

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 23, 2005

FROM: Adrienne Rothstein, Pharm.D., Postmarketing Safety Evaluator  
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THROUGH: Mark Avigan, M.D., C.M., Director  
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TO: Solomon Iyasu, M.D., MPH., Team Leader  
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Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review;  
PID #D030716  
Drug: Norgestimate/ethinyl estradiol (ORTHO TRI-CYCLEN® & ORTHO TRI-CYCLEN® Lo, ORTHO-McNEIL, NDAs 019697 & 021241)  
Pediatric Exclusivity Approval Date: 12/18/2003

**I. Executive Summary**

The AERS database was searched for reports of adverse events occurring with the use of norgestimate/ethinyl estradiol in pediatric patients. Overall, AERS contains 1,005 cases (raw count) for all ORTHO TRI-CYCLEN® and ORTHO TRI-CYCLEN® Lo (norgestimate/ethinyl estradiol) products, including both adult and pediatric cases. Pediatric cases represent 40 of the total cases. We were asked to focus on the 1-year period following the approval of pediatric exclusivity, 12/18/2003 to 12/18/2004 (referred to hereafter as the *pediatric exclusivity period*). We used an AERS “cut-off” date of 01/18/2005 to allow an additional month for all reports received by 12/18/2004 to be entered into AERS. A total of 416 cases (raw count) were received in the pediatric exclusivity period, including both adult and pediatric cases and cases with no age reported. Sixteen (raw count) of the 416 cases received in the pediatric exclusivity period reported events in pediatric patients.

We reviewed 14 unique pediatric cases (2 cases did not involve adverse events) reported to the FDA during the pediatric exclusivity period. The following events were reported more than one time each in pediatric patients including 2 neonatal cases during the pediatric exclusivity period: *Headache, convulsion, drug exposure during pregnancy, and metrorrhagia*. Of these events, only headache and metrorrhagia are labeled events for norgestimate/ethinyl estradiol. Three patients were hospitalized (a neonate in the breech presentation born prematurely, another neonate with cerebral artery occlusion, convulsions, and apneic attacks, and a 16-year-old with benign intracranial hypertension, increased CSF pressure, and visual field defect who was also

receiving isotretinoin and prednisone at the time of the event. In addition, there was 1 report of hospitalization that was also regarded as life-threatening by the reporter (a 14 year old patient who developed cerebral thrombosis and headache). None of the patients died.

This review did not reveal any new safety concerns for the use of ORTHO TRI-CYCLEN® and ORTHO TRI-CYCLEN® Lo (norgestimate/ethinyl estradiol) products in pediatric patients. We will continue to routinely monitor adverse events in pediatric patients.

**II. AERS Search Results: Norgestimate/ethinyl estradiol**

AERS search results including all sources - U.S. & foreign. The following table and figure display raw counts of cases, which may include duplicate reports or cases without a reported age or report source (null values).

*A. From marketing approval date (07/03/1992) through AERS cut-off date (01/18/2005)*

