

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-690

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY for NDA # NDA 21-690 SUPPL #

Trade Name Ortho Tri-Cyclen Generic Name norgestimate/ethinyl estradiol

Applicant: Ortho-McNeil Pharmaceutical, Inc.; Johnson & Johnson
Pharmaceutical Research & Development, L.L.C., US Agent

Approval Date: May 13, 2005

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ XX / NO / ___/

Please note; this is a Type 6 NDA, meaning it is actually an efficacy supplement for an existing NDA. However, because the new indication is reviewed by a different division, it is given a new NDA # for administrative purposes.

b) Is it an effectiveness supplement? YES / ___/ NO / ___/

If yes, what type(SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / XX / NO / ___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Note: The sponsor requested a new indication but this was not granted or supported by the clinical data. The NDA was approved when the sponsor accepted the Division's proposed labeling (addition of a sentence describing lack of effectiveness) in the pediatric subsection of the PRECAUTIONS section.

d) Did the applicant request exclusivity?

YES /___/ NO /XX/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /XX/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /XX/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /**xx**/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

For Norgestimate:

NDA # 19-653 Ortho Cyclen-28
NDA # 19-697 Ortho Tri-Cyclen
NDA # 20-681 Ortho Tri-Cyclen
NDA # 21-241 Ortho Tri-Cyclen

For Ethinyl Estradiol:

Many many NDAs

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / XX / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / XX / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / X / NO / ___ /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NO / X /

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the

applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /x/

If yes, explain:

- (c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # **CAPPS-169**
Investigation #2
Investigation #3

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /x/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO / X /

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # **CAPPS-169**

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 61,239 YES / X / ! NO / ___ / Explain:
!
!
!

Investigation #2 !
IND # _____ YES / ___ / ! NO / ___ / Explain:
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES / ___ / Explain _____ ! NO / ___ / Explain _____
!

!

!

Investigation #2 !
YES / ___ / Explain _____ ! NO / ___ / Explain _____
!

!

!

!

- (c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Date: {See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Date: {See appended electronic signature page}

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDES/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Patricia Madara
5/18/05 08:40:51 AM

David Orloff
5/20/05 12:01:15 PM

Madara, Patricia

From: Healy, Tracy L. [PRDUS] [THEALY@PRDUS.JNJ.COM]
Sent: Tuesday, May 10, 2005 10:27 AM
To: 'MadaraP@cder.fda.gov'
Subject: RE: NDA 21-690 email noting minor wording change and acceptance

Hi Pat,

Please refer to our correspondence to FDA, DMEDP, dated 03 May 2005 in which we stated that we will revise the ORTHO TRI-CYCLEN[®] Physician Insert, Prescribing Information, PRECAUTIONS section, Pediatric Use subsection to incorporate the Agency's proposed labeling (e-mail dated 20 April 2005).

In addition to incorporating the Agency's proposed wording (sentence #3 of the above), the following (which was omitted in error in the 20 April 2005 e-mail will be added to the end of the 2nd sentence:

...under the age of 16 and for users 16 years and older.

Please do not hesitate to contact me if you have any questions or need additional information.

Thank you,
Tracy Healy, RN, MBA
Manager, Regulatory Affairs
J&JPRD, L.L.C.
Phone 908-704-5067
Fax 908-704-1501

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-----Original Message-----

From: Madara, Patricia [mailto:MadaraP@cder.fda.gov]
Sent: Monday, May 09, 2005 7:18 PM
To: 'Healy, Tracy L. [PRDUS]'
Subject: NDA 21-690 email noting minor wording change and acceptance

Hi Tracy;

I believe an email accepting the change in wording (back to the approved language) and noting that the rest of the sentence ("under the age of 16 and for users 16 years and older.") was left out in error (by us) will suffice.

Please contact me if there are any questions or problems. Thanks.

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

5/10/2005

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Patricia Madara
5/17/05 02:54:46 PM
CSO

(2/28/05)

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
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

TO: Solomon Iyasu, M.D., MPH., Team Leader
Division of Pediatric Drug Development, HFD-960
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.

