CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-808

Name: Tri-Sprintec™ Tablets
(Norgestimate and Ethinyl Estradiol Tablets, USP, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)

Sponsor: Barr Laboratories, Inc.

Approval Date: December 29, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-808

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-808

APPROVAL LETTERS

ANDA 75-808

DEC 29 2003

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tri-Sprintec™ Tablets [Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg (gray tablet), 0.215 mg/0.035 mg (light blue tablet), and 0.250 mg/0.035 mg (blue tablet)], respectively), packaged in a 28-day cycle regimen.

Reference is made to the agency's initial approval letter for this ANDA dated December 18, 2002. Reference is also made to the agency's tentative approval letter dated August 20, 2003, informing you that, in light of the July 30, 2003, Consent Judgement and Order that was entered by Judge Garrett E. Brown, Jr. in Ortho-McNeil Pharmaceuticals, Inc. v. Barr Laboratories, Inc., in the U.S. District Court for the District of New Jersey, the final approval granted to Barr Laboratories, Inc. (Barr) on December 18, 2002, for this application including all amendments thereto, was rescinded, and the status of Barr's ANDA was changed to that of tentative approval. The Order also stated that the effective date of approval for any ANDA submitted by Barr covering the oral contraceptive drug described in, and the subject of, Barr's ANDA 75-808, shall not be earlier than the date of expiration of U.S. Patents 4,544,554 (the '554 patent) and 4,616,006 (the '006 patent), which was September 26, 2003.

Subsequent to the July 30, 2003, Consent Judgement and Order, on July 31, 2003, Barr amended this ANDA to include a patent certification under Section 505(j)(2)(A)(vii)(III) of the Act ("paragraph III certification") to the '554 and '006 patents. This paragraph III certification stated the date on which the patents would expire and indicated that Barr did not intend to seek final approval before that date.

We also refer to a second tentative approval letter issued by this office on September 26, 2003. That letter informed Barr that final approval of this ANDA could not be granted upon the expiration of the '554 and '006 patents on September 26, 2003, because the NDA holder, Ortho McNeil Pharmaceutical, Inc. (Ortho) had submitted data in response to the agency's written request for information concerning the use of the reference listed drug product, Ortho Tri-Cyclin Tablets, in a pediatric population. The filing of that submission by Ortho precluded the agency from granting final approval under 21 U.S.C. 355A(e) to your ANDA for up to 90 days while the agency determined whether the pediatric use data that were submitted met the terms of the agency's written request. The agency completed its review and concluded that the pediatric data submitted by Ortho did meet the terms of the written request. As a result, on December 18, 2003, pediatric exclusivity was granted to Ortho's product, Ortho Tri-Cyclin (ethinyl estradiol; norgestimate) under NDA 19-697 and 20-690. This granting of pediatric exclusivity for Ortho Tri-Cyclin added a six-month period of marketing exclusivity to the '554 and '006 patents, and would normally preclude approval of ANDAs referring to the product until at least March 26, 2004. However, the agency is in receipt of correspondence from Ortho's counsel dated December 22, 2003. This correspondence states that Ortho has waived any pediatric exclusivity as to ANDA 75-808 as of December 29, 2003, and that Ortho has no objection to final marketing approval for this ANDA as of that date.

We also refer to your amendment dated October 20, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Tri-Sprintec™ Tablets, 28-day regimen, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ortho Tri-Cyclen® Tablets, 28-day regimen, of Ortho-McNeil Pharmaceutical, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 12/29/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-808
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-623/N.Takiar/ N. Takiar 12/24/03
HFD-623/D.Gill/ DSGill 12-24-03
HFD-617/S.Kim/ S. Kim 12/24/03
HFD-613/D.Catterson/ Debra M. Catterson 12/24/03
HFD-613/J.Grace/ Arl Dixon Jr/ 12/24/03

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F/T by: EW 12/23/03

Robert L. West
12/29/2003

APPROVAL

P.S 12/24/03

ANDA 75-808

DEC 18 2002

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Tri-Sprintec™ Tablets (Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg (gray tablet), 0.215 mg/0.035 mg (light blue tablet), and 0.250 mg/0.035 mg (blue tablet), respectively), packaged in a 28-day cycle regimen.

Reference is also made to your amendments dated May 2, and November 28, 2000; March 15, and June 1, 2001; and July 9, July 30, September 13, and September 24, 2002. We also refer to your correspondence dated June 2, 2000; and July 22, August 14, August 16, and October 25, 2002 pertaining to patent issues noted below.

The listed drug product (RLD) referenced in your application, Ortho Tri-Cyclen Tablets (28-day regimen) of Ortho McNeil Pharmaceutical, Inc., is subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, (the Orange book), each of the listed patents is scheduled to expire on September 26, 2003 (U.S. Patent No. 4,530,839, the '839 patent, U.S. Patent No. 4,544,554, the '554 patent, U.S. Patent No. 4,616,006, the '006 patent, and U.S. Patent No. 4,628,051, the '051 patent). Your application contains a paragraph IV patent certification to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Tri-Sprintec™ Tablets will not infringe on the patents or that the patents are invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately,

unless an action is brought against Barr Laboratories, Inc. (Barr) for infringement of any of the listed patents which were the subject of the paragraph IV certification. This action must have been brought against Barr prior to the expiration of forty-five (45) days from the date the notice you provided to the NDA/patent holder under paragraph (2)(B)(i) was received. You further informed the Agency that Ortho McNeil Pharmaceutical, Inc. initiated a patent infringement suit (involving the '839, '554, and '006 patents) against you in the United States District Court for the District of New Jersey (Ortho-McNeil Pharmaceutical, Inc. v. Barr Laboratories, Inc., Civil Action No. 00-CV-2805 (GEB)). With regard to this ongoing litigation, the Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Tri-Sprintec™ Tablets, 28-day regimen, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ortho Tri-Cyclen® Tablets, 28-day regimen, of Ortho McNeil Pharmaceutical, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Robert Lumpkin for
12/18/2002

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-808
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-623/N.Takiar/ N. Takiar 10/23/02
HFD-623/D.Gill/ DSGill 10-23-02
HFD-617/S.Kim/ S. Kim 10/23/02
HFD-613/D.Catterson/ OK, pending final OK from DMETS re: proprietary name. Debra M. Catterson 10/24/02
HFD-613/J.Grace/ Jsm 10/24/2002

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F/T by

APPROVAL

PJ 11/5/02

Robert Y. West
12/18/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-808

TENTATIVE APPROVAL LETTERS

ANDA 75-808

SEP 26 2003

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Sir:

This is in reference to your Abbreviated New Drug Application (ANDA) dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tri-Sprintec™ Tablets (Norgestimate and Ethinyl Estradiol Tablets, USP, 0.180 mg/0.035 mg (gray tablet), 0.215 mg/0.035 mg (light blue tablet), and 0.250 mg/0.035 mg (blue tablet), respectively), packaged in a 28-day cycle regimen.

Reference is made to our tentative approval letter dated August 20, 2003, and to your amendmentS dated August 21, and September 11, 2003, requesting that the agency grant final approval to this abbreviated application.

You have requested final approval of this application based upon the expected expiration of the patents listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", for the reference listed drug product, Ortho Tri-Cyclin Tablets (28-day regimen) of Ortho McNeil Pharmaceutical, Inc. The following U.S. patents and their expected expiration dates are currently listed in the Orange Book:

4,530,839	September 26, 2003
4,544,554	September 26, 2003
4,616,006	September 26, 2003
4,628,051	September 26, 2003

We are unable to grant final approval to your ANDA at this time because Ortho McNeil Pharmaceutical, Inc. (Ortho) has submitted data to their NDA to provide for the use of Ortho Tri-Cyclin in the pediatric population. Because Ortho's data was submitted to the agency prior to the expiration of the patents and in response to the agency's written request, up to 90 days of marketing exclusivity will be added immediately to the expiration date of each of the patents. During this 90-day review period, the agency is precluded from approving ANDAs for this drug product (21 U.S.C. 355A(e).

The patent extension is permitted under Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The Modernization Act resulted in the creation of Section 505(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505(A) permits certain applications to obtain an additional 6 months of marketing exclusivity (pediatric exclusivity) if, in accordance with the requirements of the statute, the NDA-holder submits information requested by the agency relating to the use of the drug in the pediatric population. Ortho has submitted such information to the agency. The agency has up to 90 days to make a determination as to whether the data submitted by Ortho meet the criteria stated in the statute and the agency's written request letter. If the data are found to meet the criteria, the agency will grant Ortho an additional 6 months of marketing exclusivity for Ortho Tri-Cyclen Tablets. This exclusivity will effectively add 6 months to each of the listed patents. Depending on the nature of the data submitted, Ortho may also be eligible for an additional period of Hatch-Waxman exclusivity for changes made to the approved labeling for Ortho Tri-Cyclen Tablets. We urge you to remain in contact with the project manager who will inform you of the agency's decision(s) and their impact on the final approval date for this application.

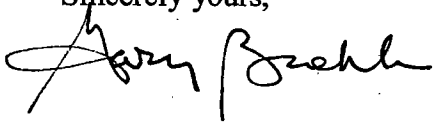
The agency notes that based upon the information you have presented to date, the drug remains safe and effective for use as recommended in the submitted labeling. Therefore, as noted, the application remains **tentatively approved.** This determination is based upon information available to the agency at this time, i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug products. The determination is subject to change on the basis of new information that may come to our attention.

Because the agency is granting a second **tentative approval** for this application, when you believe that your ANDA may be considered for final approval, you must amend your application to notify the agency whether circumstances have arisen that may affect the effective date of final approval. To reactivate your application, please submit a MINOR AMENDMENT – FINAL APPROVAL REQUESTED approximately 90 days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. In addition to this amendment, at any time prior to the final date of approval, the agency may request that you submit an additional amendment containing the information described above. Any changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to agency review before the application will receive final approval.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery or introduction into interstate commerce of these drug products before the effective final approval date is prohibited under section 301(d) of the Act. Also, until the Agency issues the final approval letter, these drug products will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book").

If you have any questions or require further information regarding this application, please contact Sarah Kim, Pharm.D., R.Ph., Project Manager, at (301) 827-5848.

Sincerely yours,



Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-808
Division File
Field Copy

Drafted by: RLWest/9/16/03

Robert L. West
9/26/2003

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TENTATIVE APPROVAL (2ND)

ANDA 75-808

AUG 20 2003

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Mr. Tantillo:

This is in reference to your Abbreviated New Drug Application (ANDA) dated February 16, 2000, ANDA 75-808, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tri-Sprintec™ Tablets (Norgestimate and Ethinyl Estradiol Tablets, USP, 0.180 mg/0.035 mg (gray tablet), 0.215 mg/0.035 mg (light blue tablet), and 0.250 mg/0.035 mg (blue tablet), respectively), packaged in a 28-day cycle regimen. This letter is to inform you that, in light of the July 30, 2003, Consent Judgment and Order that was entered by Judge Garrett E. Brown, Jr. in Ortho-McNeil Pharmaceuticals, Inc. v. Barr Laboratories, Inc., Civil Action No. 00-CV-02805 (GEB), in the U.S. District Court for the District of New Jersey (Order), the final approval given to Barr Laboratories on December 18, 2002, for this application including all amendments thereto, is hereby rescinded.

In addition, in a letter dated August 1, 2003, which was received via facsimile on August 14, 2003, you requested withdrawal of your pending supplements dated March 28, 2003, April 14, 2003, May, 1, 2003, July 24, 2003, and your August 1, 2003 "amendment" requesting final approval. This letter also informs you that these pending supplements and "amendment" are hereby considered to be withdrawn as of the date of this letter.

The listed drug product referenced in your ANDA is Ortho-McNeil Pharmaceuticals, Inc.'s NDA 19-697, Ortho Tri-Cyclen Tablets (28-day regimen). This drug is subject to periods of patent protection under U.S. Patent No. 4,530,839 ('839 patent), U.S. Patent No. 4,544,554 ('554 patent), U.S. Patent No. 4,616,006 ('006 patent), and U.S. Patent No. 4,628,051 ('051 patent), which expire on September 26, 2003. You originally filed a certification under section 505(j)(2)(A)(vii)(IV) of the Act ("paragraph IV certification") stating that each of these patents was invalid, unenforceable, or not infringed. You notified the NDA applicant and patent owner of this certification and were sued for infringement of the '839, '554, and '006 patents in Ortho-McNeil Pharmaceuticals, Inc. v. Barr Laboratories, Inc., Civil Action No. 00-CV-02805 (GEB). Your ANDA was approved on December 18, 2002, at the termination of the 30-month stay under section 505(j)(5)(B)(iii). No decision in the patent infringement litigation had been rendered at that time.

On July 30, 2003, a Consent Judgment and Order was entered in Ortho-McNeil Pharmaceuticals, Inc. v. Barr Laboratories, Inc., Civil Action No. 00-CV-02805 (GEB). The Order holds that the '554 and '006 patents are valid and enforceable and that the defendant has infringed claim 10 of the '554 patent and claim 9 of the '006 patent under 35 U.S.C. 271(e)(2). The Order also states that pursuant to 35 U.S.C. 271(e)(4)(A), the effective date of approval for any ANDA submitted by Barr covering the oral contraceptive drug described in, and the subject of, Barr's ANDA 75-808, shall not be earlier than the date of expiration of the '554 and '006 patents, which is September 26, 2003.

The legislative history of the 1984 Drug Price Competition and Patent Term Restoration Act makes clear that a court is permitted to reset the effective date of an ANDA approved upon expiration of the 30-month stay where the court subsequently finds patent infringement:

> If the infringing party has not begun commercial marketing of the drug, injunctive relief may be granted to prevent any commercial activity with the drug and the FDA would be mandated to make the effective date of any approved ANDA not earlier than the expiration date of the infringed patent. . . . *In the case where an ANDA had been approved, the order would mandate a change in the effective date.*
>
> If the infringing party has begun commercial marketing of the drug, damages and other monetary relief and injunctive relief may be awarded . . . . In addition, *the FDA would be mandated to change the effective date of the approved ANDA to the expiration date of the infringed patent.*

H.R. Rep. No. 857, 98th Cong., 2d Sess., part 1, at 46 (1984) (emphasis added).

Subsequent to the July 30, 2003 Consent Judgment and Order, on July 31, 2003, you amended your ANDA to include a patent certification under section 505(j)(2)(A)(vii)(III) of the Act ("paragraph III certification") to the '554 and '006 patents. A paragraph III certification states the date on which the patent will expire and indicates that the ANDA applicant does not seek final approval of its product before that date. Under section 505(j)(5)(B)(ii), if an ANDA contains a paragraph III certification, approval may be made effective no earlier than the date certified under paragraph III.

The July 30, 2003, Order is enclosed. It is based upon a finding that the '554 patent and the '006 patent are valid and enforceable, and that Barr has infringed claim 10 of the '554 patent and claim 9 of the '006 patent. As stated above, this letter informs you that, in light of the Court's Order and the change in your certifications to the '554 and '006 patents from paragraph IVs to paragraph IIIs, the final approval issued to Barr on December 18, 2002 for this application including all amendments, thereto, is hereby rescinded.

The Agency notes that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, as noted, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the

drug products, and is subject to change on the basis of new information that may come to our attention.

Because the Agency is granting a **tentative approval** for this application, when you believe that your ANDA may be considered for final approval, you must amend your application to notify the Agency whether circumstances have arisen that may affect the effective date of final approval. To reactivate your application, please submit an amendment prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as labeling, chemistry, manufacturing, and controls data as appropriate. In addition to this amendment, at any time prior to the final date of approval, the Agency may request that you submit an additional amendment containing the information described above. Any changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before the application will receive final approval.

The drug products that are the subject of this ANDA may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery or introduction into interstate commerce of these drug products before the effective final approval date is prohibited under section 301(d) of the Act. Also, until the Agency issues the final approval letter, these drug products will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book").

If you have any questions or require further information regarding this issue, please contact Cecelia Parise, R.Ph., Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845.

Sincerely yours,

Robert Lee Sest for
8/20/2003

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Court Order

cc: ANDA 75-808
Division File
Field Copy
GCF-1/E. Dickinson/K.Dettelbach, GCF-1
HFD-600/G.Buehler/R. West/C.Parise/R.Hassall/D.Hare
HFD-610/P. Rickman/G.Davis
HFD-630/T. Ames/S.Kim
HFD-629/R. Patel/P.Schwartz/D.Gill/N.Takiar
HFD-650/D.Conner/B.Davit/L.Sanchez
HFD-330
HFD-205
RESCIND APPROVAL LETTER
TENTATIVE APPROVAL LETTER
WITHDRAWAL SUPPLEMENTS

Drafted by: S.Kim 8/8/03, 8/11/03
Edited by: K.Dettelbach 8/19/03
Edited by: C.Parise 8/8/03, 8/20/03

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TENTATIVE APPROVAL OF ANDA

WITHDRAWAL OF S-003, S-004, S-005, S-006,

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Thomas Hastings (TH0501)
Smith, Stratton, Wise, Heher & Brennan
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Vicki Margolis
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(202) 962-4800

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Cohen, Pontani, Lieberman
and Pavane
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Attorneys for Defendant
Barr Laboratories, Inc.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ORTHO-MCNEIL PHARMACEUTICAL, INC.,

Plaintiff,

v.

BARR LABORATORIES, INC.,

Defendant.

Civil Action No. 00-CV-02805 (GEB)

CONSENT JUDGMENT AND ORDER

Plaintiff Ortho-McNeil Pharmaceutical, Inc. and Defendant Barr Laboratories, Inc. having agreed to a settlement of this action and having consented to the entry of this Judgment, IT IS HEREBY ORDERED, ADJUDGED, AND DECREED that:

1. This Court has jurisdiction over the parties and the subject matter of this action.

2. Plaintiff is the owner of the entire right, title and interest in and to United States Letters Patent No. 4,544,554 ("the '554 Patent") and United States Letters Patent No. 4,616,006 ("the '006 Patent").

3. The '554 Patent and the '006 Patent are valid and enforceable.

4. Defendant has infringed claim 10 of the '554 Patent and claim 9 of the '006 Patent under 35 U.S.C. § 271(e)(2).

5. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of approval for any Abbreviated New Drug Application submitted by Barr covering the oral contraceptive drug described in, and the subject of, Barr's Abbreviated New Drug Application No. 75-808, shall not be earlier than the date of expiration of the '554 Patent and the '006 Patent, which is September 26, 2003.

6. If Plaintiff licenses Defendant under the '554 and '006 Patents, then the date set forth in Paragraph 5 shall be adjusted accordingly.

7. All counterclaims filed by Defendant are hereby dismissed with prejudice.

8. Each of the parties shall bear its own costs and attorney fees.

9. This Order constitutes a final disposition of all disputes between the parties concerning this action.

10. The parties waive any right to appeal from this Judgment.

SO ORDERED, this 30th day of July, 2003

GARRETT E. BROWN, JR.
UNITED STATES DISTRICT JUDGE

CONSENTED AND AGREED TO:

William J. Brennan, III (WB 9673)
Thomas Hastings (TH0501)
Smith, Stratton, Wise, Heher & Brennan
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Princeton, New Jersey 08540
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Washington, D.C. 20005
(202) 962-4800

Attorneys for Plaintiff
Ortho-McNeil Pharmaceutical, Inc.

Michael J. Herbert (MJH 2750)
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Attorneys for Defendant
Barr Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-808

APPROVED LABELING

Labeling Approved December 29, 2003

75-808

Tri-Sprintec™
(norgestimate and ethinyl estradiol tablets-triphasic regimen)

Revised NOVEMBER 2002
31090180102
Rx only

BARR LABORATORIES, INC.

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION:

Tri-Sprintec™ Tablets are a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol.

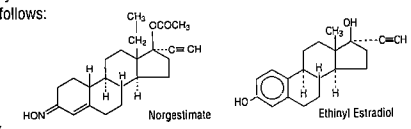
Each gray tablet contains 0.180 mg of the progestational compound, norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-oxime, (17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients include anhydrous lactose, lactose monohydrate, lake blend black LB 636 (ingredients include aluminum sulfate solution, aluminum-chloride solution, FD&C blue no. 2, FD&C red no. 40, FD&C yellow no. 6, sodium bicarbonate and sodium carbonate), magnesium stearate, and pregelatinized starch.

Each light blue tablet contains 0.215 mg of the progestational compound norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime, (17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients include anhydrous lactose, FD&C blue no. 2 aluminum lake, (ingredients include aluminum sulfate solution, aluminum-chloride solution, sodium bicarbonate and sodium carbonate), lactose monohydrate, magnesium stearate, and pregelatinized starch.

Each blue tablet contains 0.250 mg of the progestational compound norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients include anhydrous lactose, FD&C blue no. 2 aluminum lake, (ingredients include aluminum sulfate solution, aluminum-chloride solution, sodium bicarbonate and sodium carbonate), lactose monohydrate, magnesium stearate, and pregelatinized starch.

Each white tablet contains only inert ingredients as follows: anhydrous lactose, hydroxypropyl methylcellulose 2208, magnesium stearate, and microcrystalline cellulose.

The structural formula is as follows:



Norgestimate

Ethinyl Estradiol

CLINICAL PHARMACOLOGY:

Oral Contraception:

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor binding studies, as well as studies in animals and humans, have shown that norgestimate and 17-deacetyl norgestimate, the major serum metabolite, combine high progestational activity with minimal intrinsic androgenicity.[90-93]

Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in sex hormone binding globulin (SHBG), resulting in lower serum testosterone.[90,91,94]

Acne:

Acne is a skin condition with a multifactorial etiology. The combination of ethinyl estradiol and norgestimate may increase sex hormone binding globulin (SHBG) and decrease free testosterone resulting in a decrease in the severity of facial acne in otherwise healthy women with this skin condition.

Norgestimate and ethinyl estradiol are well absorbed following oral administration of *Tri-Sprintec*™. On the average, peak serum concentrations of norgestimate and ethinyl estradiol are observed within two hours (0.5-2.0 hr for norgestimate and 0.75-3.0 hr for ethinyl estradiol) after administration followed by a rapid decline due to distribution and elimination. Although norgestimate serum concentrations following single or multiple dosing were generally below assay detection within 5 hours, a major norgestimate serum metabolite, 17-deacetyl norgestimate, (which exhibits a serum half-life ranging from 12 to 30 hours) appears rapidly in serum with concentrations greatly exceeding that of norgestimate. The 17-deacetylated metabolite is pharmacologically active and the pharmacologic profile is similar to that of norgestimate. The elimination half-life of ethinyl estradiol ranged from approximately 6 to 14 hours.

Both norgestimate and ethinyl estradiol are extensively metabolized and eliminated by renal and fecal pathways. Following administration of ^{14}C-norgestimate, 47% (45-49%) and 37% (16-49%) of the administered radioactivity was eliminated in the urine and feces, respectively. Unchanged norgestimate was not detected in the urine. In addition to 17-deacetyl norgestimate, a number of metabolites of norgestimate have been identified in human urine following administration of radiolabeled norgestimate. These include 18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-hydroxy-13-ethyl,(17α)-(-);18,19-Dinor-5-17-pregnan-20-yn,3α,17-dihydroxy-13-ethyl,(17α), various hydroxylated metabolites and conjugates of these metabolites. Ethinyl estradiol is metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

INDICATIONS AND USAGE:

Tri-Sprintec™ Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Tri-Sprintec™ Tablets are indicated for the treatment of moderate acne vulgaris in females, ≥15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.

Oral contraceptives are highly effective. Table I lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE I: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR. UNITED STATES.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[3]
Method (1)	Typical Use[1] (2)	Perfect Use[2] (3)	(4)
Chance[4]	85	85	
Spermicides[5]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal[6]		2	
Post-Ovulation		1	
Withdrawal	19	4	
Cap[7]			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm[7]	20	6	56
Condom[8]			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Adapted from Hatcher et al., 1998 Ref. #1.

[1]Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

[2]Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

[3]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

[4]The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

[5]Foams, creams, gels, vaginal suppositories, and vaginal film.

[6]Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

[7]With spermicidal cream or jelly.

[8]Without spermicides.

In four clinical trials with norgestimate and ethinyl estradiol, the use-efficacy pregnancy rate ranged from 0.68 to 1.47 per 100 women-years. In total, 4,756 subjects completed 45,244 cycles and a total of 42 pregnancies were reported. This represents an overall use-efficacy rate of 1.21 per 100 women-years. One of these 4 studies was a randomized comparative clinical trial in which 4,633 subjects completed 22,312 cycles. Of the 2,312 patients on norgestimate and ethinyl estradiol, 8 pregnancies were reported. This represents an overall use-efficacy pregnancy rate of 0.94 per 100 women-years.