*1. Raw Counts of Reports*

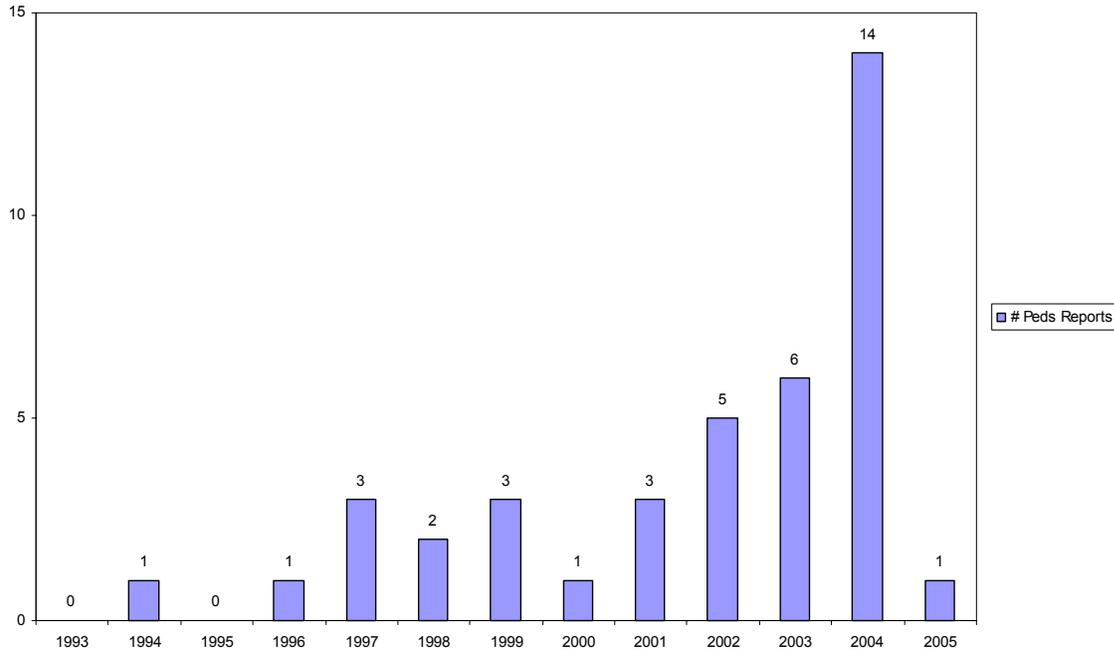
See Table 1 below.

**Table 1. Raw Report Counts\* (parentheses denote U.S. origin report counts)**

	All reports since approval (US)	Serious (US)	Death (US)
All ages	1005 (995)	420 (411)	14 (12)
Adults (17+)	642 (635)	313 (306)	12 (10)
Peds (0-16)	40 (38)	27 (26)	0 (0)

\* May include duplicate reports or cases with null values for age and source

**Figure 1: Reporting trend for pediatric reports from approval date (07/03/1992):**



*2. Counts of Top 20 Report Event Preferred Terms*

This section presents the raw counts of the top 20 report event preferred terms for all ages, adults, and pediatric age groups. *Italicized* events were among the most frequently reported events in pediatric patients, but not in adults. Underlining signifies the event is not included in the current labeling. See Table 2 below.

**Table 2. Raw Counts\* of Top 20 Reported Event Preferred Terms from Approval Date**

	Preferred Term	Raw Count
All Ages	Metrorrhagia	108
	Headache	64
	<u>Drug Exposure During Pregnancy</u>	63
	Pregnancy On Oral Contraceptive	63
	Nausea	59
	Pulmonary Embolism	55
	Acne	51
	Unintended Pregnancy	45
	Deep Vein Thrombosis	35
	Menorrhagia	35
	Vomiting	35
	Weight Increased	33
	Alopecia	30
	Menstruation Irregular	27
	<u>Condition Aggravated</u>	26
	<u>Medication Error</u>	26
	<u>Abdominal Pain</u>	25
	Amenorrhea	25
	Migraine	25

	Dizziness	24
Adults (17+ years)	Metrorrhagia	69
	Pulmonary Embolism	49
	Headache	48
	Nausea	42
	Pregnancy On Oral Contraceptive	34
	Acne	33
	<u>Drug Exposure During Pregnancy</u>	32
	Unintended Pregnancy	31
	Deep Vein Thrombosis	30
	Vomiting	26
	Menorrhagia	25
	Alopecia	23
	Migraine	21
	Weight Increased	21
	<u>Abdominal Pain</u>	20
	<u>Condition Aggravated</u>	19
	Menstruation Irregular	19
	Dizziness	18
	Depression	17
	Amenorrhea	16
Pediatrics (0-16 years)	Headache	5
	Depression	3
	Dizziness	3
	<u>Abdominal Pain</u>	2
	<u>Condition Aggravated</u>	2
	<u>Convulsion</u>	2
	<u>Crying</u>	2
	<u>Drug Exposure During Pregnancy</u>	2
	Metrorrhagia	2
	<u>No Adverse Drug Effect</u>	2
	Pregnancy On Oral Contraceptive	2
	<u>Premature Baby</u>	2
	Pulmonary Embolism	2
	Unintended Pregnancy	2
	Weight Increased	2

\* Raw counts: may include terms from duplicate reports

*B. From Pediatric Exclusivity Approval Date (12/18/2003) through AERS data cut-off date (01/18/2005)*

*1. Raw Counts of Reports*

See Table 3 below.

