

One Year Post-Exclusivity Adverse Event Review: Norgestimate/ethinyl estradiol

**Pediatric Advisory Committee Meeting
June 29, 2005**

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Background Drug Information

- **Drug:** Ortho Tri-Cyclen[®] and Ortho Tri-Cyclen Lo[®] (norgestimate/ethinyl estradiol)
- **Therapeutic Category:** oral contraceptive
- **Indication:** prevention of pregnancy (both products); treatment of moderate acne vulgaris in females ≥ 15 years of age who are unresponsive to topical anti-acne medications, have achieved menarche and desire contraception (only Ortho Tri-Cyclen[®])
- **Sponsor:** Ortho-McNeil
- **Original Market Approval:** Ortho Tri-Cyclen[®] July 3, 1992; Ortho Tri-Cyclen Lo[®] August 22, 2002
- **Pediatric Exclusivity Granted:** December 18, 2003 for study to determine if Ortho Tri-Cyclen[®] improves bone mineral density in adolescents with anorexia nervosa

Drug Use Trends (Outpatient Settings): Norgestimate/ethinyl estradiol

- **Dispensed prescriptions for oral contraceptives increased 8 % (from 92 to 99 million) from Jan 2002-Dec 2004¹**
- **Dispensed prescriptions for Ortho Tri-Cyclen® (and associated generics) decreased by 47 % during the first year post-exclusivity period (Jan 2004-Dec 2004) compared to the prior year (Jan 2003-Dec 2003)¹**
- **Ortho Tri-Cyclen® was the third most commonly dispensed oral contraceptive agent in 2004 (down from #1 in 2002)¹**

¹IIMS Health, National Prescription Audit *Plus*TM, Jan 2002- Dec 2004, Data Extracted Mar 2005

Drug Use Trends (cont.) :

- **Adolescents accounted annually for ≤ 4.3 % of Ortho Tri-Cyclen[®] and ≤ 6.6 % of Ortho Tri-Cyclen Lo[®] prescriptions (approximately 171,000 and 348,000 respectively)^{1,2*}**
- **Between 2002 and 2004, total pediatric prescription claims for Ortho Tri-Cyclen[®] decreased (from 115,586 to 28,222) while the number of Ortho Tri-Cyclen Lo prescription claims increased (from 346 to 49,962)²**
- **Similar trends in adults (Ortho Tri-Cyclen[®]: 2,553,055 to 978,611; Ortho Tri-Cyclen Lo[®]: 5,169 to 816,941)²**

¹IMS Health, National Prescription Audit *Plus*[™], Jan 2002- Dec 2004, Data Extracted Mar 2005

²Caremark Dimension Rx[™], Jan 2002- Dec 2004, Data Extracted Mar 2005

*Calculation based on application of proportions of pediatric norgestimate/EE prescriptions in Caremark Dimension Rx[™] to IMS Health, National Prescription Audit *Plus*[™] to estimate number of norgestimate/EE prescriptions dispensed nationwide to pediatric population

Drug Use Trends (cont.) :

- **Prescribers (Jan 2004- Dec 2004)¹**
 - Obstetrician/gynecologists, family practitioners and internists accounted for nearly 75% of the prescriptions written.
 - Pediatricians wrote 5% (approximately 303,000).
- **Diagnosis²**
 - Females aged 17+ years: general counseling advice and gynecological examination
 - Females aged ≤ 16 years: dysfunctional bleeding, acne, and general counseling advice

¹IMS Health, National Prescription Audit *Plus*TM, Jan 2002 – Dec 2004, Data Extracted Jan 2005

²IMS Health, National Disease and Therapeutic IndexTM, Jan 1999- Dec 2004, Data Extracted Feb 2005

- <http://www.fda.gov/cder/pediatric/Summaryreview.htm>

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Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies

as of March 17, 2005

Summaries of Medical and Clinical Pharmacology Reviews

Drug	Sponsor	Review Summary	
Methylphenidate - Concerta	McNeil	Medical 	Clinical Pharmacology 
Mirtazapine - Remeron	Organon	Medical 	Clinical Pharmacology 
Nefazodone - Serzone	Bristol-Myers Squibb	Medical 	Clinical Pharmacology 
Nelfinavir - Viracept	Agouron	Medical 	Clinical Pharmacology 
Norgestimate and Ethinyl Estradiol - ORTHO TRI-CYCLEN	Johnson & Johnson	Medical 	Clinical Pharmacology 
Ofloxacin - Ocuflax	Allergan	Medical 	Clinical Pharmacology
Orlistat - Xenical	Hoffmann-La Roche	Medical 	Clinical Pharmacology 