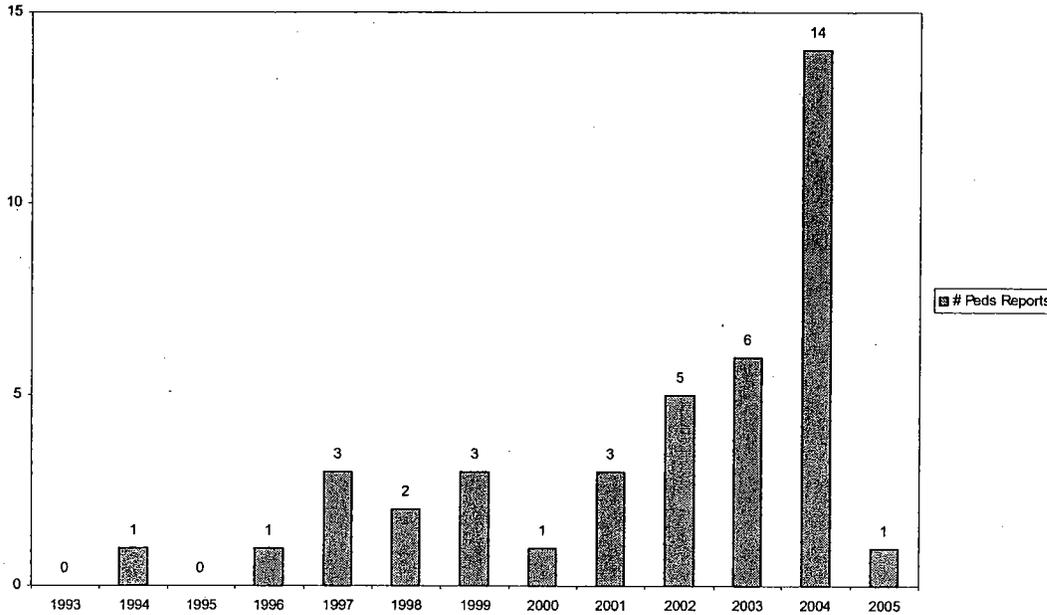
Table 1. Raw Report Counts* (parentheses denote U.S. origin report counts)

	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

**Appears This Way
On Original**

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**, **crying**, **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 insert¹ and the Deltasone® (prednisone) package insert lists increased intracranial pressure with papilledema as an adverse event.²

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.¹

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.¹ 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 WARNING¹ and the Deltasone® (prednisone) labeling lists increased intracranial pressure with papilledema as an adverse event.² 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-CYCLLEN and ORTHO TRI-CYCLLEN 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.³ 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, 21st edition. New York, NY: McGraw-Hill. 2001; Chapter 53. Neurological and Psychiatric Disorders.

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Appendix

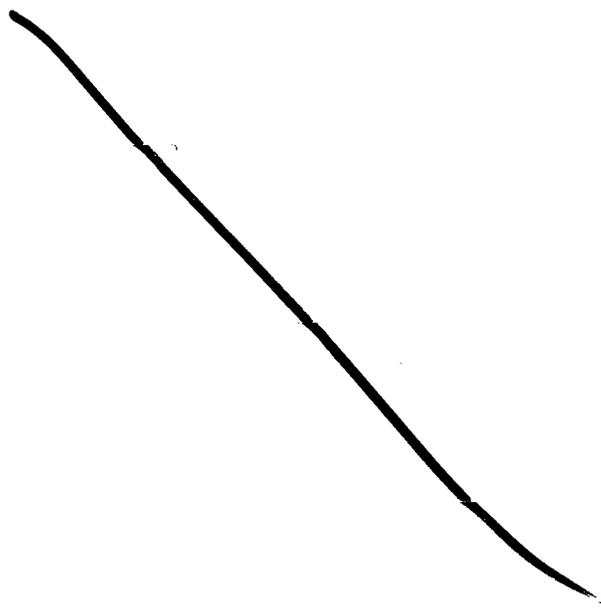
Drug Product Information

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:



1 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

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

#	Case	Country & ISR Type	Age (yr) & Gender	Outcome	Indication	Product	Dosage Text	DeC	ReC	MedDRA Reaction	Concomitant [C] or Co-Suspect [S] Medications
1	4075467	US, Periodic	14.83 F	OT	Acne	ORTHO TRI-CYCLEN (Norgestimate/Ethinyl Estradiol)	1 tab QD	Y	N	Hypertension	
2	4113588	US, Periodic	15 F	OT	Contraception	ORTHO TRI-CYCLEN Lo (Norgestimate/Ethinyl Estradiol)	1 tab QD	U	U	Amenorrhea, metrorrhagia	
3	4116497	US, Periodic	16 F	UNK	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	15 F	UNK	Contraception	ORTHO TRI-CYCLEN Lo (Norgestimate/Ethinyl Estradiol)	1 tab QD	U	U	Menorrhagia	citalopram [C]
5	4116945	US, Periodic	16 F	OT	Contraception	ORTHO TRI-CYCLEN (Norgestimate/Ethinyl Estradiol)	1 tab QD	U	U	Metrorrhagia	
6	4135626	US, Expedited	16.73 F	OT	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	15.7 F	OT	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	16 F	HO,RI	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	16.01 F	OT	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	14.77 F	LT,HO	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	Alprazolam [C], prenatal vitamins [C], penicillin [C], betamethasone [C]
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	