**Table 3. Raw Report Counts\* (parentheses denote U.S. origin report counts)**

	All reports 12/18/2003 to 01/18/2005 (US)	Serious (US)	Death (US)
All ages	416 (414)	122 (120)	3 (3)
Adults (17+)	227 (226)	78 (77)	2 (2)
Peds (0-16)	16 (15)	11 (10)	0 (0)

\* May include duplicate reports or cases with null values for age and source

## 2. Counts of Top 20 Report Event Preferred Terms

This section presents the raw counts of the top 20 report event preferred terms for all ages, adults, and pediatric age groups. *Italicized* events were among the most frequently reported events in pediatric patients, but not in adults. Underlining signifies the event is not included in the current labeling. See Table 4 below.

**Table 4. Raw Counts\* of Top 20 Reported Event Preferred Terms from Pediatric Exclusivity Approval Date (12/18/2003) through AERS data cut-off date (01/18/2005)**

	Preferred Term	Raw Count
All Ages	Metrorrhagia	92
	<u>Drug Exposure During Pregnancy</u>	61
	Pregnancy On Oral Contraceptive	56
	Nausea	31
	Menstruation Irregular	21
	Acne	19
	Headache	18
	Menorrhagia	17
	Weight Increased	16
	Amenorrhea	14
	Vomiting	14
	Breast Tenderness	13
	<u>Unevaluable Event</u>	13
	Oligomenorrhoea	10
	<u>Pharmaceutical Product Complaint</u>	9
	Pulmonary Embolism	9
	Dizziness	8
	Unintended Pregnancy	8
	<u>Uterine Spasm</u>	8
	Cerebrovascular Accident	7
Adults (17+ years)	Metrorrhagia	56
	<u>Drug Exposure During Pregnancy</u>	31
	Pregnancy On Oral Contraceptive	30
	Nausea	21
	Menstruation Irregular	13
	Menorrhagia	12
	Acne	10
	Headache	10
Oligomenorrhoea	9	

	Weight Increased	9
	Breast Tenderness	8
	<u>Pharmaceutical Product Complaint</u>	8
	Unintended Pregnancy	7
	Amenorrhea	6
	Cerebrovascular Accident	6
	Deep Vein Thrombosis	6
	Dysmenorrhoea	6
	Pulmonary Embolism	6
	<u>Uterine Spasm</u>	6
	Vomiting	6
Pediatrics (0-16 years)	Headache	3
	<u>Convulsion</u>	2
	<u>Drug Exposure During Pregnancy</u>	2

\* Raw counts: may include terms from duplicate reports

### **III. Postmarketing Hands-On Review of All Pediatric Adverse Event Reports from All Sources Received During Pediatric Exclusivity Period**

This section includes a hand-on review of all 14 pediatric reports received during the 1 year post-pediatric exclusivity period (2 cases that did not involve adverse events were excluded from this analysis).

#### *A. Characteristics of Pediatric Cases Received During the Pediatric Exclusivity Period*

All the pediatric cases occurred in female teenagers (average age 15.3 years), except for 2 cases involving male neonates exposed to ORTHO TRI-CYCLEN Lo in utero. In 6 of the 12 cases involving female teenagers, the indication for ORTHO TRI-CYCLEN or ORTHO TRI-CYCLEN Lo was contraception. The indication for use was acne in 3 cases and dysmenorrhea in 1 case; in the remaining 2 cases, the indication for use was not specified. The product used in the pediatric cases was split equally between ORTHO TRI-CYCLEN and ORTHO TRI-CYCLEN Lo.