In two double-blind, placebo-controlled, six month, multicenter clinical trials, norgestimate and ethinyl estradiol showed a statistically significant decrease in inflammatory lesion count and total lesion count (TABLE II). The adverse reaction profile of norgestimate and ethinyl estradiol from these two controlled clinical trials is consistent with what has been noted from previous studies involving norgestimate and ethinyl estradiol and are the known risks associated with oral contraceptives.

TABLE II: Acne Vulgaris Indication
Combined Results: Two Multicenter, Placebo-Controlled Trials
Primary Efficacy Variables: Evaluable-for-Efficacy Population

	Norgestimate and Ethinyl Estradiol	Placebo
	N=163	**N=161**
Mean Age at Enrollment	27.3 years	28.0
Inflammatory Lesions - Mean Percent Reduction	56.6	36.6
Total Lesions - Mean Percent Reduction	49.6	30.3

CONTRAINDICATIONS:

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

- Thrombophlebitis or thromboembolic disorders.
- A past history of deep vein thrombophlebitis or thromboembolic disorders.
- Cerebral vascular or coronary artery disease.
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use.
- Hepatic adenomas or carcinomas.
- Known or suspected pregnancy.

WARNINGS:

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

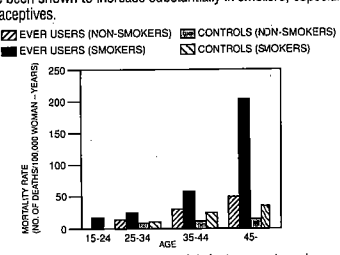
Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders and Other Vascular Problems:

a. Myocardial Infarction: An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six.[4-10] The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases.[11] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives.

TABLE III.
(Adapted from P.M. Layde and V. Beral, ref. #12.)



Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[14-18]

Oral contraceptives have been shown to increase blood pressure among users (see Section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Norgestimate has minimal androgenic activity (see CLINICAL PHARMACOLOGY), and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater[97].

b. Thromboembolism: An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.[2,3,19-24] Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization.[25] The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.[2]

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.[9] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[26] If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during any following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed or four weeks after a second trimester abortion.

c. Cerebrovascular diseases: 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. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke.[27-29]

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.[30] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who use oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.2 for normotensive users and 25.7 for users with severe hypertension.[30] The attributable risk is also greater in older women.

d. Dose-related risk of vascular disease from oral contraceptives: A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease.[31-33] A decline in serum high density lipoprotein (HDL) has been reported with many progestational agents.[14-16] A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the activity of the progestogen used in the contraceptives. The activity and amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen.

e. Persistence of risk of vascular disease: There are two studies which have shown persistence of risk of vascular disease for ever users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for five or more years, but the increased risk was not demonstrated in other age groups.[8] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small.[34] However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. Estimates of Mortality from Contraceptive Use:

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table IV). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke, and 40 and older women who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's.[35] Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

Of course, older women, as all women, who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

TABLE IV: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth-related
**Deaths are method-related

Adapted from H.W. Ory, ref. #35.

3. Carcinoma of the Reproductive Organs and Breasts:
Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. While there are conflicting reports, most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk has been reported to be related to duration of use.[36-44,79-89]

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.[95]

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[45-48] However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

4. Hepatic Neoplasia:
Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose.[49] Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.[50,51]

Studies have shown an increased risk of developing hepatocellular carcinoma[52-54,96] in oral contraceptive users. However, these cancers are rare in the U.S.

5. Ocular Lesions:
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. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. Oral Contraceptive Use Before or During Early Pregnancy:
Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.[56,57] The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned,[55,56,58,59] when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

7. Gallbladder Disease:
Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.[60,61] More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.[62-64] The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. Carbohydrate and Lipid Metabolic Effects:
Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users.[17] This effect has been shown to be directly related to estrogen dose.[65] Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[17,66] However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.[67] Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS, 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

In clinical studies with norgestimate and ethinyl estradiol there were no clinically significant changes in fasting blood glucose levels. Minimal statistically significant changes were noted in glucose levels over 24 cycles of use. Glucose tolerance tests showed no clinically significant changes from baseline to cycles 3, 12, and 24.

9. Elevated Blood Pressure:
An increase in blood pressure has been reported in women taking oral contraceptives[68] and this increase is more likely in older oral contraceptive users[69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

Women with a history of hypertension or hypertension-related diseases, or renal disease[70] should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.[68-71]

10. Headache:
The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. Bleeding Irregularities:
Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

12. Ectopic Pregnancy:
Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS:

1. Physical Examination and Follow Up:
It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. Lipid Disorders:
Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

3. Liver Function:
If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. Fluid Retention:
Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. Emotional Disorders:
Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. Contact Lenses:
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. Drug Interactions:
Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, carbamazepine, and possibly with griseofulvin, ampicillin and tetracyclines.[72]

8. Interactions with Laboratory Tests:
Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:
a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
c. Other binding proteins may be elevated in serum.
d. Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
e. High-density lipoprotein (HDL-C) and total cholesterol (Total-C) may be increased, low-density lipoprotein (LDL-C) may be increased or decreased, while LDL-C/HDL-C ratio may be decreased and triglycerides may be unchanged.
f. Glucose tolerance may be decreased.
g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. Carcinogenesis:
See WARNINGS section.

10. Pregnancy:
Pregnancy Category X: See CONTRAINDICATIONS and WARNINGS sections.

11. Nursing Mothers:
Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

12. Pediatric Use:
Safety and efficacy of Tri-Sprintec™ 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. Use of this product before menarche is not indicated.

13. Sexually Transmitted Diseases:
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

INFORMATION FOR THE PATIENT:
See Patient Labeling printed below.

ADVERSE REACTIONS:
An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (See WARNINGS section).

- Thrombophlebitis and venous thrombosis with or without embolism.
- Arterial thromboembolism.
- Pulmonary embolism.
- Myocardial infarction.
- Cerebral hemorrhage.
- Cerebral thrombosis.
- Hypertension.
- Gallbladder disease.
- Hepatic adenomas or benign liver tumors.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

- Nausea.
- Vomiting.
- Gastrointestinal symptoms (such as abdominal cramps and bloating).
- Breakthrough bleeding.
- Spotting.
- Change in menstrual flow.
- Amenorrhea.
- Temporary infertility after discontinuation of treatment.
- Edema.
- Melasma which may persist.
- Breast changes: tenderness, enlargement, secretion.
- Change in weight (increase or decrease).
- Change in cervical erosion and secretion.
- Diminution in lactation when given immediately postpartum.
- Cholestatic jaundice.
- Migraine.
- Rash (allergic).
- Mental depression.
- Reduced tolerance to carbohydrates.
- Vaginal candidiasis.
- Change in corneal curvature (steepening).
- Intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

- Pre-menstrual syndrome.
- Cataracts.
- Changes in appetite.
- Cystitis-like syndrome.
- Headache.
- Nervousness.
- Dizziness.
- Hirsutism.
- Loss of scalp hair.
- Erythema multiforme.
- Erythema nodosum.
- Hemorrhagic eruption.
- Vaginitis.
- Porphyria.
- Impaired renal function.
- Hemolytic uremic syndrome.
- Acne.
- Changes in libido.
- Colitis.
- Budd-Chiari Syndrome.

OVERDOSAGE:
Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS:
The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.[73-78]
Effects on menses:
- Increased menstrual cycle regularity.
- Decreased blood loss and decreased incidence of iron deficiency anemia.
- Decreased incidence of dysmenorrhea.

Effects related to inhibition of ovulation:
- Decreased incidence of functional ovarian cysts.
- Decreased incidence of ectopic pregnancies.

Other effects:
- Decreased incidence of fibroadenomas and fibrocystic disease of the breast.
- Decreased incidence of acute pelvic inflammatory disease.
- Decreased incidence of endometrial cancer.
- Decreased incidence of ovarian cancer.

DOSAGE AND ADMINISTRATION:

Oral Contraception:
To achieve maximum contraceptive effectiveness, Tri-Sprintec™ Tablets must be taken exactly as directed and at intervals not exceeding 24 hours. Tri-Sprintec™ Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided.

28-Day Regimen (Sunday Start):
When taking Tri-Sprintec™ 28 Tablets, the first tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first tablet should be taken that day. Take one active tablet daily for 21 days followed by one white tablet daily for 7 days. After 28 tablets have been taken, a new course is started the next day (Sunday). For the first cycle of a Sunday Start regimen, another method of contraception should be used until after the first seven consecutive days of administration.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should continue taking one tablet every day until Sunday. On Sunday the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling ("How to Take the Pill" section).

28-Day Regimen (Day 1 Start):
The dosage of Tri-Sprintec™ 28 Tablets, for the initial cycle of therapy is one active tablet administered daily from the 1st day through the 21st day of the menstrual cycle, counting the first day of menstrual flow as "Day 1" followed by one white tablet daily for 7 days. Tablets are taken without interruption for 28 days. After 28 tablets have been taken, a new course is started the next day.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling ("How to Take the Pill" section).

The use of Tri-Sprintec™ for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing Mothers.") The possibility of ovulation and conception prior to initiation of medication should be considered.

(See Discussion of Dose-Related Risk of Vascular Disease from Oral Contraceptives.)

ADDITIONAL INSTRUCTIONS FOR ALL DOSING REGIMENS:
Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of oral contraceptives in the event of a missed menstrual period:
1. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptive use should be discontinued until pregnancy is ruled out.
2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

Acne:
The timing of initiation of dosing with Tri-Sprintec™ for acne should follow the guidelines for use of Tri-Sprintec™ as an oral contraceptive. **Consult the DOSAGE AND ADMINISTRATION section for oral contraceptives.** The dosage regimen for Tri-Sprintec™ for treatment of facial acne, as available in the Blister Pack Tablet Dispenser, utilizes a 21-day active and a 7-day placebo schedule. Take one active tablet daily for 21 days followed by one white tablet for 7 days. After 28 tablets have been taken, a new course is started the next day.

(over)

HOW SUPPLIED:

Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets) 0.180mg/0.035 mg are gray, round, unscored tablets debossed with ɓ on one side and **985** on the other side; 0.215mg/0.035 mg are light blue, round, unscored tablets debossed with ɓ on one side and **986** on the other side; 0.250mg/0.035 mg are blue, round, unscored tablets debossed with ɓ on one side and **987** on the other side.

Tri-Sprintec™ **28** (norgestimate and ethinyl estradiol tablets) are packaged in cartons of six blister cards. Each card contains 28 tablets as follows: Each gray tablet contains 0.180 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each light blue tablet contains 0.215 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each blue tablet contains 0.250 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol, and the 7 white placebo tablets contain inert ingredients (Placebo tablets are white, round, unscored tablets, debossed with ɓ on one side and **143** on the other side). **(NDC 0555-9018-58)**.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

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BRIEF SUMMARY PATIENT PACKAGE INSERT

Oral contraceptives, also known as "birth-control pills" or "the pill", are taken to prevent pregnancy. *Tri-Sprintec*™ may also be taken to treat moderate acne in females who are able to use the pill. When taken correctly to prevent pregnancy, oral contraceptives have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be fatal or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, or malignant or benign liver tumors.

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics may decrease oral contraceptive effectiveness.

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

Taking the combination pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. Your pharmacist should have given you the detailed patient information labeling which gives you further information which you should read and discuss with your healthcare provider.

Tri-Sprintec™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. *Tri-Sprintec*™ tablets are also used to treat moderate acne in females who are able to take oral contraceptives.

Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DETAILED PATIENT LABELING

PLEASE NOTE: This labeling is revised from time to time as important new medical information becomes available. Therefore, please review this labeling carefully.

Tri-Sprintec™ Tablets: Each gray tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

INTRODUCTION:

Any woman who considers using oral contraceptives (the birth-control pill or the pill) should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your revisits. You should also follow your healthcare provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES FOR CONTRACEPTION

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

In comparison, typical failure rates for other nonsurgical methods of birth control during the first year of use are as follows:

Implant: <1%
Injection: <1%
IUD: 1 to 2%
Diaphragm with spermicides: 20%
Spermicides alone: 26%
Vaginal sponge: 20 to 40%
Female sterlization: <1%
Male sterlization: <1%
Cervical Cap with spermicides: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
Periodic abstinence: 25%
Withdrawal: 19%
No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES:

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

Tell your healthcare provider if you have ever had any of these conditions. Your healthcare provider can recommend a safer method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES:

Tell your healthcare provider if you have or have had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their healthcare provider if they choose to use oral contraceptives.

Also, be sure to inform your doctor or healthcare provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES:

1. Risk of developing blood clots:
Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for least four weeks after delivery if you are not breast-feeding or four weeks after a second trimester abortion. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast-Feeding in GENERAL PRECAUTIONS.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

2. Heart attacks and strokes:
Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. Gallbladder disease:
Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. Liver tumors:
In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

5. Cancer of the reproductive organs and breasts:
There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer.

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

ESTIMATED RISK OF DEATH FROM A BIRTH-CONTROL METHOD OR PREGNANCY:
All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related
**Deaths are method-related

In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of deathwas highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceed those for other methods of birth control. If a woman isover the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNALS:
If any of these adverse effects occur while you ae taking oral contraceptives, call your doctor immediately:
- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in tle leg)
- Crushing chest pain or heaviness in the chest(indicating a possible heart attack)
- Sudden severe headache or vomiting, dizzines or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stoke)
- Sudden partial or complete loss of vision (indcating a possible clot in the eye)
- Breast lumps (indicating possible breast cancr or fibrocystic disease of the breast; ask your doctor or healthcare provider to show you how to examine your beasts)
- Severe pain or tenderness in the stomach are (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energ, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicatingpossible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES:

1. Vaginal bleeding:
Irregular vaginal bleeding or spotting may occur wile you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding whichis a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, bulmay also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate an serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts formore than a few days, talk to your doctor or healthcare provider.

2. Contact lenses:
If you wear contact lenses and notice a changein vision or an inability to wear your lenses, contact your doctor or healthcare provider.

3. Fluid retention:
Oral contraceptives may cause edema (fluid retntion) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or healthcare provider.

4. Melasma:
A spotty darkening of the skin is possible, particularly of the face, which may persist.

5. Other side effects:
Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects bother you, call yourdoctor or healthcare provider.

GENERAL PRECAUTIONS:

1. Missed periods and use of oral contraceptives before or during early pregnancy:
There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your healthcare provider before doing so. If you hav not taken the pills daily as instructed and missed a menstrual period, you may be pregnant. If you missed two consecutive menstrual periods, you may be pregnant. Check with your healthcare provider immediately to determine whether youare pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use anotter method of contraception.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previous, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have notbeen seen in more recent studies. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

2. While breast-feeding:
If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, combination oral contraceptives may decrease the amount and quality of your milk. If possible, do not use combination oral contraceptives while breast-feeding. You should use another method of contraception since breast-feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting combination oral contraceptives only after you have weaned your child completely.

3. Laboratory tests:
If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

4. Drug Interactions:
Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually transmitted diseases:
Tri-Sprintec™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. *Tri-Sprintec*™ tablets are also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking your pills.
   Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
   On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

***BEFORE* YOU START TAKING YOUR PILLS**

1. DECIDE WHATTIME OF DAY YOU WANT TO TAKE YOUR PILL.
   It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 28 PILLS:
   The 28-pill packhas 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" white pills (without hormones).
   Tri-Sprintec™: There are 7 gray "active" pills, 7 light blue "active" pills, and 7 blue "active" pills.
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills
   CHECK PICTURE OF THE FOLD-OVER-DOSE CARD
   AND ADDITIONAL INSTRUCTIONS FOR USING
   THIS PACKAGE AT THE END OF THE BRIEF SUMMARY PATIENT PACKAGE INSERT
4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up method in case you miss pills.
   AN EXTRA, FULL PILL PACK

WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. *Tri-Sprintec*™ Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:
Take the first "active" gray pill of the first pack on the Sunday *after your period starts*, even if you are still bleeding.
If your period begins on Sunday, start the pack that same day.
Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:
1. Take the first "active" gray pill of the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
   Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
   Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**
   28 pills: Start the next pack on the day after your last "reminder" white pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** gray, light blue, or blue "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** gray or light blue "active" pills in a row in **WEEK 1** OR **WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3rd WEEK:**
1. **If you are a Sunday Starter:**
   Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** gray, light blue, or blue "active" pills in a row (during the first 3 weeks):
1. **If you are a Sunday Starter:**
   Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pill pack and start a new pack of pills that same day.
   If you are a DAY 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:

If you forget any of the 7 white "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking one pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE:
The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year if taken every day as directed, but more typical failure rates are about 3%. If failure does occur, the risk to the fetus is minimal.

PREGNANCY AFTER STOPPING THE PILL:
There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE:

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your healthcare provider or pharmacist.

OTHER INFORMATION:

Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your healthcare provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your healthcare provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES:

In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits. They are:

- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your doctor/healthcare provider or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The professional labeling is also published in a book entitled Physicians' Desk Reference, available in many book stores and public libraries.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised NOVEMBER 2002
BR-9018

808-SL

R4-02
07-0188

BARR LABORATORIES, INC.
Pomona, NY 10970

DEC 29 2003

DIRECTIONS FOR USE OF THIS STICKER:
The Tablet Dispenser indicates Sunday as the day you start your pills. If you are starting the pills on any other day but Sunday, peel the attached sticker by selecting the day you plan to start. Place the sticker over the pre-printed days of the week and make sure it lines up with the pills. This sticker will help to remind you to take your pill every day.

NOTICE: Oral contraceptives are intended to prevent pregnancy. They do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases.

SAT	SUN	MON	TUE	WED	THU	FRI
FRI	SAT	SUN	MON	TUE	WED	THU
THU	FRI	SAT	SUN	MON	TUE	WED
WED	THU	FRI	SAT	SUN	MON	TUE
TUE	WED	THU	FRI	SAT	SUN	MON
MON	TUE	WED	THU	FRI	SAT	SUN

APPROVED
DEC 29 2003

BARR LABORATORIES, INC.

COMBINATION DETAILED PATIENT LABELING AND BRIEF SUMMARY

Tri-Sprintec™ 28 Day Regimen

APPROVED
DEC 29 2003

(norgestimate and ethinyl estradiol tablets)
triphasic regimen

℞ only

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

31590180102
Revised NOVEMBER 2002

BARR LABORATORIES, INC.

DETAILED PATIENT LABELING

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PLEASE NOTE: This labeling is revised from time to time as important new medical information becomes available. Therefore, please review this labeling carefully.

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INTRODUCTION:

Any woman who considers using oral contraceptives (the birth-control pill or the pill) should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your revisits. You should also follow your healthcare provider's advice with regard to regular check-ups while you are on the pill.

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Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle. In comparison, typical failure rates for other non-surgical methods of birth control during the first year of use are as follows:

Implant: <1%
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IUD: 1 to 2%
Diaphragm with spermicides: 20%
Spermicides alone: 26%
Vaginal sponge: 20 to 40%
Female sterlization: <1%
Male sterlization: <1%
Cervical Cap with spermicides: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
Periodic abstinence: 25%
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No methods: 85%

APPROVED
DEC 29 2003

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

Tell your healthcare provider if you have ever had any of these conditions. Your healthcare provider can recommend a safer method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES:

Tell your healthcare provider if you have or have had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their healthcare provider if they choose to use oral contraceptives.

Also, be sure to inform your doctor or healthcare provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES:

1. Risk of developing blood clots:
Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for least four weeks after delivery if you are not breast-feeding or four weeks after a second trimester abortion. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast Feeding in GENERAL PRECAUTIONS.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 12,000 per year, whereas for users the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

2. Heart attacks and strokes:
Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. Gallbladder disease:
Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. Liver tumors:
In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

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5. Cancer of the reproductive organs and breasts:
There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer.

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

ESTIMATED RISK OF DEATH FROM A BIRTH-CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related
** Deaths are method-related

In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceed those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNALS:

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech,weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or healthcare provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES:

1. Vaginal bleeding:
Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or healthcare provider.

2. Contact lenses:
If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or healthcare provider.

3. Fluid retention:
Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or healthcare provider.

4. Melasma:
A spotty darkening of the skin is possible, particularly of the face, which may persist.

5. Other side effects:
Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects bother you, call your doctor or healthcare provider.

GENERAL PRECAUTIONS:

1. Missed periods and use of oral contraceptives before or during early pregnancy:
There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your healthcare provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, you may be pregnant. If you missed two consecutive menstrual periods, you may be pregnant. Check with your healthcare provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have not been seen in more recent studies. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

2. While breast-feeding:
If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, combination oral contraceptives may decrease the amount and quality of your milk. If possible, do not use combination oral contraceptives while breast-feeding. You should use another method of contraception since breast-feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting combination oral contraceptives only after you have weaned your child completely.

3. Laboratory tests:
If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

4. Drug Interactions:
Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for

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example, phenobarbital), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually transmitted diseases:
Tri-Sprintec™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. *Tri-Sprintec*™ tablets are also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.

2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 28 PILLS:
The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks, followed by 1 week of "reminder" white pills (without hormones).
Tri-Sprintec™: There are 7 gray "active" pills, 7 light blue "active" pills, and 7 blue "active" pills.

3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills
CHECK PICTURE OF THE FOLD-OVER-DOSE CARD AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE AT THE END OF THE BRIEF SUMMARY PATIENT PACKAGE INSERT.

4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up method in case you miss pills.
AN EXTRA, FULL PILL PACK

WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. *Tri-Sprintec*™ Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:

1. Take the first "active" gray pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:

1. Take the first "active" gray pill of the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea). Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
28 pills: Start the next pack on the day after your last "reminder" white pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** gray, light blue, or blue "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** gray or light blue "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3rd WEEK:**
1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** gray, light blue, or blue "active" pills in a row (during the first 3 weeks):
1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
If you are a DAY 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS

If you forget any of the 7 "reminder" white pills in Week 4:
THROW AWAY the pills you missed.
Keep taking one pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE:

The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are about 3%. If failure does occur, the risk to the fetus is minimal.

PREGNANCY AFTER STOPPING THE PILL:

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE:

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your healthcare provider or pharmacist.

OTHER INFORMATION:

Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your healthcare provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your healthcare provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES:

In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits. They are:
- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your doctor/healthcare provider or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The professional labeling is also published in a book entitled *Physicians' Desk Reference*, available in many book stores and public libraries.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised NOVEMBER 2002
PL-9018

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Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets-triphasic regimen)
28 Tablets

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets): Each gray tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

APPROVED DEC 29 2003

BRIEF SUMMARY
PATIENT PACKAGE INSERT

Rx only

Oral contraceptives, also known as "birth-control pills" or "the pill", are taken to prevent pregnancy. Tri-Sprintec™ may also be taken to treat moderate acne in females who are able to use the pill. When taken correctly to prevent pregnancy, oral contraceptives have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be fatal or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, or malignant or benign liver tumors.

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed patient labeling given to you with your supply of pills. Notify your doctor or healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics may decrease oral contraceptive effectiveness.

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

Taking the combination pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient labeling gives you further information which you should read and discuss with your healthcare provider.

Tri-Sprintec™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. Tri-Sprintec™ tablets are also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

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1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 28 PILLS:
The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" white pills (without hormones).
Tri-Sprintec™ : There are 7 gray "active pills", 7 light blue "active" pills, and 7 blue "active" pills.
3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills.
CHECK PICTURE OF THE FOLD-OVER-DOSE CARD AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE AT THE END OF THE BRIEF SUMMARY PATIENT PACKAGE INSERT.
4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up in case you miss pills.
AN EXTRA, FULL PILL PACK

WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. Tri-Sprintec™ Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

(Over)

SUNDAY START:
Take the first "active" gray pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:
Take the first "active" gray pill of the first pack during the *first 24 hours of your period.*
You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**
28 pills: Start the next pack on the day after your last "reminder" white pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** gray, light blue, or blue "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.
If you **MISS 2** gray or light blue "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT is you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.
If you **MISS 2** blue "active" pills in a row in **THE 3rd WEEK:**
1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.

If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.
If you **MISS 3 OR MORE** gray, light blue, or blue "active" pills in a row (during the first 3 weeks):
1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.

If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS

If you forget any of the 7 white "reminder" pills in WEEK 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method.

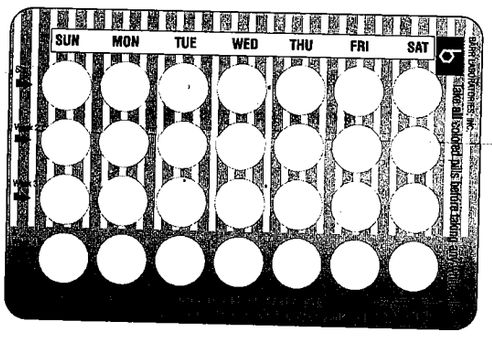
FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD anytime you have sex. KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

INFORMATION FOR PATIENTS
PLEASE READ ME!

