market in December 2003 and April 2004, respectively. Since Ortho Tri-Cyclen<sup>®</sup> was granted pediatric exclusivity in December 2003 sales of these two generic equivalents have increased from a total of 165,000 tablets sold in 2003 to almost 136 million tablets sold in 2004.

## II. Dispensed Prescriptions

Outpatient prescriptions of the selected contraceptive market increased 8%, from over 92 million prescriptions dispensed in 2002 to over 99 million prescriptions dispensed in 2004. During the time period reviewed, dispensed prescriptions of the selected market peaked in 2003 with 99.7 million prescriptions (see Table 2). This was an 8% increase from 2002 in which 92.6 million outpatient prescriptions were dispensed.

In 2002 Ortho Tri-Cyclen<sup>®</sup> had the highest market share, accounting for 23% of the selected market. By 2004, Ortho Tri-Cyclen<sup>®</sup> dropped to the third most commonly dispensed contraceptive product in this market, accounting for only 6%. Including the generic products, they account for 10.2%. During the three-year period, Ortho Tri-Cyclen<sup>®</sup> was the product with the most significant decrease of dispensed prescriptions in the selected market, falling 71% from 2002 to 2004. Including the generic products, the decrease was 52% from 2002 to 2004. Ortho Tri-Cyclen<sup>®</sup> Lo entered the market in late 2002 and captured only 0.1% of the annual market share. By 2004 it rose to hold 6% of the market share, which represented an increase from 47,000 prescriptions to just over 6 million prescriptions.

There was a 47% decline in dispensed prescriptions for Ortho Tri-Cyclen<sup>®</sup> brand and generic products in the first year post-exclusivity (January 2004-December 2004) compared to the prior year (January 2003- December 2003). In addition, there was a 9.6% decline in dispensed prescriptions in the one-year pre-exclusivity period (January 2003- December 2003) relative to the previous year (January 2002- December 2002).

**Table 2: Total Number of Prescriptions Dispensed (in thousands) in Retail Pharmacies Nationwide for Selected Contraceptive Market for the period of January 2002 - December 2004**

	January - December 2002		January - December 2003		January - December 2004	
	N (000)	(%)	N (000)	(%)	N (000)	(%)
<b>Total Selected Contraceptive Market</b>	92,585	(100)	99,760	(100)	99,681	(100)
Ortho-Evra <sup>®</sup>	1,264	(1)	8,701	(9)	10,185	(10)
Yasmin <sup>®</sup>	3,213	(3)	6,109	(6)	8,422	(8)
<b>Ortho Tri-Cyclen<sup>®</sup></b>	<b>21,006</b>	<b>(23)</b>	<b>18,995</b>	<b>(19)</b>	<b>6,103</b>	<b>(6)</b>
<b>Ortho Tri-Cyclen Lo<sup>®</sup></b>	<b>47</b>	<b>(0.1)</b>	<b>2,618</b>	<b>(3)</b>	<b>6,001</b>	<b>(6)</b>
NuvaRing <sup>®</sup>	145	(0.2)	1,010	(1)	1,832	(2)
Depo-Provera <sup>®</sup>	1,743	(2)	1,848	(2)	1,821	(2)
Tri-Sprintec <sup>®1</sup>	----	----	----	----	3,844	(4)
Tri-Previfem <sup>®1</sup>	----	----	----	----	173	(0.2)
<b>Others (140)</b>	65,163	(70)	60,475	(60)	61,301	(62)

IMS Health, NPA Plus<sup>™</sup>, January 2002 to December 2004, data extracted 03-2005 (Original file: 0503cont.xls)

<sup>1</sup>Ortho Tri-Cyclen<sup>®</sup> generic products

Obstetrics/gynecology and family practice were the most frequent prescribers of Ortho Tri-Cyclen<sup>®</sup> from 2002-2004 (Table 3). In 2004, Obstetricians/Gynecologists were responsible for over 3.1 million (53%) dispensed prescriptions, followed by family practitioners with 917,000 (13%). Nurse Practitioners, Osteopathic Physicians, and Internists each accounted for 6% of dispensed prescriptions of Ortho Tri-Cyclen<sup>®</sup>. Together, these specialties accounted for 84% of the dispensed prescriptions for Ortho Tri-Cyclen<sup>®</sup> in 2004. Of all specialties, pediatricians ranked 8<sup>th</sup> in prescribing Ortho Tri-Cyclen<sup>®</sup>, accounting for no more than 5% (or 303,000) dispensed prescriptions in each of the three years surveyed in this analysis. Prescribing patterns for Ortho Tri-Cyclen<sup>®</sup> Lo compared to Ortho Tri-Cyclen<sup>®</sup> were similar across provider specialties during the period surveyed.