**Table 5. Characteristics of Pediatric Cases (n=14)**

Gender	Female: 12 Male: 2 (neonates) Unknown: 0
Age (Standard AERS age breakdown)	0-1 month: 2 1 mo. - < 2 y/o: 0 2-5 years: 0 6-11 years: 0 12-16 years: 12
Indications	Contraception: 6 Acne: 3

	Maternal exposure: 2 Dysmenorrhea: 1 Unknown: 2
Product	ORTHO TRI-CYCLEN Lo: 7 ORTHO TRI-CYCLEN: 7
Serious Outcomes	Hospitalization: 2 Hospitalization + Life-threatening: 1 Hospitalization + Medically Significant: 1 Assessed as Medically Significant: 6
Country of Occurrence	US: 13 Canada: 1

*B. Characteristics of Adverse Events Reported in Pediatric Patients*

Two cases involved maternal exposure to norgestimate/ethinyl estradiol with transfer to the developing fetus via the placenta and are described separately under Section D since these cases are distinct from adolescent female patients taking norgestimate/ethinyl estradiol. The reported events for these 2 neonatal cases were drug exposure during pregnancy (2 events), breech presentation, premature baby, cerebral artery occlusion, convulsion, developmental delay, and neonatal apneic attack. A complete summary of these events is given in Section D below.

This paragraph summarizes the characteristics of adverse events reported in the 12 cases involving female adolescents. For these events listed below, any **bolded** event was considered **serious** and any underlined event was unlabeled according to the current product labeling: **headache** (3 events), metrorrhagia (2 events), and 1 report each of amenorrhea, **benign intracranial hypertension**, **cerebral thrombosis**, **cluster headache**, **convulsion**, **craving**, **CSF pressure increased**, **CSF test abnormal**, **decreased interest**, **depression**, **dizziness**, **dysarthria**, erythema nodosum, gingival swelling, **head injury**, **hypertension**, **hypoesthesia**, **influenza like illness**, **insomnia**, menorrhagia, **pain in extremity**, **panic attack**, **papilledema**, **pharyngitis streptococcal**, **retinopathy**, **scotoma**, **vision blurred**, and **visual field defect**.

The most frequently occurring events in pediatric patients were headache and metrorrhagia, both of which are labeled events for norgestimate/ethinyl estradiol. Very few of the events reported in pediatric patients were among the most commonly reported events in adult patients, either during the pediatric exclusivity period or since the approval of norgestimate/ethinyl estradiol. In addition, very few of the events reported in pediatric patients were labeled events for norgestimate/ethinyl estradiol. However, with only 1 case reported for each event, it would be premature to recommend any changes to the ORTHO TRI-CYCLEN and ORTHO TRI-CYCLEN Lo labels or to conclude that the pediatric adverse event profile was different from that for adults.

It is notable that isotretinoin was listed a co-suspect medication in 3 of the pediatric cases. The events reported in the first case included benign intracranial hypertension, CSF pressure increased, CSF test abnormal, and visual field defect in a 16-year-old female. This patient was also receiving prednisone concomitantly. The reported events occurred about 4 months after the initiation of norgestimate/ethinyl estradiol and 2.5 weeks after the initiation of isotretinoin. The events improved following treatment with diuretics and discontinuation of norgestimate/ethinyl

estradiol and isotretinoin. The reporting physician believed the events were related to isotretinoin. None of the reported events are considered labeled for ORTHO TRI-CYCLEN or ORTHO TRI-CYCLEN Lo. There is a WARNING about events of benign intracranial hypertension in the Accutane® (isotretinoin) package insert<sup>1</sup> and the Deltasone® (prednisone) package insert lists increased intracranial pressure with papilledema as an adverse event.<sup>2</sup>

In the second case with isotretinoin, crying, decreased interest, depression, dizziness, headache, insomnia, and panic attack were reported in a 16-year-old female. The patient was also receiving prednisone at the time of the event, which the reporting physician considered a suspect medication. The reported events began about 2 months after the initiation of norgestimate/ethinyl estradiol, 1.5 months after the initiation of isotretinoin, and 1 month after the initiation of prednisone. The patient discontinued both prednisone and norgestimate/ethinyl estradiol. The patient was given fluoxetine, but then began to experience panic attacks. One month later, isotretinoin was discontinued and the depression resolved 1 week later. The reporting physician considered these events related to norgestimate/ethinyl estradiol, isotretinoin, and prednisone. The ORTHO TRI-CYCLEN label has a **PRECAUTION** under the subsection **EMOTIONAL DISORDERS** indicating that women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. In addition, mental depression is listed an adverse event. The Accutane package insert contains a warning about events of severe depression with the use of this product.<sup>1</sup>