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/s/

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

Division of Metabolic and Endocrine Drug Products
REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-690

Name of Drug: Ortho Tri-Cyclen (norgestimate/ethinyl estradiol) Tablets

Applicant: Ortho-McNeil Pharmaceutical, Inc.
Johnson & Johnson Pharmaceutical Research & Development, L.L.C., US Agent

Material Reviewed: Draft labeling (text for package insert)

Submission Date(s): November 18, 2004 and May 3, 2005 and May 10, 2005(email)

Background and Summary

Ortho Tri-Cyclen is currently approved in the Division of Reproductive and Urologic Drug Products for prevention of pregnancy and treatment of acne (in women also requesting birth control). On August 15, 2003 a written request (WR) was issued by the Division of Metabolic and Endocrine Drug Products for a one year study to determine the effect of Ortho Tri-Cyclen on bone mineral density in anorexic pediatric girls. Six-month interim data was submitted on September 24, 2004 and the Division issued an approvable letter (AE) on March 23, 2004. The letter noted that Approval was contingent on the results of the one year trial.

A complete response to our action letter was submitted on November 18, 2004 and was reviewed by Brenda Gierhart, M.D., from this division.

Review

After review of the data, the Division determined that the following sentence (underlined) should be added to the **Pediatric Use** subsection of the **PRECAUTIONS** section of the prescribing information. This was done incorporate the results from the CAPPS-169 study entitled "The Effect of Ortho TriCyclen on Bone Mineral Density in Pediatric Subjects with Anorexia Nervosa". The subsection was revised as follows:

- 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.

Please note that the original proposed revision sent to the sponsor inadvertently deleted the end of sentence #2 to read:

- 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.~~[deleted end of sentence]~~ 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.

This was an error. The sponsor notified the Division of the mistake and confirmed agreement to revise the package insert to include the end of sentence #2.

The sponsor agreed to this revision on May 3, 9 (via tcon, corrected version), and 10 (via email, corrected version), 2005. All other sections of the currently approved PI were unchanged. (Note: referenced email is attached to the end of this review.)

The currently approved PI (Identifier 635-50-900-5, revised January 2000) was approved with supplement -022 to NDA 19-697, on June 5, 2000.

Per agreement with the sponsor, this reviewer obtained a WORD version of the label referenced above and inserted the agreed upon language into the **Pediatric Use** subsection.

This label was attached to the approval letter.

Conclusions

The sponsor has accepted the Division's proposed revision to the **Pediatric Use** subsection of the **PRECAUTIONS** section. There will be no other changes to the approved label. An approval letter can issue.

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Supervisory Comment/Concurrence:

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-690

Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.
Attn: Tracy L. Healy, RN, MBA
Manager, Regulatory Affairs
Global Marketed Products
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Healy:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ortho Tri-Cyclen [®] (norgestimate/ethinyl estradiol) Tablets
Review Priority Classification:	Priority (P)
Date of Application:	September 24, 2003
Date of Receipt:	September 25, 2003
Our Reference Number:	NDA 21-690

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 24, 2003 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be March 25, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-690

Page 2

If you have any questions, call me at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Patricia Madara

10/9/03 08:12:22 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,239

Johnson & Johnson Pharmaceutical Research and Development, LLC
Attention: Tracy Healy, RN, MBA
Manager, Regulatory Affairs
Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Healy:

Please refer to the meeting between representatives of your firm and FDA on July 8, 2003. The purpose of the meeting was to discuss issues involving the pediatric supplemental NDA to be submitted on September 25, 2003.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 8, 2003
TIME: 3:00 PM, DST
LOCATION: Teleconference
APPLICATION: IND 61,239; ORTHO TRI-CYCLEN² Tablets
(norgestimate/ethinyl estradiol)
TYPE OF MEETING: Type B
MEETING CHAIR: Eric C. Colman, M.D.
MEETING RECORDER: Pat Madara