There are two ways to start taking birth control pills, Sunday Start or Day 1 Start. Your healthcare provider will tell you which to use.

How to Use the Blister Cards for the 28 Tablets:
1. Pick the Days of the Week Sticker that starts the first day of your period. (This is the day you begin bleeding or spotting, even if it is midnight when bleeding begins.) When you have picked the right sticker, throw away the others and place the sticker on the blister card over the pre-printed days of the week and make sure it lines up with the pills.
2. Your blister package consists of three parts, the foil pouch, wallet, and a blister pack containing 28 individually sealed pills. Note that the pills are arranged in four numbered rows of 7 pills, with the pre-printed days of the week printed above them. There are 7 gray "active" pills, 7 light blue "active" pills, and 7 blue "active" birth control pills, and 7 white "reminder" pills. Refer to the sample of the blister card below:



3. After taking the last white pill, start a new blister card the **very next day** no matter when your period started. You will be taking a pill every day without interruption. Anytime you start the pills later than directed, protect yourself by using another method of birth control until you have taken a pill a day for seven consecutive days. After taking the last white pill, start taking the first gray pill from the blister card the very next day.
4. Take the pills in each new package as before. Start with the gray pill on row #1 and take one pill each day, left to right, until the last white pill has been taken.

THREE WAYS TO REMEMBER IN WHAT ORDER TO TAKE THE PILLS

1. Follow the sticker with the days of the week (placed above the pills).
2. Always go from left to right.
3. Always finish all your pills.

Side Effects:
Some side effects are normal and will go away after the first 1, 2 or 3 months as your body gets used to the pill. For more information on side effects, refer to this Brief Summary. The Detailed Patient Information Labeling that came with your pills, or ask your healthcare provider or pharmacist.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised NOVEMBER 2002
BS-9018

SUN MON TUE WED THU FRI SAT
Start
Week 2
Week 3
Week 4
Tri-Sprintec
(norgestimate and ethinyl estradiol tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
28 Day
BARR LABORATORIES, INC.
Take all colored pills before taking any white pills
R9-02
901801
SAMPLE
DEC 2 9 2009
EXP:
LOT:
BARR LABORATORIES, INC.
Pomona, NY 10970

93

Seal Line

Usual Dosage: One tablet daily as prescribed.
See enclosed package information.
Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

80857

N 3 05559 01858 3

Fold Line

NDC 0555-**9018**-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets– triphasic regimen)

28 DAY REGIMEN

Contents: One cyclic tablet dispenser of 28 tablets

Each gray tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

℞ only

THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

BARR LABORATORIES, INC.

SHAPING WOMEN'S HEALTH™
Barr Laboratories, Inc.

APPROVED
FEB 18 2002

Fold Line

BARR LABORATORIES, INC.
Pomona, NY 10970

READ PATIENT LABELING

If this is the first time you are taking birth control pills, wait until the day your period starts, then follow the instructions in the patient labeling. Make sure to check if you are a Sunday Start or Day 1 Start.

R9-02
2169018580101

SAMPLE

Seal Line

75-808

6 Blister Cards, 28 Tablets Each | 28 DAY REGIMEN

NDC 0555-9018-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets–triphasic regimen)

DEC 29 2009

APPROVED

℞ only

6 Blister Cards, 28 Tablets Each | 28 DAY REGIMEN

NDC 0555-9018-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets–triphasic regimen)

Contains 6 blister cards, each containing 28 tablets. Each gray tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

℞ only

THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

BARR LABORATORIES, INC.

SHAPING WOMEN'S HEALTH™ Barr Laboratories, Inc.

N3 05559 01858 3

LOT:

EXP:

2149018580102 R11-02

6 Blister Cards, 28 Tablets Each | 28 DAY REGIMEN

NDC 0555-9018-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets–triphasic regimen)

6 Blister Cards, 28 Tablets Each | 28 DAY REGIMEN

NDC 0555-9018-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets–triphasic regimen)

Usual Dosage: One tablet daily for 28 consecutive days per menstrual cycle as prescribed. See enclosed package information.

℞ only

To the Dispenser: This carton contains one combination labeling piece of information intended for the patient. Informational pieces are to be provided to the patient with each prescription.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

BARR LABORATORIES, INC.
Pomona, NY 10970

BARR LABORATORIES, INC.

SHAPING WOMEN'S HEALTH™
Barr Laboratories, Inc.

Labeling Approved December 18, 2002

Tri-Sprintec™
(norgestimate and ethinyl estradiol tablets-triphasic regimen)

SAMPLE

Revised SEPTEMBER 2002
31090180101

Rx only

BARR LABORATORIES, INC.

DEC 18 2002

APPROVED

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION:

Tri-Sprintec™ Tablets are a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol.

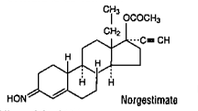
Each gray tablet contains 0.180 mg of the progestational compound, norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-oxime, (17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients include anhydrous lactose, lactose monohydrate, lake blend black LB 636 (ingredients include aluminum sulfate solution, aluminum-chloride solution, FD&C blue no. 2, FD&C red no. 40, FD&C yellow no. 6, sodium bicarbonate and sodium carbonate), magnesium stearate, and pregelatinized starch.

Each light blue tablet contains 0.215 mg of the progestational compound norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime, (17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients include anhydrous lactose, FD&C blue no. 2 aluminum lake, (ingredients include aluminum sulfate solution, aluminum-chloride solution, sodium bicarbonate and sodium carbonate), lactose monohydrate, magnesium stearate, and pregelatinized starch.

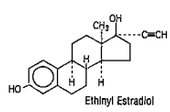
Each blue tablet contains 0.250 mg of the progestational compound norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients include anhydrous lactose, FD&C blue no. 2 aluminum lake, (ingredients include aluminum sulfate solution, aluminum-chloride solution, sodium bicarbonate and sodium carbonate), lactose monohydrate, magnesium stearate, and pregelatinized starch.

Each white tablet contains only inert ingredients as follows: anhydrous lactose, hydroxypropyl methylcellulose 2208, magnesium stearate, and microcrystalline cellulose.

The structural formula is as follows:



Norgestimate



Ethinyl Estradiol

CLINICAL PHARMACOLOGY:

Oral Contraception:

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor binding studies, as well as studies in animals and humans, have shown that norgestimate and 17-deacetyl norgestimate, the major serum metabolite, combine high progestational activity with minimal intrinsic androgenicity.[90-93]

Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in sex hormone binding globulin (SHBG), resulting in lower serum testosterone.[90,91,94]

Acne:

Acne is a skin condition with a multifactorial etiology. The combination of ethinyl estradiol and norgestimate may increase sex hormone binding globulin (SHBG) and decrease free testosterone resulting in a decrease in the severity of facial acne on otherwise healthy women with this skin condition.

Norgestimate and ethinyl estradiol are well absorbed following oral administr tion of **Tri-Sprintec™**. On the average, peak serum concentrations of norgestimate ar ethinyl estradiol are observed within two hours (0.5-2.0 hr for norgestimate and 0.75-3.0 hr ethinyl estradiol) after administration followed by a rapid decline due to distribution and e ation. Although norgestimate serum concentrations following single or multiple dosing wei nerally below assay detection within 5 hours, a major norgestimate serum metabolite, 17-deacetyl norgestimate, (which exhibits a serum half-life ranging from 12 to 30 hours) appears rapidly in serum with concentrations greatly exceeding that of norgestimate. The 17-deacetylated metabolite is pharmacologically active and the pharmacologic profile is similar to that of norgestimate. The elimination half-life of ethinyl estradiol ranged from approximately 6 to 14 hours.

Both norgestimate and ethinyl estradiol are extensively metabolized and eliminated by renal and fecal pathways. Following administration of ^{14}C-norgestimate, 47% (45-49%) and 37% (16-49%) of the administered radioactivity was eliminated in the urine and feces, respectively. Unchanged norgestimate was not detected in the urine. In addition to 17-deacetyl norgestimate, a number of metabolites of norgestimate have been identified in human urine following administration of radiolabeled norgestimate. These include 18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-hydroxy-13-ethyl,(17α)-(-);18,19-Dinor-5-17-pregnan-20-yn,3α,17-dihydroxy-13-ethyl,(17α), various hydroxylated metabolites and conjugates of these metabolites. Ethinyl estradiol is metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

INDICATIONS AND USAGE:

Tri-Sprintec™ Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Tri-Sprintec™ Tablets are indicated for the treatment of moderate acne vulgaris in females, ≥15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.

Oral contraceptives are highly effective. Table I lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE I: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR. UNITED STATES.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[3]
Method (1)	Typical Use[1] (2)	Perfect Use[2] (3)	(4)
Chance[4]	85	85	
Spermicides[5]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal[6]		2	
Post-Ovulation		1	
Withdrawal	19	4	
Cap[7]			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm[7]	20	6	56
Condom[8]			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Adapted from Hatcher et al., 1998 Ref. #1.

[1]Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experienc an accidental pregnancy during the first year if they do not stop use for any other reason.

[2]Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consis tently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not sto use for any other reason.

[3]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

[4]The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception i not used and from women who cease using contraception in order to become pregnant. Among such population about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent wh would become pregnant within one year among women now relying on reversible methods of contraception if the abandoned contraception altogether.

[5]Foams, creams, gels, vaginal suppositories, and vaginal film.

[6]Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in th post-ovulatory phases.

[7]With spermicidal cream or jelly.

[8]Without spermicides.

In four clinical trials with norgestimate and ethinyl estradiol, the use-efficacy pregnancy rate ranged from 0.68 to 1.4 per 100 women-years. In total, 4,756 subjects completed 45,244 cycles and a total of 42 pregnancies were reporte This represents an overall use-efficacy rate of 1.21 per 100 women-years. One of these 4 studies was a randomize comparitive clinical trial in which 4,633 subjects completed 22,312 cycles. Of the 2,312 patients on norgestimate an ethinyl estradiol, 8 pregnancies were reported. This represents an overall use-efficacy pregnancy rate of 0.94 per 10 women-years.

In two double-blind, placebo-controlled, six month, multicenter clinical trials, norgestimate and ethinyl estradic showed a statistically significant decrease in inflammatory lesion count and total lesion count (TABLE II). The advers reaction profile of norgestimate and ethinyl estradiol from these two controlled clinical trials is consistent with wha has been noted from previous studies involving norgestimate and ethinyl estradiol and are the known risks associat ed with oral contraceptives.

TABLE II: Acne Vulgaris Indication
Combined Results: Two Multicenter, Placebo-Controlled Trials
Primary Efficacy Variables: Evaluable-for-Efficacy Population

	Norgestimate and Ethinyl Estradiol	Placebo
	N=163	N=161
Mean Age at Enrollment	27.3 years	28.0
Inflammatory Lesions - Mean Percent Reduction	56.6	36.6
Total Lesions - Mean Percent Reduction	49.6	30.3

CONTRAINDICATIONS:

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

- Thrombophlebitis or thromboembolic disorders.
- A past history of deep vein thrombophlebitis or thromboembolic disorders.
- Cerebral vascular or coronary artery disease.
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use.
- Hepatic adenomas or carcinomas.
- Known or suspected pregnancy.

WARNINGS:

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

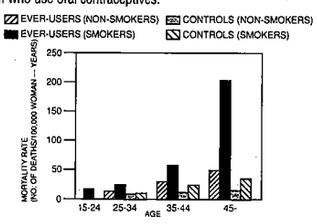
Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders and Other Vascular Problems:

a. Myocardial Infarction: An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six.[4-10] The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases.[11] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives.

TABLE III.
(Adapted from P.M. Layde and V. Beral, ref. #12.)



Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[14-16]

Oral contraceptives have been shown to increase blood pressure among users (see Section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Norgestimate has minimal androgenic activity (see **CLINICAL PHARMACOLOGY**), and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater[97].

b. Thromboembolism: An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.[2,3,19-24] Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization.[25] The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.[2]

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.[9] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[26] If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed or four weeks after a second trimester abortion.

c. Cerebrovascular diseases: 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. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke.[27-29]

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.[30] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension.[30] The attributable risk is also greater in older women.[3]

d. Dose-related risk of vascular disease from oral contraceptives: A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease.[31-33] A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents.[14-16] A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the activity of the progestogen used in the contraceptives. The activity and amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen.

e. Persistence of risk of vascular disease: There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups.[8] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small.[34] However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. Estimates of Mortality from Contraceptive Use:
One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table IV). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's.[35] Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

Of course, older women, as all women, who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

TABLE IV: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth-related
**Deaths are method-related

Adapted from H.W. Ory, ref. #35.

3. Carcinoma of the Reproductive Organs and Breasts:
Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. While there are conflicting reports, most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk has been reported to be related to duration of use.[36-44,79-89]

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.[95]

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[45-48] However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

4. Hepatic Neoplasia:
Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose.[49] Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.[50,51]

Studies have shown an increased risk of developing hepatocellular carcinoma[52-54,96] in oral contraceptive users. However, these cancers are rare in the U.S.

5. Ocular Lesions:
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. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. Oral Contraceptive Use Before or During Early Pregnancy:
Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.[56,57] The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned,[55,56,58,59] when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

7. Gallbladder Disease:
Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.[60,61] More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.[62-64] The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. Carbohydrate and Lipid Metabolic Effects:
Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users.[17] This effect has been shown to be directly related to estrogen dose.[65] Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[17,66] However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.[67] Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS, 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

In clinical studies with norgestimate and ethinyl estradiol there were no clinically significant changes in fasting blood glucose levels. Minimal statistically significant changes were noted in glucose levels over 24 cycles of use. Glucose tolerance tests showed no clinically insignificant changes from baseline to cycles 3, 12, and 24.

9. Elevated Blood Pressure:
An increase in blood pressure has been reported in women taking oral contraceptives[68] and this increase is more likely in older oral contraceptive users[69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

Women with a history of hypertension or hypertension-related diseases, or renal disease[70] should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.[68-71]

10. Headache:
The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. Bleeding Irregularities:
Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

12. Ectopic Pregnancy:
Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS:

1. Physical Examination and Follow Up:
It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. Lipid Disorders:
Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

3. Liver Function:
If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. Fluid Retention:
Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. Emotional Disorders:
Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. Contact Lenses:
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. Drug Interactions:
Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, carbamazepine, and possibly with griseofulvin, ampicillin and tetracyclines.[72]

8. Interactions with Laboratory Tests:
Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:
a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
c. Other binding proteins may be elevated in serum.
d. Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
e. High-density lipoprotein (HDL-C) and total cholesterol (Total-C) may be increased, low-density lipoprotein (LDL-C) may be increased or decreased, while LDL-C/HDL-C ratio may be decreased and triglycerides may be unchanged.
f. Glucose tolerance may be decreased.
g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. Carcinogenesis:
See WARNINGS section.

10. Pregnancy:
Pregnancy Category X: See CONTRAINDICATIONS and WARNINGS sections.

11. Nursing Mothers:
Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

12. Pediatric Use:
Safety and efficacy of **Tri-Sprintec™** 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. Use of this product before menarche is not indicated.

13. Sexually Transmitted Diseases:
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

INFORMATION FOR THE PATIENT:
See Patient Labeling printed below.

ADVERSE REACTIONS:
An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (See WARNINGS section).

- Thrombophlebitis and venous thrombosis with or without embolism.
- Arterial thromboembolism.
- Pulmonary embolism.
- Myocardial infarction.
- Cerebral hemorrhage.
- Cerebral thrombosis.
- Hypertension.
- Gallbladder disease.
- Hepatic adenomas or benign liver tumors.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

- Nausea.
- Vomiting.
- Gastrointestinal symptoms (such as abdominal cramps and bloating).
- Breakthrough bleeding.
- Spotting.
- Change in menstrual flow.
- Amenorrhea.
- Temporary infertility after discontinuation of treatment.
- Edema.
- Melasma which may persist.
- Breast changes: tenderness, enlargement, secretion.
- Change in weight (increase or decrease).
- Change in cervical erosion and secretion.
- Diminution in lactation when given immediately postpartum.
- Cholestatic jaundice.
- Migraine.
- Rash (allergic).
- Mental depression.
- Reduced tolerance to carbohydrates.
- Vaginal candidiasis.
- Change in corneal curvature (steepening).
- Intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

- Pre-menstrual syndrome.
- Cataracts.
- Changes in appetite.
- Cystitis-like syndrome.
- Headache.
- Nervousness.
- Dizziness.
- Hirsutism.
- Loss of scalp hair.
- Erythema multiforme.
- Erythema nodosum.
- Hemorrhagic eruption.
- Vaginitis.
- Porphyria.
- Impaired renal function.
- Hemolytic uremic syndrome.
- Acne.
- Changes in libido.
- Colitis.
- Budd-Chiari Syndrome.

OVERDOSAGE:
Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS:
The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.[73-78]

Effects on menses:
- Increased menstrual cycle regularity.
- Decreased blood loss and decreased incidence of iron deficiency anemia.
- Decreased incidence of dysmenorrhea.

Effects related to inhibition of ovulation:
- Decreased incidence of functional ovarian cysts.
- Decreased incidence of ectopic pregnancies.

Other effects:
- Decreased incidence of fibroadenomas and fibrocystic disease of the breast.
- Decreased incidence of acute pelvic inflammatory disease.
- Decreased incidence of endometrial cancer.
- Decreased incidence of ovarian cancer.

DOSAGE AND ADMINISTRATION:

Oral Contraception:
To achieve maximum contraceptive effectiveness, **Tri-Sprintec™** Tablets must be taken exactly as directed and at intervals not exceeding 24 hours. **Tri-Sprintec™** Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided.

28-Day Regimen (Sunday Start):
When taking **Tri-Sprintec™** 28 Tablets, the first tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first tablet should be taken that day. Take one active tablet daily for 21 days followed by one white tablet daily for 7 days. After 28 tablets have been taken, a new course is started the next day (Sunday). For the first cycle of a Sunday Start regimen, another method of contraception should be used until after the first seven consecutive days of administration.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should continue taking one tablet every day until Sunday. On Sunday the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling ("How to Take the Pill" section).

28-Day Regimen (Day 1 Start):
The dosage of **Tri-Sprintec™** 28 Tablets, for the initial cycle of therapy is one active tablet administered daily from the 1st day through the 21st day of the menstrual cycle, counting the first day of menstrual flow as "Day 1" followed by one white tablet daily for 7 days. Tablets are taken without interruption for 28 days. After 28 tablets have been taken, a new course is started the next day.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling ("How to Take the Pill" section).

The use of **Tri-Sprintec™** for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing Mothers.") The possibility of ovulation and conception prior to initiation of medication should be considered.

(See Discussion of Dose-Related Risk of Vascular Disease from Oral Contraceptives.)

ADDITIONAL INSTRUCTIONS FOR ALL DOSING REGIMENS:
Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of oral contraceptives in the event of a missed menstrual period:
1. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptive use should be discontinued until pregnancy is ruled out.
2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

Acne:
The timing of initiation of dosing with **Tri-Sprintec™** for acne should follow the guidelines for use of **Tri-Sprintec™** as an oral contraceptive. Consult the **DOSAGE AND ADMINISTRATION** section for oral contraceptives. The dosage regimen for **Tri-Sprintec™** for treatment of facial acne, as available in the Blister Pack Tablet Dispenser, utilizes a 21-day active and a 7-day placebo schedule. Take one active tablet daily for 21 days followed by one white tablet for 7 days. After 28 tablets have been taken, a new course is started the next day.

HOW SUPPLIED:
Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets) 0.180mg/0.035 mg are gray, round, unscored tablets debossed with ɓ on one side and **985** on the other side; 0.215mg/0.035 mg are light blue, round, unscored tablets debossed with ɓ on one side and **986** on the other side; 0.250mg/0.035 mg are blue, round, unscored tablets debossed with ɓ on one side and **987** on the other side.

Tri-Sprintec™ 28 (norgestimate and ethinyl estradiol tablets) are packaged in cartons of six blister cards. Each card contains 28 tablets as follows: 7 gray tablets, 7 light blue tablets, 7 blue tablets as described under the **Tri-Sprintec™ 21** listed above, and the 7 white tablets contain inert ingredients (Placebo tablets are round, unscored tablets, debossed with ɓ on one side and **143** on the other side). **(NDC 0555-9018-58).**

Store at controlled room temperature 15º-30ºC (59º-86ºF) [See USP].

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BRIEF SUMMARY PATIENT PACKAGE INSERT

Oral contraceptives, also known as "birth-control pills" or "the pill", are taken to prevent pregnancy. **Tri-Sprintec™** may also be taken to treat moderate acne in females who are able to use the pill. When taken correctly to prevent pregnancy, oral contraceptives have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be fatal or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, or malig-nant or benign liver tumors.

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics may decrease oral contraceptive effectiveness.

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

Taking the combination pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. Your pharmacist should have given you the detailed patient information labeling which gives you further information which you should read and discuss with your healthcare provider.

Tri-Sprintec™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. **Tri-Sprintec™** tablets are also used to treat moderate acne in females who are able to take oral contraceptives.

Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DETAILED PATIENT LABELING

PLEASE NOTE: This labeling is revised from time to time as important new medical information becomes available. Therefore, please review this labeling carefully.

Tri-Sprintec™ Tablets: Each gray tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

INTRODUCTION:

Any woman who considers using oral contraceptives (the birth-control pill or the pill) should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your revisits. You should also follow your healthcare provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES FOR CONTRACEPTION

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

In comparison, typical failure rates for other nonsurgical methods of birth control during the first year of use are as follows:

Implant: <1%
Injection: <1%
IUD: 1 to 2%
Diaphragm with spermicides: 20%
Spermicides alone: 26%
Vaginal sponge: 20 to 40%
Female sterlization: <1%
Male sterlization: <1%
Cervical Cap with spermicides: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
Periodic abstinence: 25%
Withdrawal: 19%
No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES:

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have had any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

Tell your healthcare provider if you have ever had any of these conditions. Your healthcare provider can recommend another method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES:

Tell your healthcare provider if you have or have had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their healthcare provider if they choose to use oral contraceptives.

Also, be sure to inform your doctor or healthcare provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES:

1. Risk of developing blood clots:

Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for least four weeks after delivery if you are not breast-feeding or four weeks after a second trimester abortion. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast-Feeding in GENERAL PRECAUTIONS.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

2. Heart attacks and strokes:

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. Gallbladder disease:

Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. Liver tumors:

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

5. Cancer of the reproductive organs and breasts:
There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer.

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

ESTIMATED RISK OF DEATH FROM BIRTH-CONTROL METHOD OR PREGNANCY:
All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth-related
**Deaths are method-related
Adapted from H.W.Ory. ref#35.

In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceed those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNALS:
If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:
- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or healthcare provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES:
1. Vaginal bleeding:
Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or healthcare provider.

2. Contact lenses:
If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or healthcare provider.

3. Fluid retention:
Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or healthcare provider.

4. Melasma:
A spotty darkening of the skin is possible, particularly of the face, which may persist.

5. Other side effects:
Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects bother you, call your doctor or healthcare provider.

GENERAL PRECAUTIONS:
1. Missed periods and use of oral contraceptives before or during early pregnancy:
There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your healthcare provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, you may be pregnant. If you missed two consecutive menstrual periods, you may be pregnant. Check with your healthcare provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have not been seen in more recent studies. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

2. While breast-feeding:
If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, combination oral contraceptives may decrease the amount and quality of your milk. If possible, do not use combination oral contraceptives while breast-feeding. You should use another method of contraception since breast-feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting combination oral contraceptives only after you have weaned your child completely.

3. Laboratory tests:
If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

4. Drug Interactions:
Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually transmitted diseases:
Tri-Sprintec™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. **Tri-Sprintec™** tablets are also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking your pills.
   Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
   It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 28 PILLS:
   The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" white pills (without hormones).
   Tri-Sprintec™: There are 7 gray "active" pills, 7 light blue "active" pills, and 7 blue "active" pills.
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills
   CHECK PICTURE OF THE FOLD-OVER-DOSE CARD
   AND ADDITIONAL INSTRUCTIONS FOR USING
   THIS PACKAGE AT THE END OF THE BRIEF SUMMARY.
4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up method in case you miss pills.
   AN EXTRA, FULL PILL PACK

WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. **Tri-Sprintec™** Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:
Take the first "active" gray pill of the first pack on the Sunday *after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:
1. Take the first "active" gray pill of the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
   Do not skip pills if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea). Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**
   28 pills: Start the next pack on the day after your last "reminder" white pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** gray, light blue, or blue "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** gray or light blue "active" pills in a row in **WEEK 1** OR **WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as back-up for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3rd WEEK:**
1. **If you are a Sunday Starter:**
   Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 3 OR MORE** gray, light blue, or blue "active" pills in a row (during the first 3 weeks):
1. **If you are a Sunday Starter:**
   Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pill pack and start a new pack of pills that same day.
   If you are a DAY 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:

If you forget any of the 7 white "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking one pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE:
The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are about 3%. If failure does occur, the risk to the fetus is minimal.