Finally, in the last case where isotretinoin was a cosuspect medication, life-threatening events of cerebral thrombosis and headache were reported in a 14-year-old female. The reported events occurred about 15 weeks after the initiation of isotretinoin and 6 months after the initiation of norgestimate/ethinyl estradiol. The patient was given anticoagulants and norgestimate/ethinyl estradiol and isotretinoin were discontinued. At last report, the patient was no longer receiving anticoagulants and the events resolved with no sequelae. The reporting physician considered the events likely related to the use of norgestimate/ethinyl estradiol. Thromboembolic events, including cerebral thrombosis, are labeled events for oral contraceptives. The Accutane package insert does not list cerebral thrombosis or other thromboembolic events.<sup>1</sup> As this case was life-threatening in nature, it is also summarized below in Section C.

### *C. Description of Fatal and Life-threatening Cases*

There were no fatalities reported during the period of this review. There was one case of cerebral thrombosis and headache in a 14-year-old female that was assessed as life-threatening. This 14-year-old female had no known history of blood clots and had no previous adverse reactions to exposures to similar classes of drugs (not further specified). The patient had been prescribed isotretinoin for an unknown indication and norgestimate/ethinyl estradiol for birth control. Approximately 15 weeks after starting treatment with isotretinoin and 6 months after initiating norgestimate/ethinyl estradiol, the patient was hospitalized due to severe headaches. An MRI at that time revealed a small blood clot in the brain and the patient was treated with an injectable anticoagulant (no further details were provided). Isotretinoin and norgestimate/ethinyl estradiol were discontinued around this time. After an unspecified period of time, the blood clot resolved and anticoagulant therapy was discontinued. At last report, the patient was doing well

and denied any lasting neurological signs and symptoms. Although the reporting physician considered the causal relationship to isotretinoin as unknown, a causal relationship with norgestimate/ethinyl estradiol is likely. As this patient was also receiving isotretinoin at the time of the event, it is also summarized above in Section B as the third case with isotretinoin as a co-suspect medication.

#### *D. Neonatal Cases Involving Placental Exposure to Norgestimate/ethinyl estradiol*

There were two cases in male neonates followed drug exposure during pregnancy in women who were using ORTHO TRI-CYCLEN Lo for contraception. In the first neonatal case, the mother took ORTHO TRI-CYCLEN Lo for approximately 2 weeks after conception (4 weeks after her last menstruation). This first neonate was born prematurely in the breech presentation with no other reported adverse events. In the second case, the neonate developed a cerebral artery occlusion, convulsions, developmental delay, and neonatal apneic attacks. The mother had taken ORTHO TRI-CYCLEN Lo for about 5 weeks after conception (7 weeks after her last menstruation). None of these reported events are labeled events for norgestimate/ethinyl estradiol. A causal role of maternal exposure to norgestimate/ethinyl estradiol in the development of these events is difficult to assess due to the variety of factors that may cause neonatal apnea and neonatal cerebral infarction and factors that may affect the delivery of an infant.

#### *E. Current Product Labeling*

We received 12 nonduplicated, nonexcluded cases for pediatric patients during the pediatric exclusivity period, reporting 33 events. In addition, there were 2 cases involving neonates whose mothers were receiving ORTHO TRI-CYCLEN Lo, which are discussed in section D. Table 6 lists all the preferred terms (PTs) for pediatric patients during the pediatric exclusivity period, including the 2 neonatal cases. There were only 2 PTs reported more than one time, headache (3 events) and metrorrhagia (2 events) which are both labeled events.