FDA ATTENDEES

Division of Metabolic and Endocrine Drug Products, HFD 510

<u>Name of FDA Attendee</u>	<u>Title</u>
1. Eric C. Colman, M.D.	Medical Officer Team Leader
2. Hae Young Ahn, Ph.D.	Clinical Pharmacology Team Leader
3. S.W. Johnny Lau, Ph.D.	Clinical Pharmacology Reviewer
4. Jon T. Sahlroot, Ph.D.	Biometrics Team Leader
5. Kati Johnson	Chief, Project Management Staff
6. Pat Madara	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>OMP:</u>	<u>Title</u>
1. Andrew Friedman, MD	Director, Women's Health Care, Clinical Trials
2. Marc Kamin, MD	Vice President, Clinical Trials
3. Debra Karvois	Assistant Dir., Women's Health Care, Clinical Trials
4. William Olson, PhD	Sr. Director, Quantitative Methodology
5. Shu-Chen Wu, PhD	Associate Director, Quantitative Methodology

J&JPRD:

Title

- | | |
|----------------------|---|
| 1. Larry Abrams, PhD | Associate Director, Global Clinical Pharmacokinetics |
| 2. Ravi Chivukula | Associate Director, Regulatory Affairs, Chem-Pharm |
| 3. Patricia DeSantis | Sr. Director, Regulatory Affairs |
| 4. Tracy Healy | Manager, Global Marketed Products, Regulatory Affairs |
| 5. Sam Maldonado, MD | Director, Pediatric Drug Development |
| 6. Bob Monaghan | Assoc. Director, Global Marketed Products, Reg. Affairs |
| 7. Sandy Rathborne | Manager, Regulatory Affairs, Chem-Pharm |

BACKGROUND:

Johnson & Johnson Pharmaceutical Research and Development (J&JPRD) and Ortho-McNeil Pharmaceutical (OMP) submitted a Proposed Pediatric Study Request to IND 61,239 on July 11, 2002. The Agency issued a Written Request for Pediatric Studies (WR) on November 12, 2002. The sponsors submitted a request to amend the WR on November 15, 2002. This request was reviewed and an amended WR was issued on January 17, 2003. The sponsors submitted additional requests to amend the amended WR on January 9, February 10, March 13, and April 14, 2003. These requests were currently under review by the Division.

On May 21, 2003 the firm submitted a meeting request for a Type B, pre-NDA meeting to discuss issues involving the pediatric NDA to be submitted on September 25, 2003.

The sponsor submitted a list of specific questions dealing with regulatory, clinical/statistical, and clinical pharmacological issues.

Regulatory:

1. The sponsor sought confirmation that the submission, although treated as an NDA in DMEDP, will be filed as an efficacy supplement with a supplemental NDA user fee.

Response: The Agency agreed. It was also pointed out that a labeling supplement should be submitted to DRUDP. All labeling negotiations would be conducted in conjunction with DRUDP.

2. The sponsor proposed to cross-reference approved NDA 19-653 (ORTHO-CYCLEN), NDA 19-697 (ORTHO TRI-CYCLEN), and NDA 21-241 (ORTHO TRI-CYCLEN LO) for portions of the CMC, Pre-Clinical, Human Pharmacokinetics, and Clinical sections. They also proposed to submit an Environmental Assessment section in support of the submission.

Response: This was acceptable.

3. The sponsor pointed out that they are not planning on providing an ISS and ISE section for this submission but will provide a risk/benefit analysis.

Response: The Agency agreed with this proposal.

4. The sponsor asked for Agency agreement that since the current submission is not a full NDA in content, it was not necessary to utilize the Common Technical Document format.

Response: The Agency agreed. It was agreed to submit the NDA using the electronic format. It may be necessary to submit a paper version at a later date. Also, one copy of the 1.1 volume would be submitted for the project manager.

5. The sponsor proposed to add information in the Pediatrics Use section of the label to describe and summarize the results of this study. They questioned whether this would be acceptable to the Agency?

Response: The Agency told the sponsor it would discuss labeling after reviewing all the data.

Additional Regulatory Items Discussed:

1. The sponsor questioned whether they should submit investigator data for all recruited investigators or only for those who had enrolled subjects.

Response: The Agency suggested submitting data only for those investigators who had treated patients.

2. The sponsor requested Agency confirmation that the Case Report Forms should be submitted only for subjects who had died or experience a serious Adverse Event.

Response: The Agency agreed.