**Table 3: Total Number of Prescriptions Dispensed (in thousands) for Ortho Tri-Cyclen<sup>®</sup> Nationwide by Physician Specialty During January 2002 – December 2004\***

Prescriber specialty	January-December 2002		January-December 2003		January-December 2004	
	N (000)	(%)	N (000)	(%)	N (000)	(%)
<b>All prescribers</b>	20,200	(100)	18,148	(100)	5,827	(100)
<b>Obstetrics/Gynecology</b>	10,857	(54)	9,474	(52)	3,112	(53)
<b>Family Practice</b>	3,143	(16)	2,923	(15)	917	(13)
<b>Nurse Practitioner</b>	879	(4)	938	(5)	363	(6)
<b>Osteopathic Medicine</b>	1,276	(6)	1,175	(6)	361	(6)
<b>Internal Medicine</b>	1,216	(6)	1,113	(6)	360	(6)
<b>Pediatrics</b>	<b>93</b>	<b>(1)</b>	<b>302</b>	<b>(2)</b>	<b>303</b>	<b>(5)</b>
<b>Other Specialties (45)</b>	2,732	(14)	2,221	(12)	407	(7)

IMS Health NPA Plus<sup>™</sup>, January 2002 to December 2004, Data extracted 01-2005, (original file: 0501otmd.dvr)

\*excludes Mail Order and Long Term Care

### III. Patient Demographics

Among a large, insured population whose outpatient pharmacy benefits are managed by Caremark, female pediatric participants ages 1-16 years accounted for no more than 4.3% of the claims for Ortho Tri-Cyclen<sup>®</sup> and 6.6% of the claims for Ortho Tri-Cyclen<sup>®</sup> Lo from 2002 to 2004 (Table 4).

The total number of claims for Ortho Tri-Cyclen<sup>®</sup> decreased from 2.7 million claims in 2002 to just over 1.0 million in 2004. This decrease is consistent with dispensed prescription data from IMS Health. Pediatric claims for Ortho Tri-Cyclen<sup>®</sup> prescriptions decreased 76% from 2002 to 2004, and adult claims decreased 62% over the same time period. Prescription claims for Ortho Tri-Cyclen<sup>®</sup> Lo increased from 5,515 claims in 2002 to 866,903 claims in 2004, although the proportion of pediatric claims decreased slightly from 6.3% in 2002 to 5.8% in 2004.

**Table 4: Total Number (Absolute) of Paid Prescription Claims for Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen Lo<sup>®</sup> for Female Participants From Caremark Pharmacy Benefit Manager Database.**

	Jan-Dec 2002		Jan-Dec 2003		Jan-Dec 2004	
	N	(%)	N	(%)	N	(%)
<b>Ortho Tri-Cyclen<sup>®</sup> (Total)</b>	<b>2,668,641</b>	<b>(100)</b>	<b>2,604,968</b>	<b>(100)</b>	<b>1,006,835</b>	<b>(100)</b>
<b>Peds (1-16 yrs)</b>	115,586	(4.3%)	101,767	(3.9%)	28,224	(2.8%)
<b>Adults (17+ yrs)</b>	2,553,055	(95.7%)	2,503,201	(96.1%)	978,611	(97.2%)
<b>Ortho Tri-Cyclen Lo<sup>®</sup> (Total)</b>	<b>5,515</b>	<b>(100)</b>	<b>357,046</b>	<b>(100)</b>	<b>866,903</b>	<b>(100)</b>
<b>Peds (1-16 yrs)</b>	346	(6.3%)	23,723	(6.6%)	49,962	(5.8%)
<b>Adults (17+ yrs)</b>	5,169	(93.7%)	333,323	(93.4%)	816,941	(94.2%)

Caremark Dimension Rx: Extracted March 2, 2005 and March 11, 2005.

Since IMS Health, NPA *Plus*<sup>TM</sup> does not include demographic information on participants for the entire time period of interest, proportions were applied for demographic subgroups from Caremark's Dimension Rx<sup>TM</sup> to IMS Health, NPA *Plus*<sup>TM</sup> data to estimate the number of prescriptions dispensed nationwide to children for Ortho Tri-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup> Lo (Table 5). To use this method, it is assumed that all dispensed prescriptions for these two products captured in the IMS Health national estimate are for females, and that the age distribution is the same for the two databases. Using this approach, approximately 171,000 prescriptions of Ortho Tri-Cyclen<sup>®</sup> and 348,000 prescriptions of Ortho Tri-Cyclen<sup>®</sup> Lo are estimated to have been dispensed for females aged 1-16 years in the U.S. during 2004 from retail pharmacies.