##### 1. Cerebral Thrombosis

The most concerning pediatric case during the period of this review was a life-threatening case of cerebral thrombosis and headache in a 14-year-old female. This patient had no known history of blood clots and had no previous adverse reactions to exposures to similar classes of drugs (unspecified). The patient fully recovered with no long-term neurological sequelae.

Both of these events are labeled for norgestimate/ethinyl estradiol. Under the **WARNINGS** section of the ORTHO TRI-CYCLEN package insert, there is a section on **THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS**, which includes **CEREBROVASCULAR DISEASE**. This section states that oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general the risk is greatest among older (>35 years), hypertensive women who also smoke. Headache has been reported in users of oral

contraceptives, although the association has neither been confirmed nor refuted. Cerebrovascular accident was among the top 30 commonly reported events in all patients since approval of norgestimate/ethinyl estradiol.

## 2. Visual Adverse Events

Of the 12 unduplicated cases reported in pediatric patients, there were 5 events occurring in 3 patients related to vision, including papilledema, retinopathy, scotoma, vision blurred, and visual field defect. All three of these cases were assessed as serious.

The pediatric case of papilledema occurred in a 14-year-old female who was also receiving oxcarbazepine. Norgestimate/ethinyl estradiol was discontinued and the event was improving at last report. Papilledema is a labeled event for oral contraceptives, but not for oxcarbazepine. The events of retinopathy, scotoma and blurred vision occurred in a 17-year-old female with no prior history of vision problems. After an unspecified duration of norgestimate/ethinyl estradiol and isotretinoin, the patient suddenly developed acute macular neuroretinopathy, scotoma and blurred vision. Norgestimate/ethinyl estradiol was discontinued and the central scotoma was improving at last report. None of these visual adverse events are considered labeled events for oral contraceptives or isotretinoin. Finally, an event of visual field defect occurred in a 16-year-old female who also developed benign intracranial hypertension, increased CSF pressure and an abnormal CSF test. This patient had received norgestimate/ethinyl estradiol for 3 months and was also receiving isotretinoin and prednisone. Visual field defect is not a labeled event for oral contraceptives. The Accutane® (isotretinoin) labeling lists benign intracranial hypertension as a WARNING<sup>1</sup> and the Deltasone® (prednisone) labeling lists increased intracranial pressure with papilledema as an adverse event.<sup>2</sup> In summary, there were 2 pediatric cases with visual events with a positive dechallenge.

A high level review was conducted of all cases with visual events since product approval due to these 3 pediatric cases with serious visual events from the pediatric exclusivity period. Individual visual adverse events did not appear among the most commonly reported adverse events in adult patients during either the pediatric exclusivity period or the entire period since product approval. Overall, there were 41 cases with events reported to the Eye Disorders System Organ Class (SOC). Of these 41 cases, 22 (53.7%) were considered serious. Since product approval there were 3 cases (7.3%) reported in pediatric patients aged 16 years or younger; all three cases were assessed as serious. There were 29 cases (70.7%) reported in adult patients aged 17 years or older, only 15 (51.7%) of these cases were considered serious. In addition, there were 9 cases with visual events where the patient age was not specified. The current product labeling for ORTHO TRI-CYCLEN and ORTHO TRI-CYCLEN Lo has information in the **OCULAR LESIONS** subsection under **WARNINGS** indicating that there have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

During this review 3 reports of visual events in pediatric patients were identified; all of them were assessed as serious. In 2 cases, an improvement in symptoms was reported after the discontinuation of norgestimate/ethinyl estradiol. However, there is not enough information at

this time to recommend a labeling change for this product. Any further cases with serious visual events in pediatric patients receiving norgestimate/ethinyl estradiol will be closely monitored.

### 3. Convulsion

An event of convulsion was reported in a 15-year-old female patient with a history of intermittent seizures. The mother of the patient reported that her daughter has one minor seizure every 2-3 years. About 3 days after the initiation of norgestimate/ethinyl estradiol for the treatment of acne, the mother reported that her daughter experienced a "minor fit" (seizure). The patient was not currently taking any medications for seizures or any other medication. There were no other changes noted in her regimen except the initiation of the norgestimate/ethinyl estradiol therapy. At last report several days after the event, the patient continued taking norgestimate/ethinyl estradiol and did not experience any additional seizures. Although there is a positive temporal relationship, oral contraceptives are not associated with an exacerbation of seizures.<sup>3</sup> Convulsion are not labeled events for norgestimate/ethinyl estradiol.