Clinical / Statistical:

1. The sponsor proposed to submit fully unblinded study data to the Agency at the time of filing of the Cycle 6 report. They proposed that OMP personnel and the study team at the CRO only review the unblinded summary statistics and a third party consisting of a programmer, statistician, QA and medical officer at the CRO would review the individual subject data in an unblinded fashion prior to submission to the Agency. Confirmation of acceptability to the Agency for this proposal was sought.

Response: The Agency found this acceptable. In addition, the Agency asked for submission of descriptive statistics summaries describing the primary outcome results for all patients, noting whether enrollment was prior to or after issuance of the Amended Written Request. It was noted that an estimated 30 – 40 patients were enrolled before the Amended WR issued. The Agency received confirmation that six month data was being submitted. It was requested that the sponsor follow the Division's biometrics guidelines for the formatting of the electronic data. It was stated that a copy of this document would be faxed to the firm.

Clinical Pharmacology:

1. In Chapter 6 of the Application Summary (Item 3) and the Human Pharmacokinetics and Bioavailability Technical Summary (Item 6), the sponsor planned to include:

- (a) A summary of the pharmacokinetic data from the pediatric study in Anorexia Nervosa patients (Study CAPSS-169)

Response: The sponsor should provide the raw individual data sets in SAS transport files as well as the full report and bioanalytical with validation reports for the pharmacokinetic portion of the clinical study (CAPSS-169). The sponsor should state whether the ORTHO TRI-CYCLEN formulation tested in Study CAPSS-169 is identical to the marketed formulation.

- (b) A summary of the pharmacokinetics of ORTHO TRI-CYCLEN in adult females (Study NRGTRI-OC-115)

Response: The Agency found this acceptable

- (c) A discussion of the comparability of the pharmacokinetic data from these two studies/populations

Response: Acceptable. However, the sponsor should also submit Study NRGTRI-OC-115's data in SAS transport files that were used for the comparison.

- (d) Cross-references to Chapter 6 and the Item 6 summary of previous submissions (indicated below) for ADME data of ORTHO TRI-CYCLEN.

Response: This was acceptable.

2. In addition to the cross-references indicated, would the agency prefer to have a copy of the full report of the NRGTRI-OC-115 study included with the present submission?

Response: This is not necessary. A summary will suffice.

ACTION ITEMS: none

Minutes Preparer: Pat Madara, Regulatory Project Manager

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/s/

Patricia Madara
9/4/03 04:13:11 PM

NDA 19-697
IND 61,239**WRITTEN REQUEST**
Amendment #2

The R. W. Johnson Pharmaceutical Research Institute
Attention: Tracy L. Healy, RN, MBA
Manager, Regulatory Affairs
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Healy:

Please refer to the following correspondences (dated January 9, February 10, March 13, and April 14, 2003) to IND 61,239 requesting changes to FDA's January 17, 2003, Amended Written Request for pediatric studies for ORTHO TRI-CYCLEN® (norgestimate/ethinyl estradiol) Tablets:

- January 9, 2003:
Requests changes to **Entry** criteria.
- February 10, 2003:
Requests changes to **Age group in which studies will be performed**.
- March 13 and April 14, 2003:
Request changes in the **Type of studies** (Study 2) and related changes in **Age group in which studies will be performed** (Study 2) and **Study endpoints** (Study 2)

We reviewed your submissions and are amending the Amended Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated January 17, 2003.

- *Type of studies:*
 - Study 1:** A randomized, double-blind, placebo-controlled study to examine the efficacy and safety of ORTHO TRI-CYCLEN® in the treatment of adolescent patients with anorexia nervosa (AN).
 - Study 2:** A pharmacokinetics (PK) study to assess the single-dose and steady-state or alternatively, population PK of ethinyl estradiol (EE), norgestrel (NG), and norelgestromin (NGMN) in pediatric patients with AN.
- *Indications to be studied (i.e., objective of each study):*
 - Study 1:** To assess the effect of ORTHO TRI-CYCLEN® on bone mineral density (BMD) of the lumbar spine and hip in patients with anorexia nervosa.
 - Study 2:** To assess the single-dose and steady-state or, alternatively, population PK of NGMN, NG, and EE in pediatric patients with AN.

- *Study design:*

Study 1: A one-year (13 cycles), randomized (1:1), double-blind, placebo-controlled study of approximately 120 adolescent women with AN. Enrollment should target patients who have a lumbar spine BMD Z-score, matched for ethnicity, of less than zero at baseline. All patients should receive appropriate care consistent with current clinical practice standards for anorexia nervosa (e.g., medical and psychiatric interventions). The primary efficacy analyses should be performed after cycle 6. Although the Agency will consider submission of the primary efficacy and standard safety data through cycle 6 as satisfying this Written Request, all patients should continue in the study for an additional 6 months of double-blind therapy for a total of 13 cycles.