PREGNANCY AFTER STOPPING THE PILL:
There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE:
Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your healthcare provider or pharmacist.

OTHER INFORMATION:
Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your healthcare provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your healthcare provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES:
In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits. They are:
- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your doctor/healthcare provider or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The professional labeling is also published in a book entitled Physicians' Desk Reference, available in many book stores and public libraries.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised SEPTEMBER 2002
BR-9018

SAMPLE

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets-triphasic regimen)
28 Tablets

Revised SEPTEMBER 2002
31590180101

Rx only

COMBINATION BRIEF SUMMARY
AND PATIENT PACKAGE INSERT

BARR LABORATORIES, INC.

APPROVED

DEC 18

DETAILED PATIENT LABELING

Rx only

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PLEASE NOTE: This labeling is revised from time to time as important new medical information becomes available. Therefore, please review this labeling carefully.

Tri-Sprintec™ Tablets: Each gray tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

INTRODUCTION:

Any woman who considers using oral contraceptives (the birth-control pill or the pill) should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your revisits. You should also follow your healthcare provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES FOR CONTRACEPTION:

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle. In comparison, typical failure rates for other non-surgical methods of birth control during the first year of use are as follows:
Implant: <1%
Injection: <1%
IUD: 1 to 2%
Diaphragm with spermicides: 20%
Spermicides alone: 26%
Vaginal sponge: 20 to 40%
Female sterlization: <1%
Male sterlization: <1%
Cervical Cap with spermicides: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
Periodic abstinence: 25%
Withdrawal: 19%
No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have had any of the following conditions:
- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

Tell your healthcare provider if you have ever had any of these conditions. Your healthcare provider can recommend another method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES:

Tell your healthcare provider if you have or have had:
- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their healthcare provider if they choose to use oral contraceptives.

Also, be sure to inform your doctor or healthcare provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES:

1. Risk of developing blood clots:
Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for least four weeks after delivery if you are not breast-feeding or four weeks after a second trimester abortion. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast Feeding in GENERAL PRECAUTIONS.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 12,000 per year, whereas for users the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

2. Heart attacks and strokes:
Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. Gallbladder disease:
Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. Liver tumors:
In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

5. Cancer of the reproductive organs and breasts:
There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer.

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

ESTIMATED RISK OF DEATH FROM BIRTH-CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related
**Deaths are method-related
Adapted from H.W.Ory. ref#35.

In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceed those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNALS:

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or healthcare provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES:

1. Vaginal bleeding:
Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or healthcare provider.

2. Contact lenses:
If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or healthcare provider.

3. Fluid retention:
Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or healthcare provider.

4. Melasma:
A spotty darkening of the skin is possible, particularly of the face, which may persist.

5. Other side effects:
Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects bother you, call your doctor or healthcare provider.

GENERAL PRECAUTIONS:

1. Missed periods and use of oral contraceptives before or during early pregnancy:
There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your healthcare provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, you may be pregnant. If you missed two consecutive menstrual periods, you may be pregnant. Check with your healthcare provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have not been seen in more recent studies. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

2. While breast-feeding:
If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, combination oral contraceptives may decrease the amount and quality of your milk. If possible, do not use combination oral contraceptives while breast-feeding. You should use another method of contraception since breast-feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting combination oral contraceptives only after you have weaned your child completely.

3. Laboratory tests:
If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

4. Drug Interactions:
Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually transmitted diseases:
Tri-Sprintec™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. **Tri-Sprintec™** tablets are also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME. If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

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6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.

2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 28 PILLS:
The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks, followed by 1 week of "reminder" white pills (without hormones).
Tri-Sprintec™: There are 7 gray "active" pills, 7 light blue "active" pills, and 7 blue "active" pills.

3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills
CHECK PICTURE OF THE FOLD-OVER-DOSE CARD AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE AT THE END OF THE BRIEF SUMMARY.

4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up method in case you miss pills.
AN EXTRA, FULL PILL PACK

WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. **Tri-Sprintec™** Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:

1. Take the first "active" gray pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:

1. Take the first "active" gray pill of the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
Do not skip pills if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea). Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
28 pills: Start the next pack on the day after your last "reminder" white pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** gray, light blue, or blue "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** gray or light blue "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as back-up for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3rd WEEK:**

1. **If you are a Sunday Starter:**

Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.

If you are a Day 1 Starter:

THROW OUT the rest of the pill pack and start a new pack that same day.

2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 3 OR MORE** gray, light blue, or blue "active" pills in a row (during the first 3 weeks):

1. **If you are a Sunday Starter:**

Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.

If you are a DAY 1 Starter:

THROW OUT the rest of the pill pack and start a new pack that same day.

2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS

If you forget any of the 7 "reminder" white pills in Week 4:
THROW AWAY the pills you missed.
Keep taking one pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE:

The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are about 3%. If failure does occur, the risk to the fetus is minimal.

PREGNANCY AFTER STOPPING THE PILL:

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE:

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your healthcare provider or pharmacist.

OTHER INFORMATION:

Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your healthcare provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your healthcare provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES:

In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits. They are:

- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your doctor/healthcare provider or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The professional labeling is also published in a book entitled *Physicians' Desk Reference*, available in many book stores and public libraries.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised SEPTEMBER 2002
PL-9018

Tear here at perforation.

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets-triphasic regimen)
28 Tablets

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets): Each gray tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

BIEF SUMMARY
PATIET PACKAGE INSERT

Rx only

Oral contraceptives, also known as "birth-control pills" or "the pill", are taken to prevent pregnancy. **Tri-Sprintec™** may also be taken to treat moderate acne in females who are able to use the pill. When taken correctly to prevent pregnancy, oral contraceptives have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be fatal or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, or malignant or benign liver tumors.

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed patient labeling given to you with your supply of pills. Notify your doctor or healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics may decrease oral contraceptive effectiveness.

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

Taking the combination pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient labeling gives you further information which you should read and discuss with your healthcare provider.

Tri-Sprintec™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. **Tri-Sprintec™** tablets are also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME. If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 28 PILLS:
The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" white pills (without hormones).
Tri-Sprintec™: There are 7 gray "active pills", 7 light blue "active" pills, and 7 blue "active" pills.
3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills.
CHECK PICTURE OF THE FOLD-OVER-DOSE CARD AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE AT THE END OF THE BRIEF SUMMARY.
4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up in case you miss pills.
AN EXTRA, FULL PILL PACK

WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. **Tri-Sprintec™** Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:
Take the first "active" gray pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:
Take the first "active" gray pill of the first pack during the *first 24 hours of your period.*
You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**
28 pills: Start the next pack on the day after your last "reminder" white pill. Do not wait any days between packs.

(Over)

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** gray, light blue, or blue "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** gray or light blue "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT is you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3rd WEEK:**

1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.

If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a newpack that same day.
2. You may not have your period this month but thisis expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 3 OR MORE** gray, light blue, or blue "active" pills in a row (during the first 3 weeks):
1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.

If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS

If you forget any of the 7 white "reminder" pills in WEEK 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

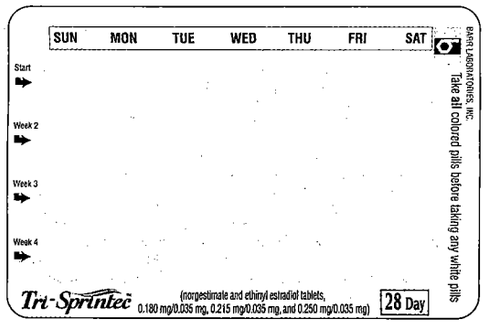
Use a BACK-UP METHOD anytime you have sex. KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

INFORMATION FOR PATIENTS
PLEASE READ ME!

There are two ways to start taking birth control pills, Sunday Start or Day 1 Start. Your healthcare provider will tell you which to use.

How to Use the Blister Cards for the 28 Tablets:

1. Pick the Days of the Week Sticker that starts the first day of your period. (This is the day you begin bleeding or spotting, even if it is midnight when bleeding begins.) When you have picked the right sticker, throw away the others and place the sticker on the blister card over the pre-printed days of the week and make sure it lines up with the pills.
2. Your blister package consists of three parts, the foil pouch, wallet, and a blister pack containing 28 individually sealed pills. Note that the pills are arranged in four numbered rows of 7 pills, with the pre-printed days of the week printed above them. There are 7 gray "active" pills, 7 light blue "active" pills, and 7 blue "active" birth control pills, and 7 white "reminder" pills. Refer to the sample of the blister card below:



3. After taking the last white pill, start a new blister card the **very next day** no matter when your period started. You will be taking a pill every day without interruption. Anytime you start the pills later than directed, protect yourself by using another method of birth control until you have taken a pill a day for seven consecutive days. After taking the last white pill, start taking the first gray pill from the blister card the very next day.
4. Take the pills in each new package as before. Start with the gray pill on row #1 and take one pill each day, left to right, until the last white pill has been taken.

THREE WAYS TO REMEMBER IN WHAT ORDER TO TAKE THE PILLS

1. Follow the sticker with the days of the week (placed above the pills).
2. Always go from left to right.
3. Always finish all your pills.

Side Effects:
Some side effects are normal and will go away after the first 1, 2 or 3 months as your body gets used to the pill. For more information on side effects, refer to this Brief Summary. The Detailed Patient Information Labeling that came with your pills, or ask your healthcare provider or pharmacist.

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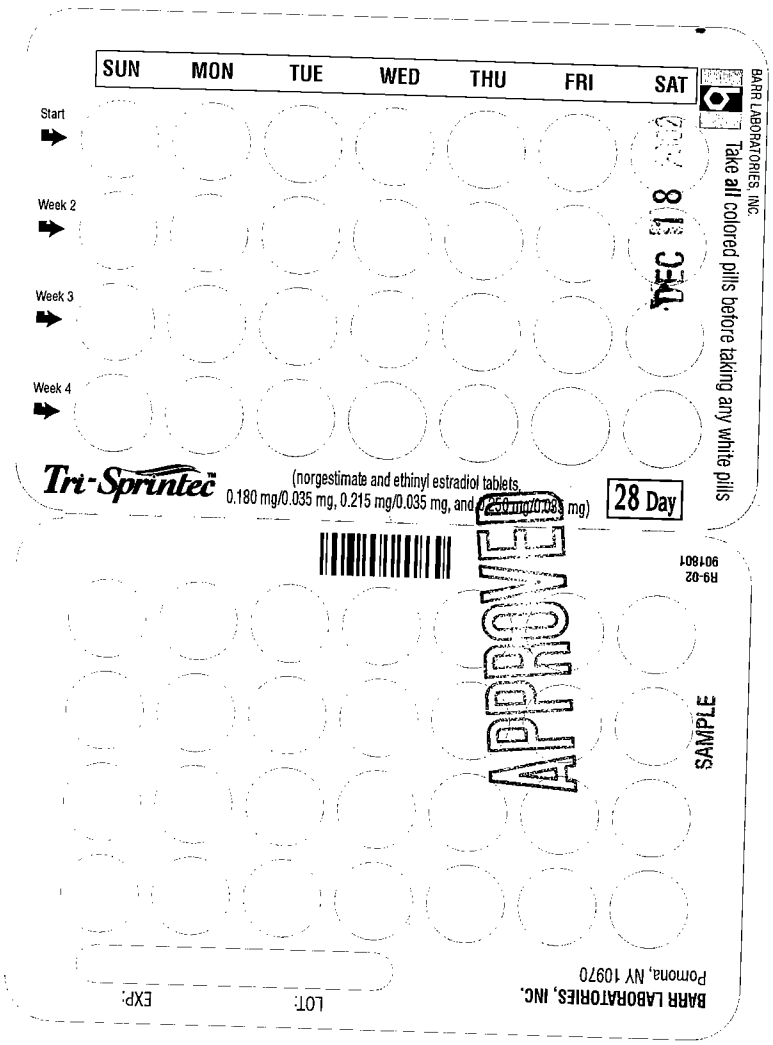
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised SEPTEMBER 2002
BS-9018

75-808
AP 12/18/02



NDC 0555-**9018**-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets– triphasic regimen)

28 DAY REGIMEN

Contents: One cyclic tablet dispenser of 28 tablets

Each gray tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

℞ only

THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

BARR LABORATORIES, INC.

SHAPING WOMEN'S HEALTH™
Barr Laboratories, Inc.

Usual Dosage: One tablet daily as prescribed.
See enclosed package information.
Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

APPROVED

N 3 05559 01858 3

BARR LABORATORIES, INC.
Pomona, NY 10970

READ PATIENT LABELING

If this is the first time you are taking birth control pills, wait until the day your period starts, then follow the instructions in the patient labeling. Make sure to check if you are a Sunday Start or Day 1 Start.

R9 -02
2169018580101

SAMPLE

Seal Line | Fold Line | Fold Line | Seal Line

6 Blister Cards, 28 Tablets Each

28 DAY REGIMEN

NDC 0555-9018-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets–triphasic regimen)

℞ only

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

BARR LABORATORIES, INC.
Pomona, NY 10970

6 Blister Cards, 28 Tablets Each

28 DAY REGIMEN

NDC 0555-9018-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets–triphasic regimen)

Usual Dosage: One tablet daily as prescribed. See enclosed package information.

To the Dispenser: This carton contains one combination labeling piece of information intended for the patient. Informational pieces are to be provided to the patient with each prescription.

BARR LABORATORIES, INC.

SHAPING WOMEN'S HEALTH™
Barr Laboratories, Inc.

6 Blister Cards, 28 Tablets Each **28** DAY REGIMEN

NDC 0555-**9018**-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets– triphasic regimen)

℞ only

THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

6 Blister Cards, 28 Tablets Each **28** DAY REGIMEN

NDC 0555-**9018**-58

Tri-Sprintec™

(norgestimate and ethinyl estradiol tablets– triphasic regimen)

APPROVED

Contains 6 blister cards, each containing 28 tablets. Each gray tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

℞ only

BARR LABORATORIES, INC.

SHAPING WOMEN'S HEALTH™
Barr Laboratories, Inc.

N 3 05559 01858 3

LOT:

SAMPLE

EXP:

2149018580101 R9-02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-808

LABELING REVIEW(S)

FIRST GENERIC

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-808

Date of Submission: February 16, 2000 (Original draft labeling)

Applicant's Name: Barr Laboratories, Inc.

Established Name: Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— 28 day regimens)

Labeling Deficiencies:

1. **GENERAL COMMENT:**

   We believe that your proposed proprietary name "———™" would be misleading as defined under 21 CFR 201.10(c)(5) since it sounds like or looks like the currently marketed oral contraceptives *Tri-Norinyl*, and *Tri-Levlen*. Please revise and/or comment.

2. **CONTAINER** (Fold-over blister dose card, ——— 28 Day):

   Satisfactory in draft.

3. **AUXILIARY LABEL**

   Satisfactory in draft.

4. ——— 28 Day):

   Satisfactory in draft.

5. **CARTON** ——— 6 x 28 Day):

   Satisfactory in draft.

6. **INSERT** (Physician Labeling, Detailed Patient Labeling, and Brief Summary Patient Labeling):

   a. GENERAL COMMENT:

   We note that you have modeled your labeling after the reference listed drug's labeling, Ortho Tri-Cyclen® by RW Johnson, revised May 1998. However, this labeling is not the most recently approved. 21 CFR 314.94(a)(8)(iv) requires that your labeling be the same as that approved for the reference listed drug. Please revise your physician insert labeling to be in accordance with the reference listed drug's labeling, revised January 2000 and approved June 5, 2000; and revise your Detailed Patient Labeling and Brief Summary Patient Labeling to be in accordance with the

reference listed drug's patient labeling, revised April 2000 and approved Jan. 16, 2001. Please refer to our fax dated April 6, 2001, concerning your ANDA 75-804, for a copy of the aforementioned reference listed drug labeling.

b. DESCRIPTION – (Physician Labeling only.):

Please correct the description of the contents of each gray, light blue, and blue tablet. For example, for the gray tablet, your labeling incorrectly states:

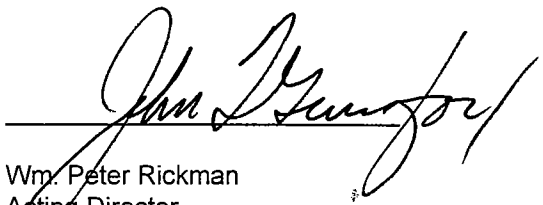
"Each gray tablet contains 0.180 mg [redacted] ..and 0.035 mg of the estrogenic compound, ethinyl estradiol...".

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?	x		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	x		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?	x		
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? **The proposed name "[redacted]™" was not recommended by OPDRA on Jan. 9, 2001 (Consult #00-0275).**	x		
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	

Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			

Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Ortho Tri-Cyclen® Tablets (21 Day Regimen) by R.W. Johnson (NDA 19-697/S-022; revised January 2000 and approved June 5, 2000; and S-024, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-697

No.	Expiration	Use Code	Use	File
4530839	Sept. 26, 2003	U-112	Contraception	IV
4544554	Sept. 26, 2003	U-66	Triphasic Regimen	IV
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	IV
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	IV

Exclusivity Data– NDA 19-697

Code	Reference	Expiration
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A

The firm's statements are correct. [Vol. A1.1 pg. 03-0001 and 03-00002.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Barr Laboratories, Inc.
2 Quaker Road, [redacted]
Pomona, NY 10970-0519 [Vol. A1.2 pg. 09-00002.]

4. CONTAINER/CLOSURE

Blister Film: [redacted] clear transparent plastic film.
Blister Backing: [redacted] push thru Aluminum Foil with [redacted] on bright side and [redacted] on matte side.
[Vol. A1.3 pg. 13-00004 and 13-00005.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.2 pg. 07-00003 and 07-00004.]

6. PACKAGING CONFIGURATIONS

RLD: Cartons of 6 x 21-Day and 6 x 28-Day Dialpak® Tablet Dispensers.
1 x 21-Day and 1 x 28-Day Veridate® Tablet Dispensers (unfilled) for clinic use.
ANDA: Cartons of [redacted] 6 x 28-Day Fold-Over Dose Card with sleeve.

[Vol. A1.1 pg. 04-00013, 04-00016, and 04-0099.]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: None.
ANDA: Store at [redacted]
[Vol. A1.1 pg. 04-00099.]

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: **Important:** Each pouch contains a combination Brief Summary Patient Package Insert and Detailed Patient Labeling. This should be included with each package dispensed to the patient.
ANDA:**To the Dispenser:** This carton contains two pieces of information intended for the patient. All informational pieces are to be provided to the patient with each prescription.
[Vol. A1.1 pg. 04-00013, and 05-00015.]

9. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

0.180 mg/0.035 mg tablet: "gray, round, unscored tablet debossed with **b** on one side and **985** on the other side."
0.215 mg/0.035 mg tablet: "light blue, round, unscored tablet debossed with **b** on one side and **986** on the other side."
0.250 mg/0.035 mg tablet: "blue, round, unscored tablet debossed with **b** on one side and **987** on the other side."
placebo tablet: "white, round, unscored tablet debossed with **b** on one side and **143** on the other side."

[Vol. A1.3 pg. 14-00005B, 5F, 5J, and 14-00029.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on March 26, 2001, that the firm's bioequivalency data were acceptable.
[Vol. A5.1]

11. NOMENCLATURE:

The firm proposed the proprietary name "[redacted]" for their product. OPDRA concluded on January 9, 2001, that they did not recommend the use of the name "[redacted]" for this drug product [Consult # 00-0275]. I notified the firm of this decision in a fax dated January 24, 2001.

Date of Review: 4/4/01 Date of Submission: 2/16/00

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 4/11/01

Team Leader: John Grace Date:

John D Grace 4/11/2001

cc:

ANDA: 75-808
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

TENTATIVE APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-808

Date of Submission: July 30, 2002 (Amendment) and June 1, 2001 (Amendment)

Applicant's Name: Barr Laboratories, Inc.

Established Name: Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (21 and 28 day regimens)

Proprietary Name: Tri-Sprintec™ ——— 28 Tablets

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? ? **No**. – The firm submitted 4 draft copies of their labels and labeling, which is acceptable for a Tentative Approval. Final Printed Labeling will be submitted by the firm 60 days prior to full approval of this application.

CONTAINER Labels: (Fold-over blister dose card - ——— 28 Day):
Satisfactory in **draft** as of the July 30, 2002 submission.

FOIL POUCH: (Overwrap for container and wallet – ——— 28 Day):
Satisfactory in **draft** as of the July 30, 2002 submission.

CARTON: (——————— 6 x 28 Day):
Satisfactory in **draft** as of the July 30, 2002 submission.

DAYS OF THE WEEK STICKER (To be affixed to the blister dose card – ——— 28 Day):
Satisfactory in **draft** as of the February 16, 2000 submission.

PROFESSIONAL PACKAGE INSERT – ——— 28 Day Combined):
Satisfactory in **draft** as of the July 30, 2002 submission.

COMBINATION DETAILED PATIENT LABELING AND BRIEF SUMMARY INSERT–
——— 28 Day Combined):
Satisfactory in **draft** as of the July 30, 2002 submission.

Revisions needed post-approval: **Yes**. There were several labeling revisions that were editorial in nature, and therefore could be "post-tentative approval" revisions. I communicated these post-tentative approval revisions to Salvatore Peritore, of Barr Laboratories, Inc., by telephone and by facsimile on August 9, 2002.

Patent Data – NDA 19-697

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4530839	Sept. 26, 2003	U-112	Contraception	IV	None

4544554	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None

Exclusivity Data– NDA 19-697

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: ORTHO-TRI-CYCLEN® Tablets

NDA Number: 19-697

NDA Drug Name: Norgestimate and Ethinyl Estradiol Tablets

NDA Firm: R.W. Johnson

Date of Approval of NDA Insert and supplement : NDA 19-697/S-022: Approved June 5, 2000; and S-024 (Combination Detailed Patient and Brief Summary Insert only): Approved January 16, 2001

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? No.

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?	x		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	x		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? **The proposed name "Tri-Sprintec™" was found acceptable by OPDRA on August 15, 2001 (Consult #01-0160).**	x		

PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		X	

Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Ortho Tri-Cyclen® Tablets (21 Day Regimen) by R.W. Johnson (NDA 19-697/S-022; revised January 2000 and approved June 5, 2000; and S-024, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-697

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4530839	Sept. 26, 2003	U-112	Contraception	IV	None
4544554	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None

Exclusivity Data– NDA 19-697

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The firm's statements are correct. [Vol. A1.1 pg. 03-0001 and 03-00002.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Barr Laboratories, Inc.
2 Quaker Road, [redacted]
Pomona, NY 10970-0519 [Vol. A1.2 pg. 09-00002.]

4. CONTAINER/CLOSURE

Blister Film: [redacted] clear transparent plastic film.
Blister Backing: [redacted] push thru Aluminum Foil with [redacted], on bright side and [redacted] on matte side.
[Vol. A1.3 pg. 13-00004 and 13-00005.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.2 pg. 07-00003 and 07-00004.]

6. PACKAGING CONFIGURATIONS

RLD: Cartons of 6 x 21-Day and 6 x 28-Day Dialpak® Tablet Dispensers.
1 x 21-Day and 1 x 28-Day Veridate® Tablet Dispensers (unfilled) for clinic use.
ANDA: Cartons of [redacted] 6 x 28-Day Fold-Over Dose Card with wallet.

[Vol. A1.1 pg. 04-00013, 04-00016, and 04-0099.]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: None.
ANDA: Store at [redacted]
[Vol. A1.1 pg. 04-00099.]

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: **Important:** Each pouch contains a combination Brief Summary Patient Package Insert and Detailed Patient Labeling. This should be included with each package dispensed to the patient.
ANDA:**To the Dispenser:** This carton contains one combination labeling piece of information intended for the patient. All informational pieces are to be provided to the patient with each prescription.

[Vol. A1.1 pg. 04-00013, and 05-00015.]

9. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

0.180 mg/0.035 mg tablet: "gray, round, unscored tablet debossed with **b** on one side and **985** on the other side."
0.215 mg/0.035 mg tablet: "light blue, round, unscored tablet debossed with **b** on one side and **986** on the other side."
0.250 mg/0.035 mg tablet: "blue, round, unscored tablet debossed with **b** on one side and **987** on the other side."
placebo tablet: "white, round, unscored tablet debossed with **b** on one side and **143** on the other side."