In addition, convulsions occurred in a male neonate following a cerebral infarction. The reporting physician considered the convulsions to be the result of the cerebral infarction and not the remote maternal use of ORTHO TRI-CYCLEN Lo.

## V. Summary

The AERS database was searched for reports of adverse events occurring with the use of norgestimate/ethinyl estradiol in pediatric patients. We focused on the 1-year period following approval of pediatric exclusivity with an additional month for the cases to be entered into AERS, specifically 12/18/2003 to 01/18/2005. The profile of the adverse event preferred terms for pediatric patients was compared with events reported for adult patients and to the product labeling.

We reviewed 12 unduplicated pediatric cases and 2 unduplicated neonatal cases reported to the FDA during the pediatric exclusivity period. No pediatric patients died and only 1 case was considered life-threatening during the period of this review. Only 2 PTs were reported more than one time, headache (3 reports) and metrorrhagia (2 reports), both of which are labeled events for norgestimate/ethinyl estradiol.

No new safety concerns were identified as a result of this review. We will continue routine monitoring of adverse events in pediatric patients.

## References:

1. Accutane® (isotretinoin) [package insert]. Nutley, NJ: Roche Pharmaceuticals; June 2002.
2. Deltasone® (prednisone) [package insert]. New York, NY: Pfizer Pharmaceuticals; April 2002.

3. Cunningham FG, Gant NF, Leveno KJ, Gilstrap LC, Hauth JC, Wenstrom KD. WILLIAMS OBSTETRICS, 21<sup>st</sup> edition. New York, NY: McGraw-Hill. 2001; Chapter 53. Neurological and Psychiatric Disorders.

## Appendix

### Drug Product Information

The labeling for ORTHO TRI-CYCLEN® (norgestimate/ethinyl estradiol) can be accessed at <http://www.orthotri-cyclen.com/index.html>.

The labeling for ORTHO TRI-CYCLEN® Lo (norgestimate/ethinyl estradiol) can be accessed at <http://www.orthotri-cyclenlo.com/>.

### Relevant Pediatric Labeling

The ORTHO TRI-CYCLEN and ORTHO TRI-CYCLEN Lo labeling contains information regarding pediatric use in the **PRECAUTIONS** Section:

#### **PRECAUTIONS**

**Pediatric Use:** Safety and efficacy of ORTHO TRI-CYCLEN and ORTHO TRI-CYCLEN Lo 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 of age and older. Use of this product before menarche is not indicated.

Additionally, the **CONTRAINDICATIONS, WARNINGS and PREGNANCY Sections** give information about the use of ORTHO TRI-CYCLEN and ORTHO TRI-CYCLEN Lo during pregnancy:

#### **CONTRAINDICATIONS:**

Oral contraceptives should not be used in women who currently have the following conditions:

- Known or suspected pregnancy, etc.

#### **WARNINGS:**

##### **Oral Contraceptive Use Before or During Pregnancy:**

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy. The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