Study 2: A randomized, open-label study in pediatric patients with AN, who should be administered 3 consecutive 28-day cycles of 0.18 mg norgestimate (NGM)/ 0.035 mg EE for Days 1 – 7, 0.215 mg NGM/0.035 mg EE for Days 8 – 14, 0.25 mg NGM/0.035 mg EE for Days 15 – 21, and inactive tablets for Days 22 - 28. Serial blood samples should be drawn at specified times upon single-dose administration and during the 3rd cycle of administration for measuring serum NGMN, NG, and EE concentrations.

- Alternatively, a population PK study with an appropriate sampling approach (per the Guidance for Industry: Population Pharmacokinetics document of Feb. 1999) may be conducted as a substudy of Study 1. This population PK substudy must use an appropriate sampling plan as per the February 1999, Guidance for Industry: Population Pharmacokinetics guidance.

- *Age group in which studies will be performed:*

Study 1: Pediatric patients 12 through 17 years of age.

Study 2: Eighteen completed patients who are 12 through 17 years of age for the single-dose and steady-state PK study. Alternatively, at least 40 patients, who are 12 through 17 years of age, for the population PK study.

- *Entry criteria (Studies 1 and 2):*

- Patients should be 12 through 17 years of age, and have AN as defined by DSM-IV criteria. Patients may not be pregnant or lactating or using any form of hormonal birth control, including parenteral forms of contraception such as levonorgestrel intrauterine system, levonorgestrel implants, and medroxyprogesterone acetate injectable suspension.

Exclusion criteria should include:

1. Smoke 15 or more cigarettes per day
2. History of venous thromboembolic disease
3. Uncontrolled hypertension
4. History of liver tumor
5. History of cholestatic jaundice
6. Any impairment in liver or kidney function
7. Diabetes mellitus with vascular involvement
8. Primary amenorrhea due to a condition other than anorexia nervosa
9. Current use of bisphosphonates, thiazides, or anti-seizure medication
10. TSH outside of the normal range

- *Study endpoints:*

Study 1: The primary endpoint is a comparison of the absolute change in lumbar spine BMD from baseline to the end of Cycle 6 between the ORTHO TRI-CYCLEN[®] and placebo groups. Secondary endpoints should include the mean percent changes in lumbar spine and total hip BMD from baseline to the end of Cycle 6 and the mean percent changes in lumbar spine and total hip BMD from baseline to the end of Cycle 13. The mean percent change in body weight from baseline to the end of Cycles 6 and 13 should also be considered secondary endpoints.

Study 2: Single-dose and steady-state NGMN, NG, and EE PK parameters such as $AUC_{0-\infty}$, AUC_{0-24h} , CL/F , V_d/F , C_{max} , T_{max} , λ_z , $t_{1/2}$, and their descriptive statistics should be evaluated. The effect of demographic covariates (for example age, race, and body weight) on the PK parameters should also be evaluated. Alternatively, for the population PK study, there should be an estimation of clearance for NGMN, NG, and EE. The effect of demographic covariates (for example age, race, and body weight) on the PK parameters should be evaluated in the population PK approach.

- *Drug information*

- *dosage form:* Tablet
- *route of administration:* Oral
- *regimen:* One tablet per day from a 28-day blistercard for 13 cycles

- Use an age-appropriate formulation in the studies described above. Any unapproved formulation will need to be supported by study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency.

- *Drug-specific safety concerns:* The primary safety concern with ORTHO TRI-CYCLEN[®] is vascular disease (i.e., venous thromboembolism, myocardial infarction, cerebrovascular accident). The risk for cardiovascular disease increases with the age of the patient and with heavy smoking (15 or more cigarettes per day). Patients with a history of venous thromboembolic or cardiovascular disease should be excluded from the study, as should girls who smoke 15 or more cigarettes per day.

- *Statistical information, including power of study and statistical assessments:*

The two treatment groups should be compared on the primary endpoint using analysis of covariance (ANCOVA). The ANCOVA model should include treatment and center as factors and screening total lumbar spine BMD as a covariate. The same analysis technique should also be used for the analysis of hip BMD.

Sixty patients per group is expected to provide 80% power to detect a 0.050 gm/cm² difference in total lumbar spine BMD change from baseline between the two treatment groups at the end Cycle 6 with a common SD = 0.096 gm/cm².