[Vol. A1.3 pg. 14-00005B, 5F, 5J, and 14-00029.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on March 26, 2001, that the firm's bioequivalency data were acceptable.
[Vol. A5.1]

11. NOMENCLATURE:

The firm proposed the proprietary name "Tri-Sprintec™ " for their product. OPDRA concluded on August 15, 2001, that "Tri-Sprintec" was an acceptable name for this drug product (Consult #01-0160)

Date of Review: 8/9/02 Dates of Submission: 7/30/02 and 6/1/01

Primary Reviewer: Debra Catterson Date:
Debra M. Catterson 8/9/02

Team Leader: John Grace Date:
John J Grace 8/12/2002

cc:
ANDA: 75-808
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

(This ~~TA~~ AP Summary supersedes the TA Summary dated 8/12/02.)

~~TENTATIVE~~ FULL APPROVAL SUMMARY

OK for full approval pending final OK from DMETS on proprietary name.
D Catterson
10/24/02

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-808

Date of Submission: September 24, 2002 (Amendment-FPL)

Applicant's Name: Barr Laboratories, Inc.

Established Name: Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28 day regimen)

Proprietary Name: Tri-Sprintec™ 28 Tablets

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes*.
*Although 12 copies of FPL would be acceptable for a full approval, this ~~is~~ was a "Tentative Approval Summary" because we have not received a final OK from DMETS on the proprietary name. The final OK from DMETS ~~will not be~~ was requested~~, until this application is within 90 days of a full approval~~.

CONTAINER Labels: (Fold-over blister dose card - 28 Day):
Satisfactory as of the September 24, 2002 submission. [Vol. 7.1, page 91]

FOIL POUCH: (Overwrap for container and wallet – 28 Day):
Satisfactory as of the September 24, 2002 submission. [Vol. 7.1, page 93]

CARTON: (6 x 28 Day):
Satisfactory as of the September 24, 2002 submission. [Vol. 7.1, page 95]

DAYS OF THE WEEK STICKER (To be affixed to the blister dose card – 28 Day):
Satisfactory as of the February 16, 2000 submission.

PROFESSIONAL PACKAGE INSERT:
Satisfactory as of the September 24, 2002 submission. [Vol. 7.1, Revised September 2002; Code: 31090180101]

COMBINATION DETAILED PATIENT LABELING AND BRIEF SUMMARY INSERT:
Satisfactory as of the September 24, 2002 submission. [Vol. 7.1, Revised September 2002; Code: 31590180101]

Revisions needed post-approval: **Yes**. There were several labeling revisions that were editorial in nature, and therefore could be "post-tentative approval" revisions. I communicated these post-tentative approval revisions to Nicholas Tantillo, of Barr Laboratories, Inc., by telephone

and by facsimile on October 8, 2002.

Patent Data – NDA 19-697

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4530839	Sept. 26, 2003	U-112	Contraception	IV	None
4544554	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None

Exclusivity Data– NDA 19-697

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: ORTHO-TRI-CYCLEN® Tablets

NDA Number: 19-697

NDA Drug Name: Norgestimate and Ethinyl Estradiol Tablets

NDA Firm: R.W. Johnson

Date of Approval of NDA Insert and supplement : NDA 19-697/S-022: Approved June 5, 2000; and S-024 (Combination Detailed Patient and Brief Summary Insert only): Approved January 16, 2001

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? No.

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?	x		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	x		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	

Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? **The proposed name "Tri-Sprintec™" was found acceptable by OPDRA on August 15, 2001 (Consult #01-0160). Because this application is in the "Tentative Approval" phase, I did not ask DMETS to perform a final review on the proprietary name. I will ask DMETS for the final OK on the name when the application is within 90 days of full approval.**	x		
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	

Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Ortho Tri-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-697/S-022; revised January 2000 and approved June 5, 2000; and S-024, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-697

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4530839	Sept. 26, 2003	U-112	Contraception	IV	None
4544554	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	IV	None

Exclusivity Data– NDA 19-697

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The firm's statements are correct. [Vol. A1.1 pg. 03-0001 and 03-00002.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Barr Laboratories, Inc.
2 Quaker Road —
Pomona, NY 10970-0519 [Vol. A1.2 pg. 09-00002.]

4. CONTAINER/CLOSURE

Blister Film: — clear transparent plastic film.
Blister Backing: — push thru Aluminum Foil with — on bright side and — on matte side.
[Vol. A1.3 pg. 13-00004 and 13-00005.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.2 pg. 07-00003 and 07-00004.]

6. PACKAGING CONFIGURATIONS

RLD: Cartons of 6 x 28-Day Dialpak® Tablet Dispensers.
1 x 28-Day Veridate® Tablet Dispensers (unfilled) for clinic use.
ANDA: Cartons of 6 x 28-Day Fold-Over Dose Card with wallet.

[Vol. A1.1 pg. 04-00013, 04-00016, and 04-0099.]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: None.
ANDA: Store at controlled room temperature 15°- 30°C (59°- 86°F) [See USP].
[Vol. A1.1 pg. 04-00099.]

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: **Important:** Each pouch contains a combination Brief Summary Patient Package Insert and Detailed Patient Labeling. This should be included with each package dispensed to the patient.
ANDA:**To the Dispenser:** This carton contains one combination labeling piece of information intended for the patient. All informational pieces are to be provided to the patient with each prescription.

[Vol. A1.1 pg. 04-00013, and 05-00015.]

9. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

0.180 mg/0.035 mg tablet: "gray, round, unscored tablet debossed with **b** on one side and **985** on the other side."
0.215 mg/0.035 mg tablet: "light blue, round, unscored tablet debossed with **b** on one side and **986** on the other side."
0.250 mg/0.035 mg tablet: "blue, round, unscored tablet debossed with **b** on one side and **987** on the other side."
placebo tablet: "white, round, unscored tablet debossed with **b** on one side and **143** on the other side."

[Vol. A1.3 pg. 14-00005B, 5F, 5J, and 14-00029.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on March 26, 2001, that the firm's bioequivalency data were acceptable.
[Vol. A5.1]

11. NOMENCLATURE:

The firm proposed the proprietary name "Tri-Sprintec™ " for their product. OPDRA concluded on August 15, 2001, that "Tri-Sprintec" was an acceptable name for this drug product (Consult #01-0160). Because this application is in the "Tentative Approval" phase, I did not ask DMETS to perform a final review on the proprietary name. I will ask DMETS for the final OK on the name when the application is within 90 days of full approval.

Date of Review: 10/7/02 Date of Submission: 9/24/02

Primary Reviewer: Debra Catterson Date:
Debra M. Catterson 10/8/02

Team Leader: John Grace Date:
John J Grace 10/8/2002

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cc:
ANDA: 75-808
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\barr\ltrs&rev\75808TAP2.L.doc
Review

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-808

Date of Submission: September 11, 2003 and August 21, 2003 (Amendments-FPL)

Applicant's Name: Barr Laboratories, Inc.

Established Name: Norgestimate and Ethinyl Estradiol Tablets (Triphasic Regimen) (28 day regimen)

Proprietary Name: Tri-Sprintec™ 28 Tablets

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes.

CONTAINER Labels: (Fold-over blister dose card - 28 Day):
Satisfactory as of the September 11, 2003 submission. [Vol. 8.1, "R9-02"]

FOIL POUCH: (Overwrap for container and wallet – 28 Day):
Satisfactory as of the September 11, 2003 submission. [Vol. 8.1, "R9-02"]

CARTON: (6 x 28 Day):
Satisfactory as of the August 21, 2003 submission. [Vol. 8.1, "R11-02"]

DAYS OF THE WEEK STICKER (To be affixed to the blister dose card – 28 Day):
Satisfactory as of the August 21, 2003 submission. [Vol. 8.1, "R4-02"]

PROFESSIONAL PACKAGE INSERT:
Satisfactory as of the August 21, 2003 submission. [Vol. 8.1, Revised November 2002; Code: 31090180102]

COMBINATION DETAILED PATIENT LABELING AND BRIEF SUMMARY INSERT:
Satisfactory as of the August 21, 2003 submission. [Vol. 8.1, Revised November 2002; Code: 31590180102]

Revisions needed post-approval: **Yes**. The following two labeling revisions are editorial in nature, and therefore can be "post-approval" revisions. I communicated these post-approval revisions to Nicholas Tantillo, of Barr Laboratories, Inc., by telephone and by facsimile on September 16, 2003.

1. CONTAINER:

   Expression of established name and strength: To minimize confusion and to be consistent with your foil pouch, carton and insert labeling, revise "(norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)" to read "(norgestimate and ethinyl estradiol tablets – triphasic regimen)".

2. FOIL POUCH, CARTON, PROFESSIONAL and PATIENT INSERTS :

Wherever the "Each tablet contains..." statement appears, delete the terminal zeros, e.g., "0.18 mg" instead of "0.180 mg".

Patent Data – NDA 19-697

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4530839	Sept. 26, 2003	U-112	Contraception	III	None
4544554	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	III	None

Exclusivity Data– NDA 19-697

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: ORTHO-TRI-CYCLEN® Tablets

NDA Number: 19-697

NDA Drug Name: Norgestimate and Ethinyl Estradiol Tablets

NDA Firm: R.W. Johnson

Date of Approval of NDA Insert and supplement : NDA 19-697/S-022: Approved June 5, 2000; and S-024 (Combination Detailed Patient and Brief Summary Insert only): Approved January 16, 2001

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? No.

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?	x		
Error Prevention Analysis			

Has the firm proposed a proprietary name? If yes, complete this subsection.	x		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? **The proposed name "Tri-Sprintec™" was found acceptable by OPDRA on August 15, 2001 (Consult #01-0160). On Oct. 21, 2002, I asked DMETS to perform a final review on the proprietary name, and on Nov. 5, 2002, DMETS gave the final OK (Consult #01-0160-2).**	x		
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	

Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Ortho Tri-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-697/S-022; revised January 2000 and approved June 5, 2000; and S-024, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-697

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4530839	Sept. 26, 2003	U-112	Contraception	III	None
4544554	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	III	None

Exclusivity Data– NDA 19-697

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The firm's statements are correct. [Vol. A1.1 pg. 03-0001 and 03-00002.; Vol. A8.1, 7-31-03 submiss.]

Note:

The firm had originally filed a Paragraph IV certification for all four patents, and was granted full approval for this application on December 18, 2002 at the termination of the 30-month stay. (See product listing in Orange Book below):

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
075808	AB	No	ETHINYL ESTRADIOL; NORGESTIMATE	Tablet; Oral-28	0.035MG;0.035MG;0.035MG;0.18MG;0.215MG;0.25MG	TRI-SPRINTEC	BARR

However, due to a court ruling, the full approval was rescinded on August 20, 2003, and the application was changed to tentative approval status. The firm changed their filing status to Paragraph III, and is now requesting full approval again, since the patents will expire on September 26, 2003.

The labeling amendment of August 21, 2003 provides for updated carton and insert labeling to include "post-approval" revisions I had requested on October 8, 2002.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Barr Laboratories, Inc.
2 Quaker Road
Pomona, NY 10970-0519 [Vol. A1.2 pg. 09-00002.]

4. CONTAINER/CLOSURE

Blister Film: clear transparent plastic film.
Blister Backing: push thru Aluminum Foil with on bright side and on matte side.
[Vol. A1.3 pg. 13-00004 and 13-00005.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.2 pg. 07-00003 and 07-00004.]

6. PACKAGING CONFIGURATIONS

RLD: Cartons of 6 x 28-Day Dialpak® Tablet Dispensers.
1 x 28-Day Veridate® Tablet Dispensers (unfilled) for clinic use.
ANDA: Cartons of 6 x 28-Day Fold-Over Dose Card with wallet.
[Vol. A1.1 pg. 04-00013, 04-00016, and 04-0099.]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: None.
ANDA: Store at controlled room temperature 15°- 30°C (59°- 86°F) [See USP].
[Vol. A1.1 pg. 04-00099.]

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: **Important:** Each pouch contains a combination Brief Summary Patient Package Insert and Detailed Patient Labeling. This should be included with each package dispensed to the patient.
ANDA:**To the Dispenser:** This carton contains one combination labeling piece of information intended for the patient. All informational pieces are to be provided to the patient with each prescription.
[Vol. A1.1 pg. 04-00013, and 05-00015.]

9. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

0.18 mg/0.035 mg tablet: "gray, round, unscored tablet debossed with **b** on one side and **985** on the other side."
0.215 mg/0.035 mg tablet: "light blue, round, unscored tablet debossed with **b** on one side and **986** on the other side."
0.25 mg/0.035 mg tablet: "blue, round, unscored tablet debossed with **b** on one side and **987** on the other side."
placebo tablet: "white, round, unscored tablet debossed with **b** on one side and **143** on the other side."

[Vol. A1.3 pg. 14-00005B, 5F, 5J, and 14-00029.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on March 26, 2001, that the firm's bioequivalency data were acceptable.
[Vol. A5.1]

11. NOMENCLATURE:

The firm proposed the proprietary name "Tri-Sprintec™ " for their product. OPDRA concluded on August 15, 2001, that "Tri-Sprintec" was an acceptable name for this drug product (Consult #01-0160). On Oct. 21, 2002, I asked DMETS to perform a final review on the proprietary name, and on Nov. 5, 2002, DMETS gave the final OK (Consult #01-0160-2).

Because this application was originally approved on Dec. 18, 2002 and therefore, available on the market, I did not ask DMETS to perform any more re-reviews of this name.

Date of Review: 9/15/03 Date of Submission: 9/11/03 and 8/21/03

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 9/16/03

Team Leader: John Grace Date:

John G Grace 9-16-2003

cc:

ANDA: 75-808
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\barr\ltrs&rev\75808APL.doc
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-808

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.** **(First Generic)**
1

2. **ANDA NUMBER**
75-808

3. **NAME AND ADDRESS OF APPLICANT**
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P. O. Box 2900
Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
The listed reference drug product is **Ortho-Tri Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19697) manufactured by Johnson RW.

The applicant certifies that the U.S. Patents No. 4,628,051, 4,616,006, 4,544,554, and 4,530,839 are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of this drug product based on 505(j)(2)(A)(vii)(IV). (Section III page 03-00001 and 2)

Exclusivity: None

SUPPLEMENT(s)
None

6. **NAME OF DRUG**

7. **NONPROPRIETARY NAME**
Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
None

9. **AMENDMENTS AND OTHER DATES**

02-16-2000	Original submission
03-03-2000	Correspondence (DMF authorization)
04-04-2000	Letter of acceptance
04-18-2000	Correspondence (Bio Amendment)
05-02-2000	Correspondence (Bio Amendment)
06-02-2000	Correspondence (Patent Amendment)

10. **PHARMACOLOGICAL CATEGORY**
Oral Contraceptive

HOW DISPENSED
Prescription

12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
		(II)	v1.2, p08-00004
		(II)	v1.2, p08-00078
		(III)	v1.3, p13-00011
		(III)	v1.3, p13-00019

13. DOSAGE FORM

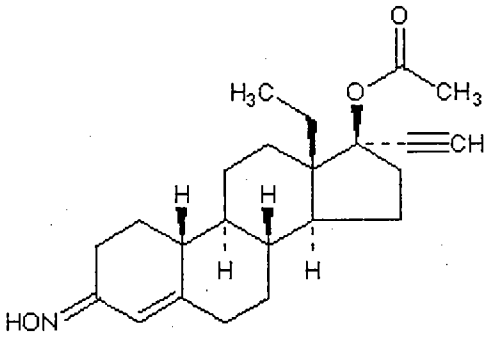
Tablet

14. POTENCY

0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (———28 day regimens)

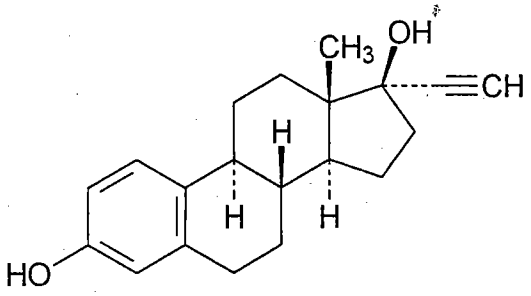
15. CHEMICAL NAME AND STRUCTURE

Norgestimate: 18,19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17)- (+)-.



C23H31NO3, Molecular Weight: 369.51

Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. RECORDS AND REPORTS

None

17. COMMENTS

The following sections are not satisfactory:

22. Synthesis
23. Raw Material Controls
26. Container
28. Laboratory Controls (In-Process and Finished Dosage Form)
29. Stability

The following sections are pending:

32. Labeling
33. Establishment Inspection

18. **CONCLUSIONS AND RECOMMENDATIONS**
The application is not approvable - Major.

19. **REVIEWER AND DATE COMPLETED**
Neeru B. Takiar/July 26, 2000
Revised on 8/02/00

Redacted 23 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

1. A satisfactory compliance evaluation of all of the facilities for drug product manufacturing and quality control in the application is necessary at the time of the approval of the application.

2. The agency's district office will request samples for the drug substance and finished dosage form for the methods validation at the appropriate time.

3. Your labeling review is pending. Any comments found will be communicated in a separate letter.

4. Please provide all room temperature stability data.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-808
Division File
Field Copy

Endorsements:

HFD-623/Neeru Takiar/7-26-00; revised on 8-02-00 N. Takiar 8/2/00
HFD-623/D. Gill/ DGill 8-2-00
HFD-617/R.Yu/ RYu 8-3-00
\\CDV008\WP51F99\FIRMSAM\BARR\LTRS&REV\75808.RV1.BARR.DOC
F/T by:

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.** **(First Generic)**
2

2. **ANDA NUMBER**
75-808

3. **NAME AND ADDRESS OF APPLICANT**
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P. O. Box 2900
Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
The listed reference drug product is **Ortho-Tri Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19697) manufactured by Johnson RW.

The applicant certifies that the U.S. Patents No. 4,628,051, 4,616,006, 4,544,554, and 4,530,839 are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of this drug product based on 505(j)(2)(A)(vii)(IV). (Section III page 03-00001 and 2)

Exclusivity: None

SUPPLEMENT(s)
None

6. **NAME OF DRUG**
[redacted]

7. **NONPROPRIETARY NAME**
Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
None

9. **AMENDMENTS AND OTHER DATES**

02-16-2000	Original submission
11-28-2000	Major Amendment – Response to def. letter (CMC and BA/BE) of August 22, 2000
01-02-2001	Electronic Submission - CMC Amendment
02-01-2001	Amendment - Filing of [redacted] new manufacturing site for [redacted]
02-09-2001	Amendment - Correction to February 01, 2001 amendment regarding [redacted] manufacturing site for [redacted]
03-09-2001	Amendment - Updated blend uniformity limits
03-15-2001	Amendment – Bio-equivalence

10. **PHARMACOLOGICAL CATEGORY**
Oral Contraceptive

11. **HOW DISPENSED**

Prescription

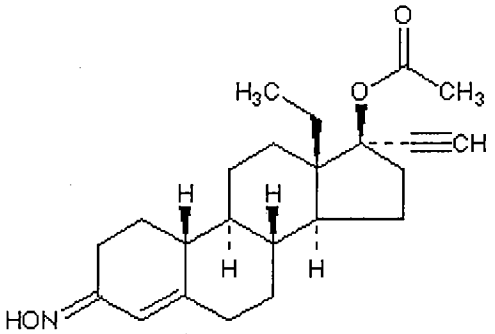
12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
		(II)	v1.2, p08-00004
		(II)	v1.2, p08-00078
		(III)	v1.3, p13-00011
		(III)	v1.3, p13-00019

13. DOSAGE FORM
Tablet

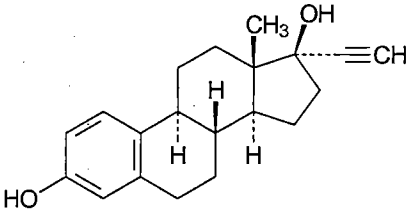
14. POTENCY
0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (—— 28 day regimens)

15. CHEMICAL NAME AND STRUCTURE
Norgestimate: 18,19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)- (+)-.



C23H31NO3, Molecular Weight: 369.51

Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS
The following sections are not satisfactory:

22. Synthesis
23. Raw Material Controls
28. Laboratory controls – Finished product
29. Stability

The following section is pending:

32. Labeling

18. CONCLUSIONS AND RECOMMENDATIONS
The application is NOT approvable - Minor.

REVIEWER AND DATE COMPLETED
Neeru B. Takiar/May 1, 2001; revised May 5, 2001

Redacted 18 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #2

CC: ANDA 75-808
Division File
Field Copy

Endorsements:

HFD-623/Neeru Takiar/5-1-2001; revised 5-7-01 N. Takiar 5/7/01;
HFD-623/D.Gill/ DSGill 5-9-01
HFD-617/R.Yu/ for Rosa Patel 5/9/01
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F/T by:

NA- MINOR

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
   3
2. **ANDA NUMBER**
   75-808

3. **NAME AND ADDRESS OF APPLICANT**
   Barr Laboratories, Inc.
   Attention: Christine Mundkur
   2 Quaker Road
   P. O. Box 2900
   Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
   The listed reference drug product is **Ortho-Tri Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19697) manufactured by Johnson RW.

   The applicant certifies that the U.S. Patents No. 4,628,051, 4,616,006, 4,544,554, and 4,530,839 are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of this drug product based on 505(j)(2)(A)(vii)(IV). (Section III page 03-00001 and 2)

   Exclusivity: None

5. **SUPPLEMENT(s)**
   None

6. **NAME OF DRUG**

7. **NONPROPRIETARY NAME**
   Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   None

9. **AMENDMENTS AND OTHER DATES**
   02-16-2000 Original submission
   06-01-2001 Amendment - Labeling
   06-11-2001 Minor Amendment – Response to CMC deficiency letter of May 14, 2001

10. **PHARMACOLOGICAL CATEGORY**
    Oral Contraceptive

11. **HOW DISPENSED**
    Prescription

12. **RELATED IND/NDA/DMF(s)**

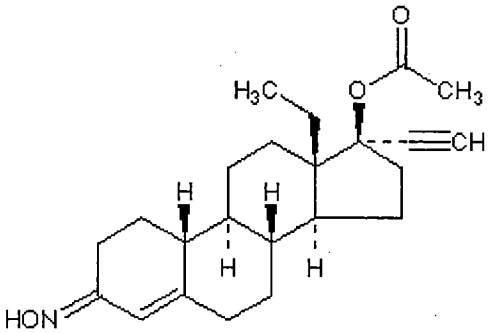
Product	Holder	DMF No.	LOA
		(II)	v1.2, p08-00004
		(II)	v1.2, p08-00078

Product	Holder	DMF No.	LOA
		(III)	v1.3, p13-00011
		(III)	v1.3, p13-00019

13. **DOSAGE FORM**
Tablet

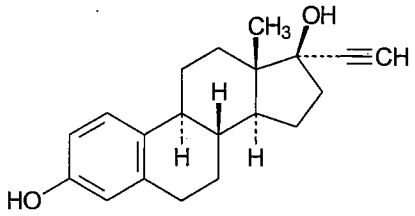
14. **POTENCY**
0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg — 28 day regimens)

15. **CHEMICAL NAME AND STRUCTURE**
Norgestimate: 18,19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)- (+)-.



C23H31NO3, Molecular Weight: 369.51

Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. **RECORDS AND REPORTS**
None

17. **COMMENTS**
The following sections are not satisfactory:
- 22. Synthesis
- 23. Raw Material Controls
- 28. Laboratory controls – Finished product

The following section is pending:
- 32. Labeling

18. **CONCLUSIONS AND RECOMMENDATIONS**
The application is NOT approvable - Minor.

19. **REVIEWER AND DATE COMPLETED**
Neeru B. Takiar/June 28, 2001

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confidential commercial

information from

CHEMISTRY REVIEW #3

cc: ANDA 75-808
Division File
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Endorsements:

HFD-623/Neeru Takiar/6-28-2001 N. Takiar 7/2/01
HFD-623/D.Gill/6/29/01 DSGill 7-2-01
HFD-617/R.Yu/6/29/01 RY 7-2-01

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F/T by: DJ 7/2/01

NA- MINOR

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
   4

2. **ANDA NUMBER**
   75-808

3. **NAME AND ADDRESS OF APPLICANT**
   Barr Laboratories, Inc.
   Attention: Christine Mundkur
   2 Quaker Road
   P. O. Box 2900
   Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
   The listed reference drug product is **Ortho-Tri Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19697) manufactured by Johnson RW.