**Table 5: Estimated Nationwide Prescriptions Dispensed for Female Pediatric Age Group (1-16) During 2004**

	Total Number of Prescriptions* Dispensed for All Age Groups (from Table 2)	% Pediatric Claims** (Age 1-16yrs) (from Table 4)	Estimated Number of Prescriptions Dispensed to Female Pediatric Population (Age 1-16 yrs)
<b>Ortho Tri-Cyclen®</b>	6,103,000	2.8%	<b>170,884</b>
<b>Ortho Tri-Cyclen® Lo</b>	6,001,000	5.8%	<b>348,058</b>

\*IMS Health, NPA Plus™, January to December 2004, Extracted 03-2005 (Original file: 0503cont.xls)  
\*\*Caremark Dimension Rx: Extracted March 2, 2005 and March 11, 2005.

**Table 6. Top Diagnoses Associated with Projected Mentions of Ortho Tri-Cyclen® and Ortho Tri-Cyclen® Lo (absolute) for Pediatric and Adult Patients During January 2002 - December 2004**

ICD-9 Code	January-December 2002		January-December 2003		January-December 2004	
	N	(%)	N	(%)	N	(%)
<b>Ortho Tri-Cyclen® Total Uses</b>	<b>1,123</b>	<b>(100.0)</b>	<b>838</b>	<b>(100.0)</b>	<b>476</b>	<b>(100.0)</b>
<b>Patient age 17+ Years</b>	<b>1,063</b>	<b>(94.7)</b>	<b>790</b>	<b>(94.3)</b>	<b>447</b>	<b>(93.9)</b>
V25.0 General Counseling/Advice	459	(43.2)	379	(48.0)	224	(50.1)
V72.3 Gynecological Examination	368	(34.6)	241	(30.5)	152	(34.0)
V24.2 Routine Post-Partum Examination	65	(6.1)	24	(3.0)	25	(5.6)
626.4 Irregular Menstrual Cycle	14	(1.3)	26	(3.3)	17	(3.8)
706.1 Acne Unspecified	16	(1.5)	12	(1.5)	7	(1.6)
Other Diagnoses (23)	141	(13.3)	108	(13.7)	21	(4.7)
<b>Patient age 1-16 Years</b>	<b>60</b>	<b>(5.3)</b>	<b>48</b>	<b>(5.7)</b>	<b>29</b>	<b>(6.1)</b>
626.8 Other Dysfun. or Funct. Uterine Hem. NOS	---	---	---	---	8	(27.6)
706.1 Acne Unspecified	7	(11.7)	11	(22.9)	6	(20.7)
V25.0 General Counseling/Advice	33	(55.0)	32	(66.7)	1	(3.4)
Other Diagnoses (7)	20	(33.3)	5	(10.4)	14	(48.3)
<b>Ortho Tri-Cyclen® Lo Total Uses</b>	<b>38</b>	<b>(100.0)</b>	<b>819</b>	<b>(100.0)</b>	<b>1,524</b>	<b>(100.0)</b>
<b>Patient age 17+ Years</b>	<b>38</b>	<b>(100.0)</b>	<b>785</b>	<b>(95.9)</b>	<b>1,475</b>	<b>(96.8)</b>
V25.0 General Counseling/Advice	10	(25.9)	357	(45.5)	772	(52.3)
V72.3 Gynecological Examination	18	(48.3)	174	(22.2)	519	(35.2)
625.3 Dysmenorrhea	5	(12.9)	30	(3.8)	56	(3.8)
V24.2 Routine Post-Partum Examination	---	---	97	(12.4)	34	(2.3)
626.4 Irregular Menstrual Cycle	---	---	39	(5.0)	24	(1.7)
Other Diagnoses (15)	5	(12.9)	87	(11.0)	70	(5.0)
<b>Patient age 1-16 Years</b>	<b>---</b>	<b>---</b>	<b>34</b>	<b>(4.1)</b>	<b>49</b>	<b>(3.2)</b>
625.3 Dysmenorrhea	---	---	5	(14.8)	16	(32.7)
V25.0 General Counseling/Advice	---	---	10	(29.6)	11	(23.2)
626.2 Excess or Freq Menstruation	---	---	7	(19.7)	8	(17.5)
Other Diagnoses (4)	---	---	12	(35.9)	12	(25.5)

IMS National Disease and Therapeutic Index™ CD-ROM, NDTI 6yr. January 1999-December 2004. Data extracted 02-11-2005 (File 0502orthicd9.xls) and 03-11-05 (File 0503otloicd9.xls)

The most common diagnosis associated with a mention of Ortho Tri-Cyclen<sup>®</sup> in office-based physician patient encounters was general counseling/advice (ICD-9 code V25.0), which accounted for an average 43-48% of mentions during the pre-exclusivity period (January 2002–December 2003) and 50% during the post-exclusivity period (January - December 2004) (Table 6). Mentions for pediatric patients accounted for 6% of all mentions associated with Ortho Tri-Cyclen<sup>®</sup> in 2004, while mentions for pediatric patients accounted for 3% of all mentions associated with Ortho Tri-Cyclen<sup>®</sup> Lo.