The primary analysis population is the intent-to-treat population consisting of all randomized patients with baseline and on-treatment data.

- *Labeling that may result from the studies:* Appropriate sections of the label may be changed to incorporate the findings of the studies.
- *Format of reports to be submitted:* Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.
- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before September 26, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. The Agency will consider the primary efficacy and standard safety data submitted for the first 6 cycles as fulfilling this Written Request. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.
- *Response to Written Request:* As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request, you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a **new drug application (NDA)** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Pat Madara, Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Robert Meyer
8/15/03 11:34:48 AM

PdIT Meeting Minutes
October 2, 2002

Attendees:

Rosemary Roberts	Eric Colman (HFD-510)
Shirley Murphy	Samuel Wu (HFD-510)
Debra Birenbaum	Todd Sahlroot (HFD-715)
Dena Hixon	S.W. Johnny Lau (HFD-870)
Lisa Mathis	Renata Albrecht (HFD-590)
Arzu Selen	Edward Cox (HFD-590)
Grace Carmouze	Barbara Davit (HFD-880)
Rosemary Addy	Diana Willard (HFD-590)
Charles Anello	Kofi Kumi (HFD-880)
Solomon Sobel	Regina Alivisatos via t-con (HFD-590)
Steve Hirschfeld	
Wiley Chambers	
Dragos Roman	
Tom Smith	
Paul Varki	
Kathy Robie-Suh	

Ortho Tri-Cyclen Written Request

1. Public Health Benefit

Bone loss is commonly seen in women with anorexia nervosa (AN) and may contribute to an increased risk for future fracture. Some doctors currently prescribe oral contraceptives off label for this indication.

2. Other products available/approved for this indication

No drugs are approved to treat the osteopenia associated with AN

3. Types of Studies

Several small studies have examined the effect of estrogen/progestin on bone mass in women with AN. While the overall results from these studies have not been positive, the drug may be beneficial in women whose weights are 70% or less of the ideal body weight.

The largest study to date has been about 50 patients with a wide range of ages participating. Some of the patients have been under age 15. One study looked at a subgroup of patients with a body weight 70% or less of the ideal body weight. In that study, that group showed some improvement.

If the company decides to complete the study in the written request and does it correctly, this study would be the largest study to date. The committee questioned the ethics of doing this study in patients who are not old enough to give informed consent. There was a lengthy discussion about why the company should not first do the study in patients 18 and older. The tendency in Division 580 has been to do studies in adults first. (That division got this request from the company first and decided the indication was not within their realm of expertise.)

If there is no other way to get the information, studies in the pediatric population might be appropriate. However, if it is possible to get the information in other populations first, ethically, it must be done in people who can consent. The division cannot say with certainty that bone density response will not be different in the pediatric population than it is in the adult population.

In the study proposed by the written request, one-half of the patients must have a body weight of 70% or less of the ideal body weight at base line. The committee was concerned that patients entered should have the best chance of benefit. Since this drug has not proven efficacious in women over 70% of ideal body weight, there were concerns about including that population in the study.

The company is proposing a six-month study and may not otherwise do the studies. The committee expressed concern that the study design should not be compromised with a shorter study.

Some on the committee were concerned that these studies would ensure anovulation in a population that already has a problem with ovulation.

Some on the committee were concerned with the exclusion criteria for the study. Those criteria would seem to exclude almost everyone.

There was also concern whether participants would receive counseling and nutritional support.

The division agreed that it would be best to see studies in older women first; however, it is their understanding that the only way this company will move forward with the studies is if they receive exclusivity.

4. Comments on Written Request

- The WR should go to the NDA, not the IND.
- The WR should consistently refer to "patient" instead of "subject."
- The division should consider adding bradycardia in the exclusion criteria.
- Consider stratifying the study to check for nutrition effect.
- Since the studies would be in adolescents, the language on page 2 regarding a formulation for children is not necessary.

5. General Comments

The committee questioned if this combination product is the appropriate product to prevent osteopenia or osteoporosis. In addition, committee members noted that there were no long-term pediatric studies to assess the effect on linear growth when this product was studied for the indication of acne.

There is no clinical support for going forward with these studies at this time because of the problems presented by physiologic plausibility and ethics.

Some on the committee expressed concern about compliance because girls with AN would be likely to stop taking medication if they believed it was causing them to gain weight.

Some on the committee thought the most appropriate route would be for NIH to issue an RFP for the studies.