Pediatric Exclusivity Study: Norgestimate/ethinyl estradiol

- **One-year efficacy and safety study evaluating the effect of treatment on low bone mineral density (BMD) in female adolescents with anorexia nervosa**
- **Exclusivity Determination: Based on six-month endpoint**

Pediatric Exclusivity Study:

- **Phase 2, double-blind, randomized, placebo-controlled, one-year clinical trial of Ortho Tri-Cyclen® vs. placebo**
- **Adolescents with anorexia nervosa per modified DSM-IV criteria (n= 123, aged 10-17 years)**
- **All on calcium and vitamin D supplements**
- **Primary efficacy endpoint: mean change in lumbar spine bone mineral density (LS BMD) from baseline to cycle 6**
- **Secondary efficacy endpoints: mean change LS BMD at cycle 13; mean change in hip BMD and body weight and mean percent change in LS BMD, hip BMD, and body weight at cycles 6 and 13**

Pediatric Exclusivity Study: Efficacy Findings at Six Months

Intent-to-treat Population (ITT) = patients with on-treatment DXA scan (n=110)

For primary efficacy endpoint: Statistically significant difference (p=0.04) between treatment groups in mean change LS BMD from baseline to cycle 6:

0.018 g/cm² vs. 0.008 g/cm² (Ortho Tri-Cyclen ® vs. Placebo)

For secondary efficacy endpoints: statistically significant difference (p=0.02) between treatment groups in mean percent change LS BMD from baseline to cycle 6:

2.362% vs. 0.888% (Ortho Tri-Cyclen ® vs. Placebo)

No labeling change at this time

Pediatric Exclusivity Study: Final Efficacy Findings at One Year

- **Intent-to-treat (ITT) population = patients with on-treatment DXA scan (n=112)**
- **No significant differences Ortho Tri-Cyclen® group vs. placebo for change from baseline to cycle 13**
 - **Mean LS BMD: 0.026 g/cm² vs. 0.019 g/cm² (p=0.244)**
 - **Mean hip BMD: 0.011 g/cm² vs. 0.013 g/cm² (p=0.784)**
 - **Mean % LS BMD: 3.1 % vs. 2.4 % (p=0.268)**
 - **Mean % Hip BMD: 1.5 % vs. 1.8 % (p=0.724)**
 - **Mean change body weight: +6.7 kg vs. +4.9 kg (p=0.174)**

Pediatric Exclusivity Study: Safety findings

- **No deaths and no thromboembolic events**
- **At least one serious adverse event reported:**
 - **Ortho Tri-Cyclen®: 8/61(13.1 %)**
 - **Placebo: 14/62 (22.6%)**
- **Most common serious adverse event :**
 - **Hospitalization for worsening anorexia nervosa**
 - **Ortho Tri-Cyclen®: 2/61 (3.3 %)**
 - **Placebo: 10/62 (16.1 %)**
- **Any adverse event (regardless of severity):**
 - **Dysmenorrhea**
 - **Ortho Tri-Cyclen®: 10/61 (16.4%)**
 - **Placebo: 3/62 (4.8%)**

Labeling Changes Resulting from Exclusivity Study

Safety and efficacy of ORTHO TRI-CYCLEN Tablets and ORTHO CYCLEN Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older.

There was no significant difference between ORTHO TRI-CYCLEN Tablets and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineral density between baseline and Cycle 13 in 123 adolescent females with anorexia nervosa in a double-blind, placebo-controlled, multicenter, one-year treatment duration clinical trial for the Intent To Treat (ITT) population.

Use of this product before menarche is not indicated.

Additional Relevant Safety Labeling

- **Contraindications include:**
 - **History or current thromboembolic disorders**
 - **Cerebral vascular or coronary artery disease**
 - **Severe hypertension**
 - **Known or suspected breast or endometrial carcinoma**
 - **Undiagnosed abnormal genital bleeding**
 - **Cholestatic jaundice of pregnancy or prior pill use**
 - **Hepatic adenomas or carcinomas**
 - **Known or suspected pregnancy**
- **Boxed warning: serious cardiovascular AE increased with tobacco use**

Relevant Safety Labeling

- **Pregnancy Category X**
- **Adverse events include:**
 - **Cardiovascular events: myocardial infarction, thromboembolism, thrombophlebitis and hypertension**
 - **Cerebral vascular events: thrombosis and hemorrhage**
 - **Ocular lesions: retinal thrombosis (visual field cuts)**
 - **Gastrointestinal (GI): gallbladder diseases, GI symptoms**
 - **Gynecologic symptoms (breakthrough bleeding, amenorrhea, change in menstrual flow)**
 - **Depression**
 - **Metabolic: decreased glucose tolerance, persistent hypertriglyceridemia, edema, weight change**
 - **Carcinoma: overall risk breast carcinoma (conflicting), possible cervical intraepithelial neoplasia, hepatic adenomas or benign hepatic tumors, hepatocellular carcinoma**