   The applicant certifies that the U.S. Patents No. 4,628,051, 4,616,006, 4,544,554, and 4,530,839 are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of this drug product based on 505(j)(2)(A)(vii)(IV). (Section III page 03-00001 and 2)

   Exclusivity: None

5. **SUPPLEMENT(s)**
   None

6. **NAME OF DRUG**
   None

7. **NONPROPRIETARY NAME**
   Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   None

9. **AMENDMENTS AND OTHER DATES**

02-16-2000	Original submission
07-26-2001	Minor Amendment – Response to CMC deficiency letter of July 5, 2001
03-29-2002	Telephone Amendment - Response to CMC deficiencies per T-con of March 27, 2002
05-15-2002	Telephone Amendment - Response to CMC deficiencies per T-con of May 5, 2002
06-10-2002	Telephone Amendment - Response to T-con dated June 10, 2002

10. **PHARMACOLOGICAL CATEGORY**
    Oral Contraceptive

    HOW DISPENSED
    Prescription

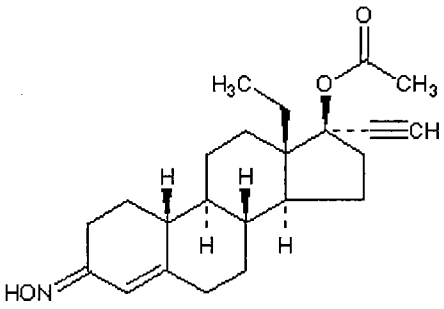
12. **RELATED IND/NDA/DMF(s)**

Product	Holder	DMF No.	LOA
		(II)	v1.2, p08-00004
		(II)	v1.2, p08-00078
		(III)	v1.3, p13-00011
		(III)	v1.3, p13-00019

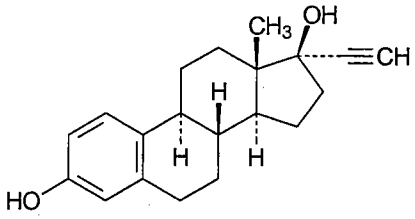
13. DOSAGE FORM
Tablet

14. POTENCY
0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (—— 28 day regimens)

15. CHEMICAL NAME AND STRUCTURE
Norgestimate: 18,19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)- (+)-
C23H31NO3, Molecular Weight: 369.51



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS See individual sections in the review.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable. NA MINOR will issue.

19. REVIEWER AND DATE COMPLETED
Neeru B. Takiar/June 19, 2002

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CHEMISTRY REVIEW #4

c: ANDA 75-808
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Endorsements:

HFD-623/Neeru Takiar/06-19-2002; Revised 7-1-02 N. Takiar 7/1/02
HFD-623/D.Gill, Ph.D./ DGill 7-1-02
HFD-617/R.Wu/

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F/T by:

NA-MINOR

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
   5
2. **ANDA NUMBER**
   75-808

3. **NAME AND ADDRESS OF APPLICANT**
   Barr Laboratories, Inc.
   Attention: Nicholas C. Tantillo
   2 Quaker Road
   P. O. Box 2900
   Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
   The listed reference drug product is **Ortho-Tri Cyclen®-28** (Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Tablet; Oral-28 Day Regimen – NDA 19697) manufactured by Johnson RW.

   The applicant certifies that the U.S. Patents No. 4,628,051, 4,616,006, 4,544,554, and 4,530,839 are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of this drug product based on 505(j)(2)(A)(vii)(IV). (Section III page 03-00001 and 2)

   Exclusivity: None

5. **SUPPLEMENT(s)**
   None

6. **NAME OF DRUG**
   Tri-Sprintec™ 28 Tablets

7. **NONPROPRIETARY NAME**
   Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   None

9. **AMENDMENTS AND OTHER DATES**
   02-16-2000 Original submission
   07-09-2002 Minor Amendment – Response to deficiency letter dated July 3, 2002

10. **PHARMACOLOGICAL CATEGORY**
    Oral Contraceptive

11. **HOW DISPENSED**
    Prescription

RELATED IND/NDA/DMF(s)

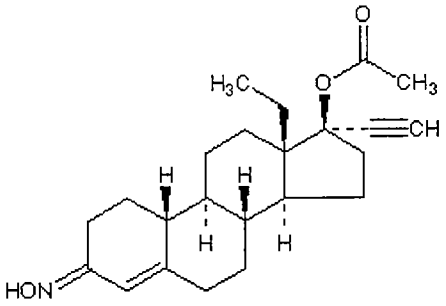
Product	Holder	DMF No.	LOA
		(II)	v1.2, p08-00004
		(II)	v1.2, p08-00078

Product	Holder	DMF No.	LOA
		(III)	v1.3, p13-00011
		III)	v1.3, p13-00019

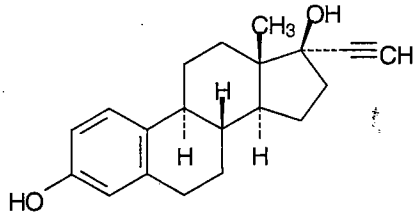
13. **DOSAGE FORM**
Tablet

14. **POTENCY**
0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28 day regimens)

15. **CHEMICAL NAME AND STRUCTURE**
Norgestimate: 18,19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)- (+)-
C23H31NO3, Molecular Weight: 369.51



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. **RECORDS AND REPORTS**
None

17. **COMMENTS**
None

18. **CONCLUSIONS AND RECOMMENDATIONS**
Approvable

19. **REVIEWER AND DATE COMPLETED**
Neeru B. Takiar/July 15, 2002

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confidential commercial

information from

CHEMISTRY REVIEW #5

cc: ANDA 75-808
Division File
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Endorsements:

HFD-623/Neeru Takiar/07-15-2002/U.S. Awtal (for)/8/26/02 N. Takiar 10/16/02
HFD-623/D.Gill, Ph.D./8/27/02 DSGill 10-17-02
HFD-617/R.Wu/S.Kim/8/27/02 S. Kim 10/17/02 12/16/02

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F/T by: sk/10/11/02

Approvable

APPEARS THIS WAY
ON ORIGINAL

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
75-808	Neeru B. Takiar	July 15, 2002

DRUG PRODUCT:
Norgestimate and Ethinyl Estradiol Tablets

FIRM:
Barr Laboratories, Inc.

DOSAGE FORM:	STRENGTHs:
Tablets	0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (———28 day regimens)

cGMP:
S. W 12/16/02
EER acceptable on July 2, 2001.

BIO:
Bio study acceptable on March 21, 2001; Signed off on March 26, 2001.

VALIDATION - *(Description of dosage form same as firm's):*
The DS Norgestimate and drug product are not covered by monographs in the USP 24 (25). Results of method validation from the FDA District Laboratory are ACCEPTABLE December 7, 2001.

STABILITY:
The firm has provided satisfactory 3 months accelerated and 25 months room temperature stability data for active (0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) tablets packaged in blisters, up to 6 months room temperature stability data in bulk, and 3 months accelerated and up to 12 months room temperature stability data for placebo tablets packaged in blister and in bulk. All stability data are satisfactory and support an expiration period of 18 months. The stability data meet the dissolution specifications recommended by DOB.

LABELING:
ACCEPTABLE on October 8, 2002

STERILIZATION VALIDATION *(If applicable)*:
N/A

SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:
Size of the bio batch for active, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg is ——— tablets ——— and for placebo is ——— tablets (———). Drug substance, Norgestimate is manufactured by ——— and drug substance, Ethinyl Estradiol is manufactured by ——— Norgestimate is found adequate on March 11, 2002 and Ethinyl Estradiol on May 7, 2002.

SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?)*:
Size of stability batch is same as that of the bio batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:
Size of the proposed production batch size for active tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— tablets) and placebo tablets (——— tablets) is the same as the bio batch. The manufacturing process is identical to the exhibit batch.

Signature of chemist:	Signature of supervisor:
Neeru B. Takiar 11/5/02	DS Gill
Neeru B. Takiar 7/15/02	Dave Gill, Ph.D. 7/16/02 11-5-02

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OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
   6
2. **ANDA NUMBER**
   75-808

3. **NAME AND ADDRESS OF APPLICANT**
   Barr Laboratories, Inc.
   Attention: Nicholas C. Tantillo
   2 Quaker Road
   P. O. Box 2900
   Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
   The listed reference drug product is **Ortho-Tri Cyclen®-28** (Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Oral-28 Day Regimen – NDA 19697) manufactured by Ortho-McNeil Pharmaceuticals, Inc. (formerly Johnson RW)

   The applicant certifies that the U.S. Patents No. 4,628,051, 4,616,006, 4,544,554, and 4,530,839 are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of this drug product based on 505(j)(2)(A)(vii)(IV). (Section III page 03-00001 and 2)

   Exclusivity: None

5. **SUPPLEMENT(s)**
   None

6. **NAME OF DRUG**
   Tri-Sprintec™ - 28 Tablets

7. **NONPROPRIETARY NAME**
   Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   None

9. **AMENDMENTS AND OTHER DATES**
   02-16-2000 Original submission
   10-20-2003 Minor Amendment – Final Approval Requested

10. **PHARMACOLOGICAL CATEGORY**
    Oral Contraceptive

11. **HOW DISPENSED**
    Prescription

?. **RELATED IND/NDA/DMF(s)**

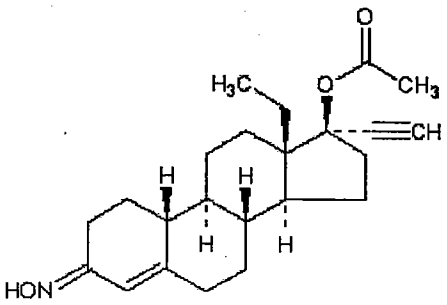
Product	Holder	DMF No.	LOA
[redacted]	[redacted]	(II)	v1.2, p08-00004
		(II)	v1.2, p08-00078

Product	Holder	DMF No.	LOA
		(III)	v1.3, p13-00011
		(III)	v1.3, p13-00019

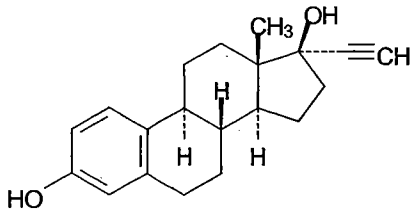
13. **DOSAGE FORM**
Tablet

14. **POTENCY**
0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28 day regimens)

15. **CHEMICAL NAME AND STRUCTURE**
Norgestimate: 18,19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)- (+)-
C23H31NO3, Molecular Weight: 369.51



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6.
USP 24, page 692.



16. **RECORDS AND REPORTS**
None

17. **COMMENTS**
None

18. **CONCLUSIONS AND RECOMMENDATIONS**
Final Approval

19. **REVIEWER AND DATE COMPLETED**
Neeru B. Takiar/December 15, 2003

Redacted 8 page(s)

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information from

CHEMISTRY REVIEW #6

cc: ANDA 75-808
Division File
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Endorsements:

HFD-623/Neeru Takiar/12-15-2003 N. Takiar 12/24/03
HFD-623/D.Gill, Ph.D. TL/12-16-2003 DSGill 12-24-03
HFD-617/S.Kim PM/12/23/03 S Kim 12/24/03

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F/T by: EW 12/23/03

Final Approval

APPEARS THIS WAY
ON ORIGINAL

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
75-808	Neeru B. Takiar	December 15, 2003

DRUG PRODUCT:
Norgestimate and Ethinyl Estradiol Tablets

FIRM:
Barr Laboratories, Inc.

DOSAGE FORM:	STRENGTHs:
Tablets	0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28 day regimen)

cGMP:
EER acceptable on December 22,2003.

BIO:
Bio study acceptable on March 26, 2001.

VALIDATION - *(Description of dosage form same as firm's):*
The DS Norgestimate and drug product are not covered by monographs in the USP 24 (25). Results of method validation from the FDA District Laboratory are ACCEPTABLE December 7, 2001.

STABILITY:
The firm has provided satisfactory 3 months accelerated and 25 months room temperature stability data for active (0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) tablets packaged in blisters, up to 6 months room temperature stability data in bulk, and 3 months accelerated and up to 12 months room temperature stability data for placebo tablets packaged in blister and in bulk. All stability data are satisfactory and support an expiration period of 18 months. The stability data meet the dissolution specifications recommended by DOB.

LABELING:
ACCEPTABLE on September 16,2003

STERILIZATION VALIDATION *(If applicable)*:
N/A

SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:
Size of the bio batch for active, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg is ——— tablets (——— and for placebo is ——— tablets (———. Drug substance, Norgestimate is manufactured by ——— and drug substance, Ethinyl Estradiol is manufactured by ——— Norgestimate is found adequate on March 11, 2002 and Ethinyl Estradiol on May 7, 2002.

SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?)*:
Size of stability batch is same as that of the bio batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:
Size of the proposed production batch size for active tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (——— tablets) and placebo tablets ——— tablets) is the same as the bio batch. The manufacturing process is identical to the exhibit batch.

Signature of chemist:	Signature of supervisor:
Neeru B. Takiar 12/24/03 Neeru B. Takiar 12/15/03	Dave Gill, Ph.D. DSG 12-24-03

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-808

BIOEQUIVALENCE REVIEW(S)

Norgestimate/Ethinyl Estradiol
0.18mg/0.035mg;0.215mg/0.035mg
0.25mg/0.035mg ——— 28 Day Tablets
Reviewer: Andre Jackson
ANDA # 75-808
V:\Firmsam\Barr\ltrs&rev\75808W.200

Barr Laboratories
Pomona, N.Y.
Submission Date:
February 16, 2000
May 2, 2000

Review of Waiver Request

Background:

The firm submitted a bioequivalence study ANDA# 75804 on February 16, 2000 for their Norgestimate/Ethinyl Estradiol 0.25mg/0.035mg tablets 28 day regimen (comparing Barr's ——— to Ortho's Ortho-Cyclen). They requested ———————————. Also on February 16 Barr submitted a separate waiver under ANDA# 75808 for their 0.18mg/0.035mg; 0.215mg/0.035mg and 0.25mg/0.035mg Norgestimate/Ethinyl Estradiol ——— tablets ——— 28 day regimens. Since the same 0.25mg/0.035mg Norgestimate/Ethinyl Estradiol tablets, 28 day regimen, were previously reviewed and found to be acceptable under ANDA # 75804 this strength does not require a waiver but the formulation and dissolution data will be presented since it is part of the Ortho Tricyclen 21 and 28 day products for which Barr is requesting waivers.

Table 1.

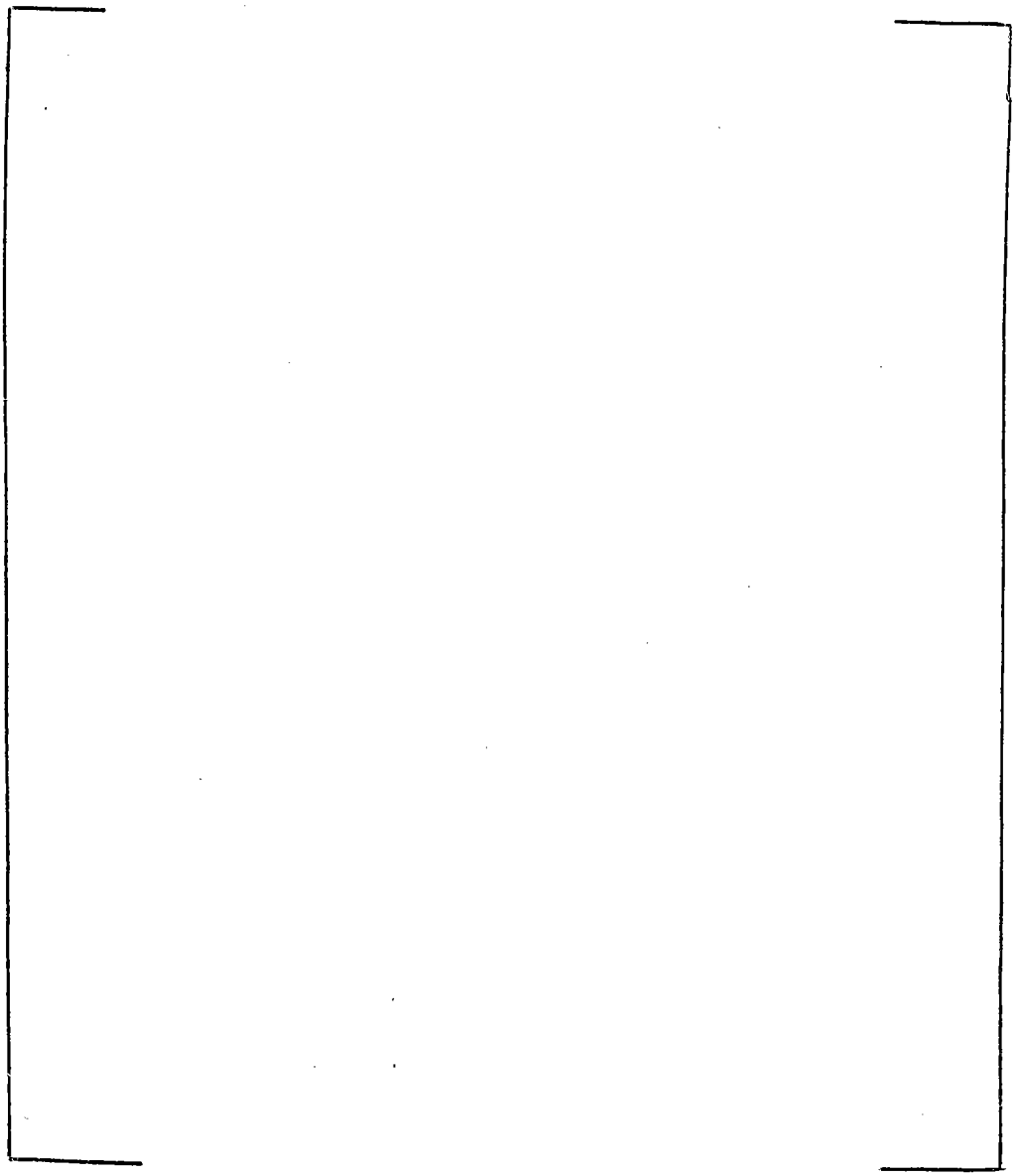

Table 2. Comparative formulations (mg/dose) of Barr's ——————— (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg)-28 Day Regimen.

	0.180mg/ 0.035mg	***0.215mg/ O.035mg***	***0.25mg/ 0.035mg***	***mg/dose***
Norgestimate	0.180	0.215	0.250	Placebo
Ethinyl Estradiol USP (——————)	0.035	0.035	0.035	
Pregelatinized Starch, NF(Starch ——)	———	———	———	

Lactose Monohydrate, NF (———)	———	———	———	
Anhydrous Lactose, NF (———)	———	———	———	———
Pregelatinized Starch, NF (Starch ——)	———	———	———	
Lake Blend Black LB 636 (———— % Pure Dye Content) • Aluminum Sulfate Solution • Sodium Carbonate • Sodium Bicarbonate, USP • Aluminum Chloride Solution • FD&C Blue #2/ ——— • FD&C Yellow #6/ ——— ——— • FD&C Red #40/ ———	———			
FD&C Blue #2 Aluminum Lake —(——— %) Aluminum Sulfate Solution • Sodium Carbonate • Sodium Bicarbonate, USP • Aluminum Chloride Solution FD&C Blue #2/ ———		———		
FD&C Blue #2 Aluminum Lake — (——— % Pure Dye Content) • Aluminum Sulfate Solution • Sodium Carbonate • Sodium Bicarbonate, USP • Aluminum Chloride Solution • FD&C Blue #2/ ———			———	
Magnesium Stearate, NF	———	———	———	———
Hydroxypropyl Methylcellulose, 2208 USP(———)				———
Microcrystalline Cellulose (———)				———
Tablet Weight	100	100	100	100

DISSOLUTION PROFILES:- The methodology is that recommended to the innovator by the NDA reviewing division.

All dissolutions were performed using a USP 24 Dissolution Apparatus II (Paddles). The dissolution conditions are listed below:

Temperature	37 ± 0.5°C
Rotation Speed	75 rpm
Distance from the Bottom	2.5 cm
Dissolution Volume:	600 mL
Dissolution Medium:	0.05% Tween 20 in water
Dissolution Vessel	1000 mL, round-bottom kettle
Time Intervals	15, 30, 45, 60 and 90 minutes (The 90-minute time interval is an additional time point)

IN-VITRO COMPARATIVE DISSOLUTION STUDY

Barr Laboratories' Norgestimate and Ethinyl Estradiol Tablets 0.180mg/0.035 mg

Batch No. 109859ROI

% Norgestimate Dissolved

Time (minutes)

Ortho Pharmaceutical Corporation, ORTHO TRI-CYCLEN 21 Tablets, Exp. Feb 2002

Batch No. 29BO24

% Norgestimate Dissolved

Time (minutes)

Tablet	15	30	45	60	90	15	30	45	60	90
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Ave	61	71	76	79	84	78	88	89	91	93
%RSD	3.9	2.3	2.3	1.7	1.7	2.4	1.8	3.2	2.5	3.4
Range										

	Barr Laboratories' Norgestimate and Ethinyl Estradiol Tablets 0.180mg/0.035 mg					Ortho Pharmaceutical Corporation, ORTHO TRI-CYCLEN 21 Tablets, Exp. Feb 2002				
	Batch No. 109859RO1					Batch No. 29BO24				
	%Ethinyl Estradiol Dissolved Time (minutes)					% Ethinyl Estradiol Dissolved Time (minutes)				
Tablet	15	30	45	60	90	15	30	45	60	90
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Ave	99	101	100	100	101	104	104	103	103	104
%RSD	1.5	3.4	1.4	1.7	1.5	1.5	1.7	1.1	1.4	1.2
Range										

Barr Laboratories' Norgestimate and Ethinyl Estradiol Tablets 0.215mg/0.035 mg

Batch No. 109859RO1

% Norgestimate Dissolved

Time (minutes)

Tablet	15	30	45	60	90
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Ave	59	67	72	76	80
%RSD	4.2	1.3	2.9	2.2	2.2
Range					

Ortho Pharmaceutical Corporation, ORTHO TRI-CYCLEN 21 Tablets, Exp. Feb 2002

Batch No. 29BO24

% Norgestimate Dissolved

Time (minutes)

15	30	45	60	90
72	87	91	95	99
3.3	2.1	2.7	1.5	2.5

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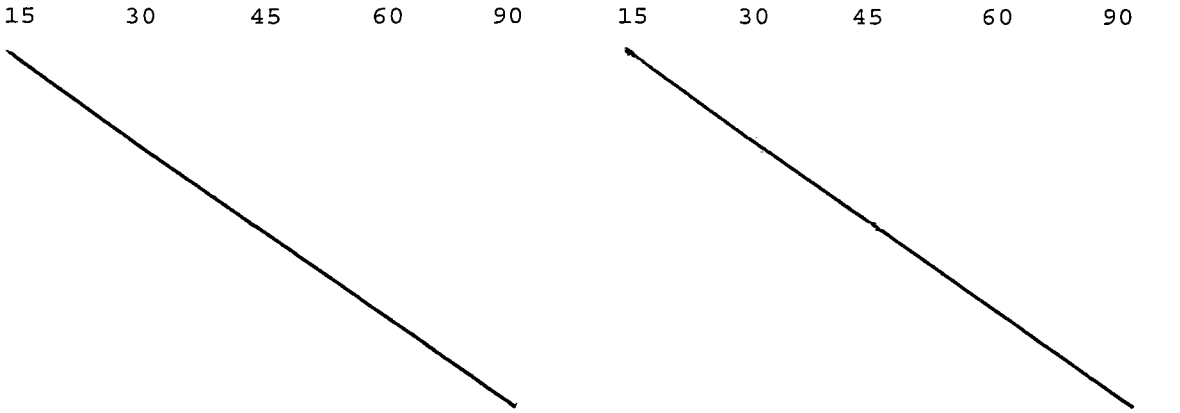
ON ORIGINAL

Barr Laboratories' Norgestimate and Ethinyl Estradiol Tablets 0.215mg/0.035 mg
Batch No. 109869RO1
%Ethinyl Estradiol Dissolved

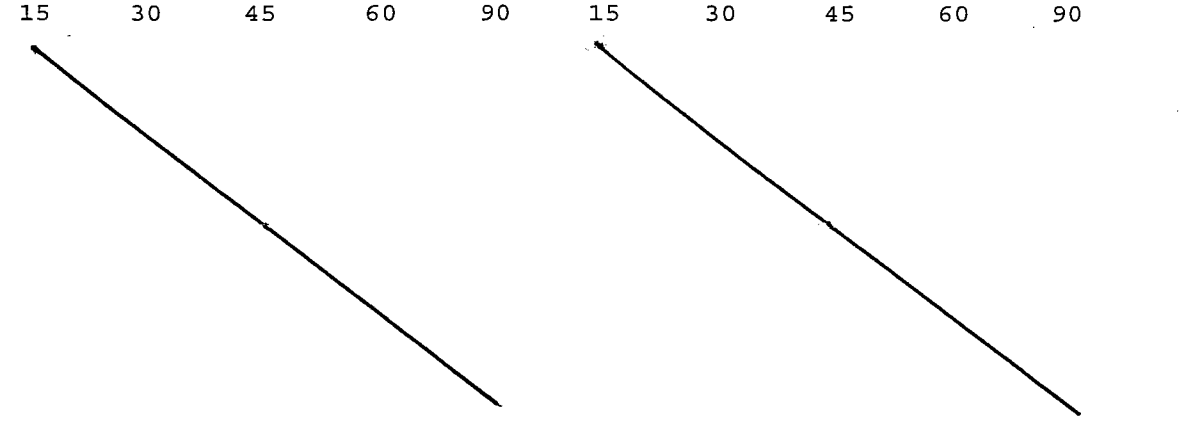
Ortho Pharmaceutical Corporation, ORTHO TRI-CYCLEN 21 Tablets
Batch No. 29BO24
% Ethinyl Estradiol Dissolved