The committee recommended that this issue be sent before the Ethics Working Group on October 9, 2002. Issues for the group to consider include informed consent vs. assent; whether all in the study should be at 70% or less of the ideal body weight; whether there should be two studies; and whether it is ethical to have the study be 6 months in duration versus 1 year in duration.

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/s/

Rosemary Addy
12/9/03 01:16:42 PM
UNKNOWN

Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? YES

• Was form 356h included with an authorized signature? YES
If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? YES
If no, explain:

• If an electronic NDA, does it follow the Guidance? YES
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Summary, labeling, chemistry, pharm/tox, biopharm, clinical, statistical, CRTs, CRFs, cover letter,
Written request and amendments.

Additional comments:

• If in Common Technical Document format, does it follow the guidance? N/A

• Is it an electronic CTD? N/A
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information submitted on form FDA 3542a? YES

• Exclusivity requested? YES, 6 months
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? YES
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: 61,239
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 07/08/03 NO
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
Cartons, containers and PPI already approved and not changing; PI only change to Pediatric section NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Not changing NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? PPI not changing NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
N/A
- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

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- _____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
- _____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

	YES	NO
--	-----	----
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

	YES	NO
--	-----	----
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

	N/A	YES	NO
--	-----	-----	----
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

	N/A	YES	NO
--	-----	-----	----

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

	YES	NO
--	-----	----
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

	YES	NO
--	-----	----
- EITHER
 The number of the applicant's IND under which the studies essential to approval were conducted.

	IND # _____	NO
--	-------------	----
- OR
 A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

	N/A	YES	NO
--	-----	-----	----

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

	YES	NO
--	-----	----

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 7, 2003

BACKGROUND:

This NDA contains the results of a pediatric study. The pediatric study was originally submitted to IND 61,239, in response to a Written Request. This is a Type 6 NDA (The original NDA resides in HFD-580.) It is a Priority review.

ATTENDEES: Eric Colman, Johnny Lau, Cynthia Liu, Todd Sahlroot

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Eric Colman
Secondary Medical:	
Statistical:	Cynthia Liu (TL = Todd Sahlroot)
Pharmacology:	NN
Statistical Pharmacology:	
Chemistry:	Yvonne Yang (TL = Mamta Gautam-Basak)
Environmental Assessment (if needed):	exclusion sought
Biopharmaceutical:	Johnny Lau (TL = Hae Young Ahn)
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Pat Madara (supervisor = Kati Johnson)
Other Consults:	

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE XX REFUSE TO FILE _____

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

CLINICAL MICROBIOLOGY NA XX

STATISTICS FILE XX

BIOPHARMACEUTICS

FILE XX

- Biopharm. inspection needed: NO

PHARMACOLOGY

NA _____

- GLP inspection needed: NO

CHEMISTRY

FILE XX

- Establishment(s) ready for inspection? Have requested this statement YES NO
- Microbiology NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

XX The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

XX No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Pat Madara
Regulatory Project Manager, HFD-510

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this page is the manifestation of the electronic signature.**

/s/

Patricia Madara
12/3/03 09:16:06 AM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-690	Efficacy Supplement Type SE	Supplement Number
Drug: Ortho Tri-Cyclen (norgestimate/ethinyl estradiol)		Applicant: Johnson&Johnson Pharmaceutical Research
RPM: Pat Madara		HFD-510 Phone # 301-827-6416
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		Type 6
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		May 19, 2005
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
Exclusivity Summary (approvals only)		
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		December 13, 2003

General Information	
Actions	
• Proposed action	(X) AP () TA (X) AE () NA
• Previous actions (specify type and date for each action taken)	AE; March 23, 2004
• Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	May 3, 2005; tcon 5-9-05; Email 5-10-05
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	none
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None requested
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	July 8, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
	NN

Clinical and Summary Information

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	3/12/04; 5-11-05
❖ Clinical review(s) (indicate date for each review)	3/16/04; 5-6-05
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NN
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) (indicate date for each review)	Feb 25, 2004; May 2, 2005
❖ Biopharmaceutical review(s) (indicate date for each review)	3/01/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NN
❖ Clinical Inspection Review Summary (DSI)	NN
• Clinical studies	
• Bioequivalence studies	

CMC Information

❖ CMC review(s) (indicate date for each review)	March 12, 2004; April 21, 2005
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	March 12, 2004
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/N
❖ Facilities inspection (provide EER report) ❖ Withhold 3/12/04; acceptable 4/21/05	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	NN
❖ Nonclinical inspection review summary	NN
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NN
❖ CAC/ECAC report	NN