**PREGNANCY:** Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections.

**Limitations of the Adverse Event Reporting System (AERS)**

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

**Table 6. Line Listing of Pediatric Cases Received During the Pediatric Exclusivity Period (n=14)**

#	Case	Country & ISR Type	Outcome	Age (yr) & Gender	Indication	Product	Dosage Text	DeC	ReC	MedDRA Reaction	Concomitant [C] or Co-Suspect [S] Medications
1	4075467	US, Periodic	OT	14.83 F	Acne	ORTHO TRI-CYCLEN (Norgestimate/Ethinyl Estradiol)	1 tab QD	Y	N	Hypertension	
2	4113588	US, Periodic	OT	15 F	Contraception	ORTHO TRI-CYCLEN Lo (Norgestimate/Ethinyl Estradiol)	1 tab QD	U	U	Amenorrhea, metrorrhagia	
3	4116497	US, Periodic	UNK	16 F	Dysmenorrhea	ORTHO TRI-CYCLEN Lo (Norgestimate/Ethinyl Estradiol)	1 tab QD	U	U	Erythema nodosum, gingival swelling, pain in extremity, pharyngitis streptococcal	
4	4116524	US, Periodic	UNK	15 F	Contraception	ORTHO TRI-CYCLEN Lo (Norgestimate/Ethinyl Estradiol)	1 tab QD	U	U	Menorrhagia	citalopram [C]
5	4116945	US, Periodic	OT	16 F	Contraception	ORTHO TRI-CYCLEN Lo (Norgestimate/Ethinyl Estradiol)	1 tab QD	U	U	Metrorrhagia	
6	4135626	US, Expedited	OT	16.73 F	UNK	ORTHO TRI-CYCLEN (Norgestimate/Ethinyl Estradiol)	1 tab QD	N	N/A	Headache, influenza like illness, retinopathy, scotoma, vision blurred	Doxycycline [C], tretinoin [C], actimycin [C]
7	4143879	Canada, Expedited	OT	15.7 F	Acne	ORTHO TRI-CYCLEN (Norgestimate/Ethinyl Estradiol)	1 tab QD	N/A	N/A	Convulsion, head injury	None. Pt had prior history of intermittent seizures.
8	4161300	US, Periodic	HO,RI	16 F	Acne	ORTHO TRI-CYCLEN (Norgestimate/Ethinyl Estradiol)	UNK	Y	N/A	Benign intracranial hypertension, CSF pressure increased, CSF test abnormal, visual field defect	Isotretinoin 40 mg [S], prednisone [C]
9	4161301	US, Periodic	OT	16.01 F	Contraception	ORTHO TRI-CYCLEN (Norgestimate/Ethinyl Estradiol)	1 tab QD	Y	N/A	Crying, decreased interest, depression, dizziness, headache, insomnia, panic attack	Isotretinoin 40 mg [S], prednisone 20 mg [S]
10	4166080	US, Periodic	LT,HO	14.77 F	Contraception	ORTHO TRI-CYCLEN (Norgestimate/Ethinyl Estradiol)	1 tab QD	Y	N/A	Cerebral thrombosis, headache	Isotretinoin 40 mg [S]

#	Case	Country & ISR Type	Outcome	Age (yr) & Gender	Indication	Product	Dosage Text	DeC	ReC	MedDRA Reaction	Concomitant [C] or Co-Suspect [S] Medications
11	4196007	US, Expedited	OT	13.99 F	UNK	ORTHO TRI-CYCLEN (Norgestimate/Ethinyl Estradiol)	UNK	U	U	Cluster headache, papilledema	oxcarbazepine 150 mg [S]
12	5650240	US, Periodic	OT	14 F	Contraception	ORTHO TRI-CYCLEN Lo (Norgestimate/Ethinyl Estradiol)	1 tab QD	N/A	N/A	Dysarthria, hypoaesthesia	
13	5658881	US, Expedited	HO,OT	Male Neonate	Maternal exposure	ORTHO TRI-CYCLEN Lo (Norgestimate/Ethinyl Estradiol)	Placental exposure	U	U	Cerebral artery occlusion, convulsion, developmental delay, drug exposure during pregnancy, neonatal apneic attack	
14	4138184	US, Expedited	HO	Male Neonate	Maternal drugs affecting fetus	ORTHO TRI-CYCLEN Lo (Norgestimate/Ethinyl Estradiol)	Placental exposure	N/A	N/A	Breech presentation, drug exposure during pregnancy, premature baby	Alprazolam [C], prenatal vitamins [C], penicillin [C], betamethasone [C]

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/s/

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Adrienne Rothstein  
2/24/05 08:18:42 AM  
DRUG SAFETY OFFICE REVIEWER

Mark Avigan  
2/28/05 12:35:44 PM  
DRUG SAFETY OFFICE REVIEWER