Tablet	15	30	45	60	90	15	30	45	60	90
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Ave	100	100	101	100	100	104	105	105	105	105
%RSD	1.8	1.9	1.7	2.0	1.7	1.7	1.6	1.2	1.7	1.5
Range										

Barr Laboratories' Norgestimate and Ethinyl Estradiol Tablets 0.25 mg/0.035 mg
Batch No. 109879R02
% Norgestimate Dissolved

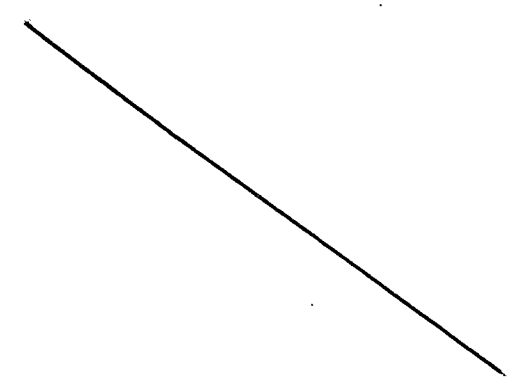
Ortho Pharmaceutical Corporation, ORTHO-CYCLEN 28 Tablets, Exp. May 2001
Batch No. 28GO75
% Norgestimate Dissolved



	15	30	45	60	90	15	30	45	60	90
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Ave	53	64	70	73	81	51	72	83	86	91
%RSD	3.6	2.2	2.0	3.1	2.0	10.3	2.2	2.0	1.9	2.2
Range										

Barr Laboratories'
Norgestimate and Ethinyl Estradiol
Tablets 0.25 mg/0.035 mg
Batch No. 109879R02
%Ethinyl Estradiol
Dissolved

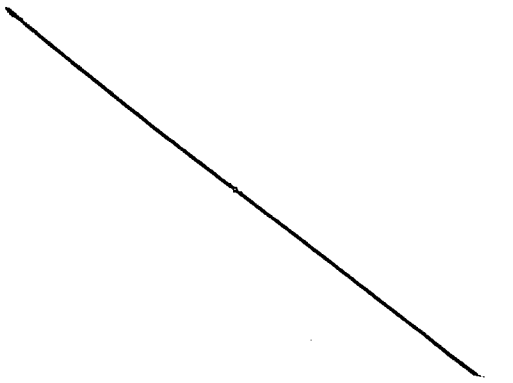
Time (minutes)



	15	30	45	60	90
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Ave	100	101	101	101	102
%RSD	2.7	1.6	1.7	1.7	1.7
Range					

Ortho Pharmaceutical Corporation,
ORTHO-CYCLEN 28 Tablets
Exp. May 2001
Batch No. 28GO75
%Ethinyl Estradiol
Dissolved

Time (minutes)



	15	30	45	60	90
Ave	96	101	99	97	98
%RSD	4.6	1.9	2.3	1.6	1.5

APPEARS THIS WAY
ON ORIGINAL

Table 3. F2 values for the formulations versus the reference Ortho-Cyclen at the same dose.

Dose	F2 Norgestimate	F2 Ethinyl Estradiol
0.18mg/0.035mg Norgestimate/ Ethinyl Estradiol	40.31	69.74
0.215mg/0.035mg Norgestimate/ Ethinyl Estradiol	34.57	63.07
0.25mg/0.035mg Norgestimate/ Ethinyl Estradiol	47.36	72.79

Table 4. F2 values for the test formulations versus the test formulation ——— 0.25 mg/0.035mg Norgestimate/ Ethinyl Estradiol on which the bioequivalence study was conducted.

Dose	F2 Norgestimate	F2 Ethinyl Estradiol
0.18mg/0.035mg Norgestimate/ Ethinyl Estradiol	57.63	92.47
0.215mg/0.035mg Norgestimate/ Ethinyl Estradiol	70.06	93.92

Comments:

1 The request for waiver of the in vivo bioequivalence study requirements may be granted based upon 21 CFR §320.22(d)(2) since:

a. The bioequivalence study report comparing Barr's ———(norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) with Ortho-McNeil Pharmaceutical, Inc.'s USA Ortho-Cyclen® has been found to be acceptable to the Division of Bioequivalence.

b.Barr's formulations for the 0.180 mg/0.035 mg, and 0.215 mg/0.035 mg strengths are dose similar to the 0.250 mg/0.035 mg strength; containing the same active ingredients and in the same dosage form.

c.The reference products for both Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg, 21 and 28 Day **(Ortho-Cyclen®)** and Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215mg/0.035 mg, and 0.250 mg/0.035 mg, 21 and 28 Day **(Ortho Tri Cyclen®)** are both manufactured by Ortho-McNeil Pharmaceutical, Inc.

d.The same 0.250 mg/0.035 mg tablets are used in both the **Ortho-Cyclen® and Ortho Tri-Cyclen®** 21 and 28 Day reference products.

e.The same 0.250 mg/0.035 mg tablets are used in both Barr's ——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg and ——— (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg) products.

f. The dissolution data for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215mg/0.035 mg, and 0.250 mg/0.035 mg are acceptable.

Recommendation:

1.The bioequivalence study conducted by Barr, ANDA # 75804, on its 0.250 mg/0.035 mg (norgestimate and ethinyl estradiol tablets has been previously found to be acceptable by the Division of Bioequivalence.

2. The dissolution study conducted on the 0.250 mg/0.035 mg norgestimate and ethinyl estradiol tablet is acceptable.

3.The dissolution testing data conducted by Barr on its 0.180 mg/0.035 mg norgestimate and ethinyl estradiol tablet lot # 109859R01 and its its 0.215mg/0.035 mg norgestimate and ethinyl estradiol tablet lot # 109859R01 are acceptable. The firm has conducted an acceptable in vivo bioequivalence study comparing its 0.250 mg/0.035 mg norgestimate and ethinyl estradiol tablet of the test product with the 0.250 mg/0.035 mg

norgestimate and ethinyl estradiol tablet of Ortho Cyclen®. The formulations for the 0.180 mg/0.035 mg and the 0.215mg/0.035 mg norgestimate and ethinyl estradiol tablet strengths are proportionally similar to the 0.250 mg/0.035 mg norgestimate and ethinyl estradiol tablet strength of the test product which underwent bioequivalency testing. The waivers of in-vivo bioequivalence study requirements for the 0.180mg/0.035 mg norgestimate and ethinyl estradiol tablet and the 0.215mg/0.035 mg norgestimate and ethinyl estradiol tablet of the test products are granted. Therefore, Barr's norgestimate and ethinyl estradiol tablets 0.180mg/0.035 mg, 0.215mg/0.035mg and 0.250 mg/0.035 mg are deemed bioequivalent to the reference product, Ortho Tri-Cyclen® 21 and 28 day tablets 0.180mg/0.035 mg, 0.215mg/0.035mg and 0.250 mg/0.035 mg norgestimate and ethinyl estradiol manufactured by Ortho-McNeil Pharmaceuticals.

4.The dissolution testing should be incorporated into the firm's manufacturing and controls programs. The dissolution testing should be conducted in 600 ml of 0.05% Tween 20 at 37°C using USP XXIV apparatus 2 (paddle) at 75 rpm. The test product should meet the following specifications:

NLT —% of Norgestimate is dissolved in 90 min
NLT —% Ethinyl Estradiol is dissolved in 30 min

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 6/27/2000

Concur: Date: 6/28/00
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

cc: ANDA 75-808 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75808 APPLICANT: Barr Laboratories

DRUG PRODUCT: Norgestimate/Ethinyl Estradiol
0.180mg/0.035 mg, 0.215mg/0.035 mg and
0.25mg/0.035mg- ——— 28 day Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 600 mL of 0.05% Tween 20 , at 37°C using USP24 Apparatus (II) at 75 rpm. The test product should meet the following specifications:

Not less than —%(Q) of the labeled amount of norgestimate in the dosage form is dissolved in 90 minutes.

Not less than —%(Q) of the labeled amount of ethinyl estradiol in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

CC: ANDA 75808
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer

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Printed in final on / /

Endorsements: (Final with Dates)
HFD-652/ Reviewer
HFD-652/ Bio team Leader 6/27/2000
HFD-650/ D. Conner 6/28/00

BIOEQUIVALENCY - ACCEPTABLE submission date:February 16, 2000

1. **Dissolution WAIVER** (WAI) Strengths: 0.180mg/0.035 mg
0.215mg/0.035 mg,0.25mg/0.035mg
Tablets
Outcome: AC

2. **STUDY AMENDMENT** (STA) Strengths: 0.180mg/0.035 mg
0.215mg/0.035 mg,0.25mg/0.035mg
Tablets
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-808 SPONSOR : Barr Laboratories

DRUG AND DOSAGE FORM : Norgestimate/Ethinyl Estradiol
28 day Tablets

STRENGTH(S) : 0.180mg/0.035 mg, 0.215mg/0.035 mg and 0.25mg/0.035mg

TYPES OF STUDIES : Waiver

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : _____ DATE : 6/26/00

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : _____ DATE : 6/27/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : _____ DATE : 6/28/00

Norgestimate/Ethinyl Estradiol
0.18mg/0.035mg;0.215mg/0.035mg
0.25mg/0.035mg ——28 Day Tablets
Reviewer: Andre Jackson
ANDA # 75-808
V:\Firmsam\Barr\ltrs&rev\75808A.N00

Barr Laboratories, Inc.
Pomona, N.Y.
Submission Date:
November 28, 2000
~~February 5, 2001~~
March 15, 2001

Review of Study Amendments

Background:

The firm submitted a bioequivalence study ANDA# 75804 on February 16, 2000 for their Norgestimate/Ethinyl Estradiol 0.25mg/0.035mg tablet 28 day regimen (comparing Barr's —— to Ortho's Ortho-Cyclen). They requested ————————. Also on February 16 Barr submitted a separate waiver under ANDA# 75808 for their 0.18mg/0.035mg; 0.215mg/0.035mg and 0.25mg/0.035mg Norgestimate/Ethinyl Estradiol ————)tablets —— —— 28 day regimens. The waiver was granted. The FDA recommended the following dissolution conditions for the product:

> The dissolution testing should be conducted in 600 mL of 0.05% Tween 20 , at 37°C using USP24 Apparatus (II) at 75 rpm. The test product should meet the following specifications:
>
> Not less than —%(Q) of the labeled amount of norgestimate in the dosage form is dissolved in 90 minutes.
>
> Not less than —%(Q) of the labeled amount of ethinyl estradiol in the dosage form is dissolved in 30 minutes.

In the amendment submitted on November 28, 2000, the firm requested to use the dissolution method in their original submission dated February 16, 2000 (paddle at 75 rpm and ———— ————————). They argue that this medium provides more bioequivalently relevant results. It should be noted that a similar amendment was submitted for the Norgestimate/Estradiol 0.25mg/0.035mg tablet 28 day regimen under ANDA # 75-804. The Division of Bioequivalence did not agree with the firm's comments and the recommended dissolution method and specifications remained unchanged.

The firm's arguments (November 28, 2000) are appended to this review. There is no need to further comment on them, since these arguments have been superceded by the February 1, 2001 reply to ANDA 75-804 and their February 5, 2001 reply to ANDA 75-808 in which the firm has accepted the FDA recommended dissolution conditions for their products.

Recommendation:

The firm has adopted the dissolution method and specifications previously recommended by the Division of Bioequivalence in the review of the original submission dated February 16, 2000. Consequently, no further action is needed.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG _____ Date: 3/21/2001

Concur: _____ Date: 3/26/01
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

cc: ANDA 75-808 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

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of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW (APPENDIX)

CC: ANDA 75808
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer

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Printed in final on / /

Endorsements: (Final with Dates)
HFD-652/ Reviewer (FI) 8/8/01
HFD-652/ Bio team Leader 4 RM 3/21/2001
HFD-650/ D. Conner NE 3/26/01

BIOEQUIVALENCY - ACCEPTABLE

Submission date:November 28, 2000
~~February 5, 2001~~ March 15, 2001

1. **STUDY AMENDMENT** (STA)(11/28/2000) OIC

Strengths: 0.180mg/0.035 mg
0.215mg/0.035 mg,0.25mg/0.035mg
Tablets

2. **STUDY AMENDMENT** (STA)~~(2/5/2001)~~ (3/15/2001)

Strengths: 0.180mg/0.035 mg
0.215mg/0.035 mg, 0.25mg/0.035mg
Tablets

Outcome: AC
Outcome Decisions: AC - acceptable

WinBio Comments:

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75808 APPLICANT: Barr Laboratories

DRUG PRODUCT: Norgestimate/Ethinyl Estradiol Tablets
0.180mg/0.035 mg, 0.215mg/0.035 mg and
0.25mg/0.035mg- [redacted] 28 day regimens

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than [redacted]% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes

Not less than [redacted]% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 minutes

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-808 SPONSOR : Barr Laboratories

DRUG AND DOSAGE FORM : Norgestimate/Ethinyl Estradiol
28 Day Tablets

STRENGTH(S) : 0.18mg/0.035mg;0.215mg/0.035mg; 0.25mg/0.035mg

TYPES OF STUDIES : Waiver

CLINICAL STUDY SITE(S): **N/A**
ANALYTICAL SITE(S) : **N/A**
STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic ____	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : _____ DATE : 3/19/01

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : _____ DATE : 3/21/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : _____ DATE : 3/26/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-808

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

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

DATE : March 1, 2000

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 3/1/00

SUBJECT: Examination of the bioequivalence request for waiver submitted with an ANDA for Norgestimate and Ethinyl Estradiol Tablets to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j)(5)(b)(iv).

Barr Laboratories Inc. has submitted ANDA 75-808 for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg and 0.035 mg —— 28 day Regimens. The ANDA contains a certification pursuant to 21 USC 355 (j)(2)(A)(vii)(iv) stating a patent expiring September 26, 2003 will not be infringed by the manufacturing or sale of the proposed product, also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the bioequivalence request for waiver submitted by Barr on February 16, 2000 for its Norgestimate and Ethinyl Estradiol product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

_____ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

__✓__ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

3/21/00

Director, Division of Bioequivalence

3/22/00
Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 75-808 DRUG NAME Norgestimate/Ethinyl Est. Ld. of FIRM Barr Laboratories

DOSAGE FORM(s) Tablets (0.180 mg/0.035 mg, 0.215 mg/0.035 mg, 0.250 mg/0.035 mg)

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol					
Assay Methodology					
Procedure SOP					
Validation					
Study Results Log/Lin					
Adverse Events					
IRB Approve					
Dissolution	✓				
Pre-screening of patients					
Chromatograms					
Consent form					
Composition	✓				
Summary of study					
Individual Data & Graphs . Linear & Semi-linear					
PKPD data disk					
Randomization Schedule					
Protocol Deviations					

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site					
Analytical site					
Study investigators					
Medical Records					
Clinical Raw Data					
Test Article Inventory					
BIO Batch Size					
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture					
Exp. Date RLD					
Biostudy lot numbers					
Statistics					
Waiver request for other strengths / supporting data	✓				

Recommendation: ~~COMPLETE~~ / INCOMPLETE

VJ – The firm may need to conduct a bio-study comparing 0.180 mg/0.035 mg drospirenone/EE, Test vs. ref. products.

CONCUR
ONLY ONE BIOSTUDY IS REQUIRED

Reviewed by:

Date 3/9/00

3/20/00

Revised 2/19/98

RECORD OF TELEPHONE CONVERSATION

Reference is made to the firm's fax dated February 1, 2001.

Ms. Gray stated that the DMF holder has already amended the DMF file with the appropriate changes.

The firm has responded to the major deficiency letters for all 4 ANDAs. I asked Ms. Gray to send in additional amendments with the new information to these ANDAs ASAP.

Ms. Gray agreed.

APPEARS THIS WAY
ON ORIGINAL

DATE:
February 1, 2001

ANDA NUMBER:
75-803, 75-804, 75-808, 75-866

PRODUCT NAME:
Oral Contraceptives

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Elizabeth Gray

PHONE NUMBER:
845-362-1100

FDA REPRESENTATIVES:

Ruby Yu

SIGNATURES:

Ruby Yu

CC: 75-803, 75-804, 75-808, 75-866
Telecon Binder

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6-1

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 06/26/01	**DUE DATE:** 8/20/01	**OPDRA CONSULT #:** 01-0160

TO: Peter Rickman
Acting Director, Division of Labeling and Program Support
Office of Generic Drugs
HFD-610

THROUGH: Harvey Greenberg,
Project Manager
HFD-600

PRODUCT NAME:	**MANUFACTURER**: Barr Laboratories, Inc.
Tri-Sprintec (Norgestimate and Ethinyl Estradiol tablets) 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.35 mg-—— 28 day regimen **ANDA #: 75-808**	

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Labeling and Program Support, OPDRA conducted a review of the proposed name, Tri-Sprintec, to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA has no objection to the use of the proprietary name, "Tri-Sprintec". OPDRA considers this a final review. However, if the approval of the ANDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary names/NDA's/ANDA's from this date forward.

Carol Holquist for 8-15-01

Carol Holquist for Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3231
Fax: (301) 480-8173

Martin H Himmel 8/15/01

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

RECORD OF TELEPHONE CONVERSATION

Barr will respond to the following cmc issues as a telephone amendment:

1. Please revise the specifications for ——— according to manufacturer's current specifications, where applicable (i.e. for melting point and ———), and please provide a copy of your and manufacturer's final specifications.
2. The firm revised the packaging and labeling of their product: replaced the ——— with a vinyl wallet and a foil pouch. The firm was asked to provide the following information about the foil pouch for CMC review: material information on the foil pouch, explain how the stability study was conducted; send samples of the final package; explain why leaching studies were not done; and revise the stability protocol to include information on the foil pouch.
3. Barr has revised the drug product release specification for the assay of norgestimate and ethinyl estradiol from ——— % to ——— %. Please revised and provide the in-process specs accordingly.
4. The current release and stability spec for ——— is NMT ———. Information about the formation of this impurity may be found in the original application, section 15; and the degradation pathway may be found on page 16. ——— ——— is produced due to degradation on stability. Therefore, the firm was asked to lower the release spec from NMT ——— based on the release data.
5. Regarding the other impurities found in the norgestimate drug substance (levonorgestrel, ———, the firm stated that the impurities may be potential degradants of the drug product. Firm was asked to set specs for these degradants.
6. Please provide data from retain samples (firm may have 12 and 18 months CRT) using the dissolution method and specs as recommended by the Division of Bioequivalency.
7. Please provided an updated stability report.

DATE:
March 27, 2002

ANDA NUMBER:
75-804 & 75-808

PRODUCT NAME:
Norgestimate and Ethinyl Estradiol Trablets

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Christine Mundkur; Liz Nobel-Gray; ———

PHONE NUMBER:
845-353-8432

FDA REPRESENTATIVES:
Dave Gill
Neeru Takiar
Ruby Wu

SIGNATURES:
Dave Gill PSGill
Neeru Takiar NT 3/28/02
Ruby Wu Ruby 4/24/02

CC: 75-808 & 75-804
Telecon Binder

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RECORD OF TELEPHONE CONVERSATION

Reference is made to the March 27, 2002 t-con.

The following requests were made:

The firm revised the packaging and labeling of their product: replaced the [redacted] with a vinyl wallet and a foil pouch. The firm was asked to provide the following information about the foil pouch for CMC review, as requested in the 3/27/02 t-con: material information on the foil pouch, explain how the stability study was conducted; send samples of the final package; explain why leaching studies were not done; and revise the stability protocol to include information on the foil pouch.

Please establish release and stability specifications for the following impurities that may be potential degradants of the drug product (as mentioned on page 37 of the March 29, 2002 telephone amendment): [redacted]

[redacted]. Please provide data, if available.

DATE:
May 8, 2002

ANDA NUMBER:
75-804 & 75-808

PRODUCT NAME:
Norgestimate and Ethinyl Estradiol Trablets

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Christine Mundkur

PHONE NUMBER:
845-353-8432

FDA REPRESENTATIVES:
Neeru Takiar
Ruby Wu

SIGNATURES:

Neeru Takiar NT 5/8/02
Ruby Wu RW 5/8/02

CC: 75-808 & 75-804
Telecon Binder

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RECORD OF TELEPHONE CONVERSATION

The following request was made:

The firm was asked to lower the acceptance limit for _____ It is high and to provide the final ___ specifications.

APPEARS THIS WAY
ON ORIGINAL

DATE:
June 10, 2002

ANDA NUMBER:
75-804 & 75-808

PRODUCT NAME:
Norgestimate and Ethinyl Estradiol Trablets

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Christine Mundkur

PHONE NUMBER:
845-353-8432

FDA REPRESENTATIVES:
Neeru Takiar

SIGNATURES:
Neeru Takiar
N. Takiar 6/10/02

CC: 75-808 & 75-804
Telecon Binder

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RECORD OF TELEPHONE CONVERSATION

Reference is made to the July 8, 2002 fax requesting a t-con.

Issue:
Firm requested redesignation of the Deficiency letter dated July 3, 2002 from a Minor to a Telephone.

Response:
The request was denied but the firm was informed that the chemist will review the amendment as soon as possible.

Issue:
Firm requested clarification on which [redacted]

Response:
[redacted]

Issue:
In the July 3, 2002 deficiency letter, the firm was asked to either [redacted] or provide [redacted]

Response:
The firm stated that they will [redacted] and will resubmit post approval. The firm will verify that [redacted]

DATE:
July 8, 2002

ANDA NUMBER:
75-804 & 75-808

PRODUCT NAME:
Norgestimate and Ethinyl Estradiol Tablets

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Christine Mundkur,
Nicholas Tantillo,
Linda O'Dea

PHONE NUMBER:
845-353-8432

FDA REPRESENTATIVES:
Paul Schwartz
Dave Gill
Neeru Takiar
Ruby Wu
Sarah Kim

SIGNATURES:
Paul Schwartz 7/11/02
Dave Gill DSG:sl
Neeru Takiar NT 7/11/02
Ruby Wu 7/11/02
Sarah Kim 7/11/02

CC: 75-808 & 75-804
Telecon Binder

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OGD APPROVAL ROUTING SUMMARY

ANDA # 75-808 Applicant Barr Laboratories, Inc.
Drug Norgestimate and Ethinyl Estradiol Tablets Strength 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035mg
(28 day regimens)

APPROVAL ☑ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:

1. Project Manager, Team Sarah Kim, 4
Review Support Br

DRAFT Package
Date 8/16/02
Initials SKim

FINAL Package
Date 8/27/02
Initials SKim

Application Summary:

Original Rec'd date 2/18/00
Date Acceptable for Filing 2/18/00 ✓
Patent Certification (type) IV
Date Patent/Exclus.expires 9/26/03
Citizens' Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☑ No ☐
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD = Ortho Tri-Cyclen Tablets
Date checked 7/17/02 NDA# 19697
Nothing Submitted ☑
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 7/02/01
Date of Office Bio Review 3/26/01
Date of Labeling Approv. Sum 8/12/02 10/18/02
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☑
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☑
Interim Dissol. Specs in AP Ltr: Yes ☐ NA

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

2. Gregg Davis **PPIV ANDAs Only**
Supv., Reg. Support Branch

Date 25-OCT-2002
Initials

Date 25-OCT-2002
Initials

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☐ No ☒
Date settled:
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Comments:

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

RLD-Ortho Tri-Cyclen-28 Tablets
RW Johnson Pharmaceutical Research Institute, NDA 19-697 (001)

PIV for '051, '006, '554, '839 rc 4/28/00
30 mos exp. 10/28/02 - OK for full approval on/after 10/28

3. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments:

Date 11/5
Initials PJ

degradant limits are acceptable

REVIEWER:

FINAL ACTION

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)
Satisfactory as revised
Also refer to ANDA 75-804 submitted by Barr for Sprintec 28 tablets (same two API's) and approved on 9/25/02.