## **DISCUSSION**

Based on the databases used for this consult, sales of Ortho Tri-Cyclen<sup>®</sup> to retail and non-retail channels decreased by 68% over the 3 years from 2002 through 2004. The decline was likely due to a market shift to two generics equivalent to OrthoTri-Cyclen<sup>®</sup>, as well as the introduction of Yasmin<sup>®</sup>, Ortho-Evra<sup>®</sup>, NuvaRing<sup>®</sup>, and Ortho Tri-Cyclen<sup>®</sup> Lo.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. NPA Plus<sup>™</sup> data provide an estimate of the total number of prescriptions dispensed in the U.S. However, NPA Plus<sup>™</sup> 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. Prescriptions or samples of products dispensed in family planning clinics (e.g. Planned Parenthood) are not captured in the data sources currently available to the Agency. Since such clinics are known to treat adolescent populations, their absence may represent a substantial limitation of our analysis.

NDTI<sup>™</sup> 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 Ortho Tri-Cyclen<sup>®</sup>.

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<sup>™</sup>, 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 based on the proportion dispensed to pediatric participants in the Caremark system are dependent upon the assumption that these patterns are similar across populations with and without prescription drug coverage. The accuracy of this assumption is not known at this time. In addition, reliable information for participants less than the age of 1 year is not available from this data source.

## CONCLUSION

Outpatient prescriptions of the selected contraceptive market increased 8%, from over 92 million prescriptions dispensed in 2002 to over 99 million prescriptions dispensed in 2004. As of 2004, Ortho Tri-Cyclen<sup>®</sup> appears to be the third-most commonly dispensed contraceptive product in this analysis. The combined number of prescriptions dispensed for Ortho Tri-Cyclen<sup>®</sup> and generic products totaled over 10.1 million prescriptions and accounted for approximately 10% of the market share for the selected contraceptive market during January-December 2004. This represented a 47% decline in dispensed prescriptions for Ortho Tri-Cyclen<sup>®</sup> brand and generic products, compared to the prior year (January 2003- December 2003). In addition, there was a 9.6% decline in dispensed prescriptions in the one-year pre-exclusivity period (January 2003-December 2003) relative to the previous year (January 2002- December 2002).

The two major prescriber specialties for Ortho Tri-Cyclen<sup>®</sup> were obstetrics/gynecology and family practice. In 2004, Obstetricians/Gynecologists were responsible for over 3.1 million (53%) dispensed prescriptions, followed by family practitioners with 917,000 (13%). Pediatricians accounted for no more than 5% of the prescriptions dispensed during the study period. The use of this product appears to be almost exclusively in the adult population.

Pediatric participants aged 1-16 years in the Caremark System accounted for no more than 4.3% of the claims for Ortho Tri-Cyclen<sup>®</sup> and 6.6% of the claims for Ortho Tri-Cyclen<sup>®</sup> Lo from January 2002-December 2004. We estimate that approximately 171,000 prescriptions of Ortho Tri-Cyclen<sup>®</sup> and 348,000 prescriptions of Ortho Tri-Cyclen<sup>®</sup> Lo were dispensed for females aged 1-16 years in the U.S. during 2004 from retail pharmacies.

The most common diagnosis associated with a mention of Ortho Tri-Cyclen<sup>®</sup> in office based physician-patient encounters was “general counseling/advice”, which accounted for an average 43-48% of mentions during the pre-exclusivity period (January 2002 - December 2003) and 50% during the post-exclusivity period (January - December 2004). Mentions for pediatric patients accounted for 6% of all mentions associated with Ortho Tri-Cyclen<sup>®</sup> in 2004, while mentions for pediatric patients accounted for 3% of all mentions associated with Ortho Tri-Cyclen<sup>®</sup> Lo.

In summary, with the recent introduction of several products to the contraceptive market, Ortho Tri-Cyclen<sup>®</sup> usage has been decreasing over the past three years. Ortho Tri-Cyclen<sup>®</sup> Lo use has increased since being approved in 2002. Pediatric prescriptions claims account for 3% of Ortho Tri-Cyclen<sup>®</sup> prescriptions and 6% of Ortho Tri-Cyclen<sup>®</sup> Lo prescriptions. During 2004, the number of prescriptions for Ortho Tri-Cyclen<sup>®</sup> Lo was more than double the number of prescriptions for Ortho Tri-Cyclen<sup>®</sup> for the pediatric population.

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