Adverse Event Reports since Market Approval: Norgestimate/ethinyl estradiol (7/3/1992- 1/3/2005)

- **Total number of reports, all ages^{†*}:**
 - **1005 reports (995 US)**
 - **420 serious (411 US)**
 - **14 deaths (12 US)**
- **Pediatric reports^{*}:**
 - **40 reports (38 US)**
 - **27 serious (26 US)**
 - **No deaths**

[†]Includes reports with unknown age

^{*}Counts may include duplicates

Adverse Event Reports during the One-Year Post-Exclusivity Period: Norgestimate/ethinyl estradiol 12/18/2003 - 01/18/2005

- **Total number of reports, all ages^{†*}:**
 - **416 reports (414 US)**
 - **122 serious (120 US)**
 - **3 deaths (3 US)**
- **Pediatric reports:**
 - **16 reports (15 US) [14 unduplicated]**
 - **11 serious (10 US)**
 - **No deaths**

[†]Includes reports with unknown age

*Counts may include duplicate reports

Pediatric Adverse Events during the One-Year Post-Exclusivity Period (n=14)

- *In utero* exposure (2); Adolescent females (12):
- Reported more than once: headache, metrorrhagia, convulsion, drug exposure during pregnancy
- Hospitalization (4):
 - In utero (2) - premature infant/breech presentation; cerebral artery occlusion, convulsion, apnea and developmental delay
 - Adolescents (2) - 16 year old with benign intracranial hypertension, cerebrospinal fluid (CSF) pressure increase and visual field defect* and 14 year old with cerebral thrombosis and headache

Pediatric Adverse Events during the One-Year Post-Exclusivity Period

Cases involving isotretinoin and norgestimate/ethinyl estradiol (n=3)

- 16 year old with benign intracranial hypertension, increased CSF pressure and visual field cut (also on prednisone)
- 16 year old with depression, crying, decreased interest, dizziness, headache, insomnia and panic attack (also on prednisone)
- 14 year old with cerebral thrombosis and headache

Underlined events are unlabeled

Note: Labels for isotretinoin and prednisone include risk of increased intracranial pressure, depression, insomnia, emotional instability, dizziness and headache

Pediatric Adverse Events during the One-Year Post-Exclusivity Period

Cases with Visual Adverse Events (n = 3 patients)

- 14 year old with papilledema and cluster headache (also on oxcarbazepine)
- 16.7 year old with retinopathy, scotoma, blurred vision, headache and influenza-like illness (also on tretinoin and doxycycline)
- 16 year old with visual field defect, benign intracranial hypertension and increased CSF pressure (also on isotretinoin, prednisone)

Label warns of retinal thrombosis and need to discontinue drug if visual symptoms occur

Underlined events are unlabeled

Pediatric Adverse Events during the One-Year Post-Exclusivity Period

- **Drug exposure during pregnancy (n=2)**
 - Neonate with premature birth and breech presentation (other maternal medications: penicillin, betamethasone, prenatal vitamins and alprazolam)
 - Neonate with cerebral artery occlusion, apnea, seizure and developmental delay
- **Convulsion (n=2)**
 - Neonate with cerebral artery occlusion, apnea, seizure and developmental delay
 - 15 year old with history of intermittent seizures

Note: Cerebrovascular events are labeled, seizures are not

Pediatric Adverse Events during the One-Year Post-Exclusivity Period

Other Serious Adverse Events (n=2)

-14 year old with hypertension

-14 year old with dysarthria and hypoaesthesia

Underlined events are unlabeled

Summary: Norgestimate/ethinyl estradiol

- **Number of pediatric reports parallel use**
- **Although serious AEs occurred, no pattern of new safety concerns identified**
- **Final assessment of pediatric exclusivity study prompted new labeling**
- **This completes the one-year post-exclusivity AE monitoring as mandated by BPCA.**
- **FDA recommends routine monitoring of AEs for this drug in all populations.**
- **Does the Advisory Committee concur?**

Acknowledgements

ODS

- Mark Avigan
- Gerald Dal Pan
- Andrea Feight
- Adrienne Rothstein
- Kendra Worthy

DMEP

- Eric Colman
- Brenda Gierhart
- Theresa Kehoe
- Patricia Madara
- David Orloff