Date 12/18/02
Initials JMA

5. Peter Rickman
Acting Director, DLPS
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 7/2/01 (Verified 12/18/02). No O.A.I. alerts noted. Bioequivalence waiver granted based upon bioequivalence study of 0.25mg/0.035mg tablet formulation under ANDA 75-804 an acceptable dissolution data under that ANDA. Dissolution data for two additional strengths under this ANDA found satisfactory. Waivers granted to 0.18mg/0.035mg and 0.215mg/0.035mg strengths. Office-level bio endorsed 6/28/00. Dissolution data reviewed and found acceptable 3/26/01. Office-level bio endorsed 3/26/01. FPL found acceptable for approval 10/18/02. Proprietary name-TriSprintec-found acceptable by ODRA, as per most recent update dated 10/29/02. OR CMC acceptable 10/17/02. Methods validation completed and acceptable. First-generic CMC audit has been completed.

Date 12/18/2002
Initials Robert West

5. Robert L. West
Acting Deputy Director, OGD
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☒ No☐; Petition: Yes☐ No☒
Comments: Barr made a PIV Certification to each of the listed patents. Barr was sued by Ortho McNeil on 3 of the 4 patents. Litigation ongoing. This approval is based upon the expiration of the 30-month period (10/29/02).

This ANDA is recommended for approval.

Date 12/18/02
Initials

6. Gary Buehler
Director, OGD
Comments: For this RLD

First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Team Sarah Kim
Review Support Branch
Date 12/18/02
Initials SSK

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
1:30 pm Time notified of approval by phone 1:24pm Time approval letter faxed

FDA Notification:
12/18/02 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/18/02 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

V :ports\approval\approvrou2.doc

RECORD OF TELEPHONE CONVERSATION

Reference is made to the amendment dated August 1, 2003.

Please withdraw the above minor amendment. You will be issued a letter rescinding the approval of ANDA 75-808 and granting a tentative approval. After you receive the rescission letter, you may at that time submit a Minor Amendment requesting final approval.

In addition, please withdraw all the supplemental applications to this ADNA.

APPEARS THIS WAY
ON ORIGINAL

DATE:
August 13, 2003

ANDA NUMBER:
75-808

PRODUCT NAME:
Tri-Sprintec
(Norgestimate and Ethinyl Estradiol Tablets,
0.180 mg/ 0.035 mg,
0.215 mg/0.035 mg, and
0.250 mg/0.035 mg)
28 day regimen

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Nicholas Tantillo,

PHONE NUMBER:
201-930-3650

FDA REPRESENTATIVES:

Sarah Kim

SIGNATURES:

Sarah Kim S. Kr 8/13/03

CC: 75-808
Telecon Binder
V:\FIRMSAM\BARR\TELECONS\75808.tc.081303.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-808 Applicant Barr Laboratories, Inc.
Drug Norgestimate and Ethinyl Estradiol Tablets Strength(s) 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg (28 day regime

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 12/23 Initials MMS	Date Initials

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA#
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☑ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter:
Comments: All patents with respect to NDA 19677 expired 9/26/2003. Ped exclusivity was granted on 12/18/03 ∴ ped extension to patents now expires 3/26/2004. Ortho has waived their ped exclusivity w/ respect to Barr. ∴ Barr is eligible for full approval on 12/29/03

2. Project Manager, Sarah Kim Team 4 Review Support Branch	Date 12/16/03 Initials SKM	Date Initials

Original Rec'd date 2/18/00
Date Acceptable for Filing 2/18/2000
Patent Certification (type) IV
Date Patent/Exclus.expires 9/26/2003
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic (TA'ed) Yes ☒ No ☐
Acceptable Bio reviews tabbed Yes ☒ No ☐
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 12/22/2003
Date of Office Bio Review 6/28/00, 3/26/01
Date of Labeling Approv. Sum 9/16/2003
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒ AC 12/7/01
MV Commitment Rcd. from Firm Yes ☒ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐ N/A
Previously reviewed and tentatively approved ☒ Date 9/26/2003
Previously reviewed and CGMP def./NA Minor issued ☐ Date
Comments:

3. Gregg Davis Deputy Dir., DLPS	Date Initials	Date Initials

This ANDA was originally approved on 12/18/02. Barr made a paragraph IV certification to each of the 4 listed patents all expiring on 9/26/03. Barr was sued by Ortho on the '839, '554, and '006 patents. Approval was granted on 12/18/02 based upon the expiration of the 30-month stay. Subsequently on 8/20/03, OGD withdrew approval of this ANDA because Ortho obtained a court judgement stating Barr did infringe the '554 and '006 patents and that the ANDA could not be granted final approval until the patents expired. 12/29

4. Div. Dir./Deputy Dir. Chemistry Div. I or II		Date Initials

Comments:

no changes

On 8/20/03 OGD issued a letter to Barr changing the status of this ANDA from approv. to tentatively approved. Thereafter, on September 14, 2003, in response to a written request for pediatric data, Ortho submitted a pediatric supplement for the RLD to the agency. On 12/18/03, the agency awarded pediatric exclusivity to Ortho for the RLD (over) See #6

REVIEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date _____
Assoc. Dir. For Chemistry Initials _____
Comments: (First generic drug review)
N/A. The first generic CMC audit was completed on 12/17/02.

6. Peter Rickman Date 12/29/03
Director, DLPS Initials
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 12/22/03 (Faxed 12/29/03) No O.A.I. Alerts noted. Refer to the administrative sign-off form completed at the time of the initial approval on 12/24/02. FR found acceptable 9/16/03. Proprietary name of TRI-SPRINTEC Tablets was found acceptable to DMETS. CMC Scientist acceptable for final approval 12/24/03. PRI Methods validation was previously completed and found acceptable.

6. Robert L. West Date 12/29/2003
~~Acting~~ Deputy Director, OGD Initials
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☐
Comments: (Continued) On 12/22/03, OGD received a communication from Ortho-McNeil Pharmaceuticals, Inc's counsel confirming the fact that "Ortho agreed to waive any pediatric exclusivity as to ANDA 75-808 as of December 29, 2003." Ortho has no objection to final marketing approval for this ANDA as of 12/29/03. Ortho also made it clear that this waiver of pediatric exclusivity effective 12/29/03 applies only to ANDA 75-808.

Based upon the settlement agreement reached between Barr and Ortho McNeil, this ANDA is recommended for final approval. OGD's general counsel, Richard Dickinson, has reviewed Ortho's waiver of pediatric exclusivity and has no objection to OGD's approval of this ANDA on 12/29/03.

7. Gary Buehler Date 12/29/03
Director, OGD Initials GB
Comments: (Methods previously approved on 12/18/02. Status was changed to
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐
Sarah Kim TA on 8/20/03 9/24/03)

8. Project Manager, Team Date 12/29/03
Review Support Branch Initials
NA Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
1:06 pm Time notified of approval by phone 1:06 pm Time approval letter faxed
FDA Notification:
12/29/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/29/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

RLD=Ortho Tri-Cyclen-28 Tablet
Formerly: R.W. Johnson Pharmaceutical Research Institute NDA 19-697 (001)
Now: Ortho McNeil Pharmaceutical, Inc.

File V:/division/dlps/approvrou4.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-808

CORRESPONDENCE

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

February 16, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
[redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg)
[redacted] 28 day regimens.

In accordance with the regulations under section 505(j) of the Federal Food and Cosmetic Act, Barr Laboratories, Inc. is submitting an Abbreviated New Drug Application for [redacted] (norgestimate and ethinyl estradiol tablets, USP 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) – [redacted] 28 day regimens.

The application is provided in duplicate, as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of 5 volumes. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 4 volumes. .As stated in the February 1999 "Guidance for Industry; Organization of an ANDA", please note that two extra separately bound copies are being submitted since [redacted] (norgestimate and ethinyl estradiol tablets, 0.180mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) is not a USP product. The bioequivalence part of the review copy is contained in an orange binder consisting of 1 volume.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, are Debarment Certification Statements from Barr and its outside contractors. Field Copies of this application have been forwarded to the New York and Chicago District Offices.

The CMC section of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

APPEARS THIS WAY
ON ORIGINAL

Acc'd for filing
Middleton
3/2/00
505(j)(2)(A)(i)

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

NEW CORRESP
Nc

March 3, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

75-808

CORRESPONDENCE TO PENDING APPLICATION

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
[redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) [redacted] 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for [redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) [redacted] 28 day regimens.

Reference is also made to Barr's February 16, 2000 ANDA submission for the above referenced products.

Please be advised that at this time we are submitting additional information regarding DMF authorization for the [redacted] In accordance with the April 8, 1994 Letter to Industry regarding the letter of authorization from the DMF holder, we are herewith submitting the following additional document:

- Copy of Page 5 of [redacted]'s DMF stating "we herewith authorize [redacted]. to represent [redacted] in all matters pertaining to this file". In addition the page states DMF # [redacted], name of bulk active drug substance, [redacted], and is signed and dated.

Please be advised that identical copies of this Correspondence have been provided to the New York and Chicago District Offices. Document certifications are attached.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 06 2000
OGD

Barr Laboratories, Inc.

NEW CORRESP

NC

March 16, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

75-808

REFERENCE: **AMENDMENT TO PENDING ANDA**
[redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 250 mg/ 0.035 mg) [redacted] 28 day regimens.
Electronic Submission of CMC

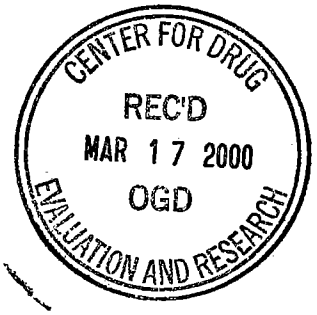
Reference is made to our Abbreviated New Drug Application submitted February 16, 2000 under 505(j) of the Food, Drug and Cosmetic Act for [redacted] (norgestimate and ethinyl estradiol tablets, USP 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 250 mg/ 0.035 mg).

As indicated in our original application, Barr Laboratories, Inc. is amending the above referenced application to provide the CMC electronic submission. The CMC electronic submission is contained on a separate diskette labeled " CMC ESD & Companion Document". A backup diskette containing identical information for the CMC section is also provided.

The CMC ESD file is named "BRL0003.003" and the Microsoft Word Companion Document file is named "BRL0003.004".

Barr Laboratories, Inc. declares that the information provided in the electronic submission is the same as the information provided in the paper submission.

A copy of this letter has been forwarded to the New York and Chicago District Offices.



If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President of Quality and
Regulatory Counsel

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-808

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. BOX 2900
Pomona, NY 10970-0519

APR 4 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your amendment dated March 8, 3rd SAM, 2000.

NAME OF DRUG: Ethinyl Estradiol; Norgestimate Tablets 0.035 mg/0.180 mg, 0.035 mg/0.215 mg and 0.035 mg/0.250 mg

DATE OF APPLICATION: February 16, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 18, 2000

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Nasser Mahmud, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ruby Yu
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-808
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/NMahmud, Chief, RSB date 3/30/00
HFD-615/SMiddleton, CSO S. Middleton date 3/29/00
Word File
V:\FIRMSAM\BARR\LTRS&REV\75808.ACK
FT/mjl/3/27/00
ANDA Acknowledgment Letter!

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 18, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW CORRESP
NC

TELEPHONE BIOEQUIVALENCE AMENDMENT

REFERENCE: ABBREVIATED NEW DRUG APPLICATION 75-808
[redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
[redacted] 28 day regimens.

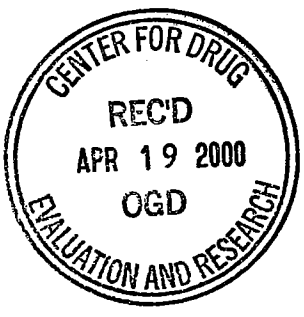
Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for [redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) [redacted] ™ 28 day regimens.

Reference is also made to a telephone conversation on April 6, 2000 between Ms. Patricia Nguyen and Moheb Makary (FDA) and Christine Mundkur (Barr Laboratories) in which Ms. Nguyen and Mr. Makary requested that Barr provide the following:

1. Batch size and description (weight, thickness, and hardness) for Barr's submission batches.

2. Assay and content uniformity for reference products.

APPEARS THIS WAY
ON ORIGINAL



REFERENCE: ABBREVIATED NEW DRUG APPLICATION 75-808
[redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
[redacted] 28 day regimens.

RESPONSE:

Enclosed please find a copy of the following proposed master formula pages which specify the batch size and description of the active and placebo tablets:

- Norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg
- Norgestimate and ethinyl estradiol tablets, 0.215 mg/0.035 mg
- Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg
- [redacted] Placebo Tablets for Oral Contraceptives used for [redacted]
- White, Biconvex, Placebo Tablets for oral contraceptives used for [redacted]

Enclosed please find copies of Barr's new In-Vitro Comparative Analytical Study Report, RD00-104 and updated reports RD99-281B and RD99-282B, comparing the assay and content uniformity tests of Barr's test batches 109879R02, 109869R01, and 109859R01 to those of Ortho Pharmaceutical Corporation's ORTHO-CYCLEN 28 Tablets USA batches. These reports were inadvertently not submitted with the original application. The data obtained indicate that the assay and content uniformity of the Barr products are similar to the reference products and that all products meet the required specifications. Please note that Barr's test batches were compared to both the USA Ortho-Cyclen and Canadian Cyclen products since Barr is interested in filing under separate cover for approval of this product in the Canadian marketplace. For the purposes of this submission, only the USA reference data is applicable. Also note that dissolution test results are already included as part of the original ANDA submission and therefore are not included in all of the enclosed comparative analytical study reports.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

May 2, 2000

ORIG AMENDMENT
N/A

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

TELEPHONE BIOEQUIVALENCE AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION 75-808**
(norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) - **28-day** regimens.

Reference is also made to a telephone conversation on April 18, 2000 between Ms. Patricia Nguyen of the FDA and Christine Mundkur of Barr Laboratories in which Ms. Nguyen requested that Barr conduct additional dissolution profiles for the submission and reference product batches using the following conditions:

Apparatus II: paddles,
Speed: 75 rpm
Volume: 600 mL
Medium: 0.05% Tween 20

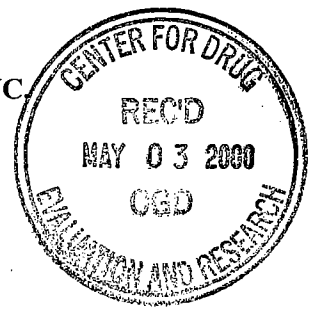
Accordingly, enclosed please find In-Vitro Comparative Dissolution Study Reports comparing Barr's submission/bio batches to the reference product's (Ortho Pharmaceutical Corporation) batches using the above specified conditions.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel



Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

June 2, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
Nc

PATENT AMENDMENT

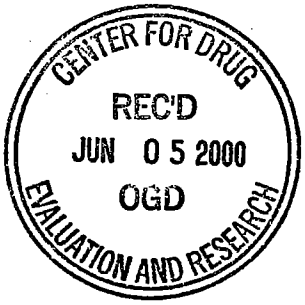
REFERENCE: **ANDA 75-808**
———— (NORGESTIMATE AND ETHINYL ESTRADIOL TABLETS, 0.180 mg/ 0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
———28 DAY REGIMENS

Reference is made to our Pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ———— (Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/ 0.035 mg, 0.215 mg/0.035 mg, 0.250 mg/0.035 mg) ——28 Day Regimens.

In accordance with our Patent Certification Statement submitted in Section III of the Application and 21 CFR §314.95(a), notice was sent by certified mail, return receipt requested to the owner of the patents claimed and to the holder of the approved application under Section 505(b) of the Act.

In accordance with 21 CFR §314.95(b), Barr is hereby submitting a Patent Amendment to certify that notice was provided to Ortho McNeil Pharmaceutical Inc. (patent holder) and RW Johnson Pharmaceutical Research Institute (holder of NDA 19-697) by Cohen, Pontani, Lieberman and Pavane LLP on behalf of Barr Laboratories **(Pages 1 to 6)**. A copy of this letter was also submitted to Johnson and Johnson, Legal Department. These letters were sent upon receipt of FDA's acknowledgement letter dated April 4, 2000 stating that Barr's Abbreviated New Drug Application was sufficiently complete to permit a substantive review.

The contents of the notice letter comply with 21 CFR §314.95(c). The notice letter cites Section 505(j)(2)(B)(ii) of the Act. In this notice letter, Barr alleges that U.S. Patent Nos. 4,530,839; 4,544,554; 4,616,006; and 4,628,051 which Johnson has certified to the FDA expire on September 26, 2003 are each invalid and/or unenforceable. Barr further alleges in this letter that U.S. Patent No. 4,530,839 and certain claims of US Patent Nos. 4,544,554, 4,616,006 and 4,628,051 will not be infringed by the manufacture, use, or sale of Barr's Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— 28 Day Regimens).



REFERENCE: **ANDA 75-808**
[(NORGESTIMATE AND ETHINYL ESTRADIOL TABLETS, 0.180 mg/ 0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
28 DAY REGIMENS

In accordance with 21 CFR §314.95(e), enclosed as **Page 7 and 8** are copies of the return receipts from Ortho McNeil Pharmaceutical Inc., RW Johnson Pharmaceutical Research Institute, and Johnson & Johnson for the notices which were delivered on April 28, 2000.

This completes Barr's Patent Amendment dated June 2, 2000.

Sincerely,

BARR LABORATORIES, INC.

for

Christine Mundkur
Vice President,
Quality and Regulatory Counsel

This submission is comprised of Pages 1 through 8.

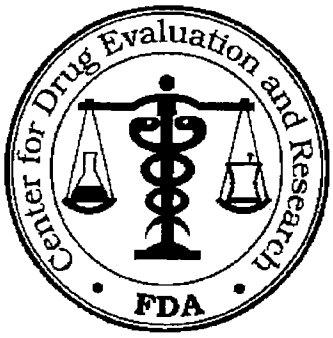
APPEARS THIS WAY
ON ORIGINAL

Pages 3-8 were not located.

MAJOR AMENDMENT

AUG 28 2000

ANDA 75-808



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Barr Laboratories, Inc. PHONE: 914-353-8432

ATTN: Christine Mundkur FAX: 914-353-3859

FROM: Ruby Yu PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg.

Reference is also made to your amendment(s) dated May 2, 2000.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

Chemistry and Bioequivalency comments are provided. Labeling comments will be provided when the review is completed.

X:\new\ogdadmin\macros\faxmaj.frm

RPM
8-25-00

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

8/28/2000 FDA FAX

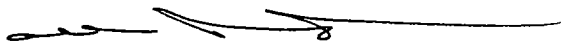
1. A satisfactory compliance evaluation of all of the facilities for drug product manufacturing and quality control in the application is necessary at the time of the approval of the application.

2. The agency's district office will request samples for the drug substance and finished dosage form for the methods validation at the appropriate time.

3. Your labeling review is pending. Any comments found will be communicated in a separate letter.

4. Please provide all room temperature stability data.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75808 APPLICANT: Barr Laboratories

DRUG PRODUCT: Norgestimate/Ethinyl Estradiol
0.180mg/0.035 mg, 0.215mg/0.035 mg and
0.25mg/0.035mg- ——— 28 day Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 600 mL of 0.05% Tween 20 , at 37°C using USP24 Apparatus (II) at 75 rpm. The test product should meet the following specifications:

Not less than —% (Q) of the labeled amount of norgestimate in the dosage form is dissolved in 90 minutes.

Not less than —% (Q) of the labeled amount of ethinyl estradiol in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 28, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT
N/Ac

MAJOR AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
[redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg) [redacted] 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for [redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg) [redacted] day regimens.

Reference is also made to the August 28, 2000 major deficiency letter. The deficiencies identified in the comment letter and Barr's responses are as follows:

COMMENT 1:

Please note that the DMF [redacted] is currently inadequate. The DMF holder, [redacted], has been notified.

Response 1:

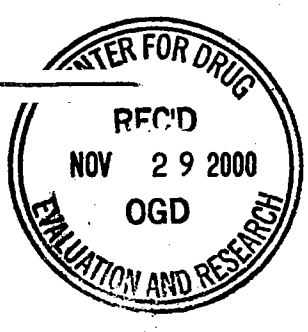
[redacted] responded to the Agency's Deficiency Letter on October 23, 2000.

COMMENT 2:

Please add test and specification for [redacted] per supplier specifications and provide the revised specifications.

Response 2:

Barr has added tests and specifications for [redacted] based on data from the vendor.



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confidential commercial

information from

11/28/2000 BARR LETTER

COMMENT 2:

The agency's district office will request samples for the drug substance and finished dosage form for the methods validation at the appropriate time.

Response 2:

Acknowledged.

COMMENT 3:

Your labeling review is pending. Any comments found will be communicated in a separate letter.

Response 3:

Acknowledged.

COMMENT 4:

Please provide all room temperature stability data.

Response 4:

All of the room temperature stability data collected for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035mg, and 0.250 mg/0.035 mg as well as placebo tablets is provided in **Attachment 10.**

Identical copies of this Amendment have been provided to the New York and Chicago District Offices. A Document certification is attached. Also enclosed is a copy of Barr's Bioequivalence Amendment.

This completes the present Amendment. If you have any questions please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Cc: New York and Chicago District Offices
Division of Bioequivalence

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 28, 2000

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AB

BIOEQUIVALENCE AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
——— (norgestimate and ethinyl estradiol tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg)
——— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ——— (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg) ——— 28 day regimens.

Reference is also made to the August 28, 2000 bioequivalence letter that stated:

Bioequivalency Comments:

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

> The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:
>
> > Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes.
> > Not less than — % (Q) of the labeled amount of Ethinyl Estradiol is dissolved in 30 minutes.

Response:

On May 2, 2000, Barr submitted additional in-vitro comparative dissolution reports using the dissolution testing described above [600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm]. Barr followed Test Method, TM-461C that states the dissolution specifications as "—% (Q) of the labeled amount of Norgestimate and Ethinyl Estradiol is dissolved in 60 minutes". This was done in response to an April 18, 2000 telephone call from Patty Nguyen, Div. of Bioequivalence. Barr did not and does not agree with adopting this testing nor the specifications as part of our stability and quality control programs for the following reasons:

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

11/28/2000 BARR LETTER (RE: BIOEQUIVALENCE)

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

January 2, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT

REFERENCE: **AMENDMENT TO PENDING ANDA**
ANDA # 75-808
[redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035mg) [redacted] 28 day regimens.
Electronic Submission of CMC Amendment

Reference is made to our Abbreviated New Drug Application submitted November 28, 2000 under 505(j) of the Food, Drug and Cosmetic Act for [redacted] (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg).

Barr Laboratories, Inc. is amending the above referenced application to provide the CMC electronic version of our response to the Major Amendment dated November 28, 2000.

Enclosed please find the CMC ESD files "BRL0026.003" and the Microsoft Word Companion Document file "BRL0026.004". Backup diskettes containing identical information for the CMC section is also provided.

Barr Laboratories, Inc. declares that the information provided in the electronic submission is the same as the information provided in the paper submission.

A copy of this letter has been forwarded to the New York and Chicago District Offices.

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

NDA Rpt 1/9/01

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President of Quality and Regulatory Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 03 2001
OGD

1-8-01

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 1, 2001

ORIG AMENDMENT
N/AC

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg
——— 28 day regimens

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg, ——— 28 day regimens.

Reference is also made to a February 1, 2001 phone conversation between Ruby Yu, CSO, OGD, FDA and Elisabeth Noble Gray, Barr Laboratories, Inc. regarding the filing of a change in the manufacturing site of the ——————————— (supplied by ——————————. In accordance with Ms. Yu's instructions, we are filing this change in an Amendment to the pending application.

The manufacturing site change is as follows:

Old Site: \

New Site: \

——————— site was inspected and approved by FDA in 1998. In July 1999, FDA set forth requirements for both ——— and their customers for the transfer of products to the new facility. ——— fulfilled all requirements and submitted an amendment to the relevant DMF's (see updated authorization letter to reference ——— DMF No. ——, which includes the ——— facility).

Barr Laboratories, Inc.

REFERENCE: **ANDA # 75-808**
Norgestimate and Ethinyl Estradiol Tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg
——— 28 day regimens

In accordance with FDA's ——— communication to ———(see attached), Barr hereby commits to place the first commercial batch of norgestimate and ethinyl estradiol tablets, USP using the new source of drug (new site) on stability under Barr's proposed stability protocol to support Barr's approved packaging configurations.

Please note that the processes at the ——— site do not differ materially from those of the ——— site. Also, a GMP inspection covering the processes that are representative of process used for the four new drug substances was performed in ———. A 483 was issued and contained minor comments. ———. believes they provided more than adequate responses in their ——— correspondence that satisfied FDA's concerns. There have been no further communications regarding this 483 issued to ——— by FDA. Please note that FDA does not issue an acknowledgment or "approval" letter upon receipt of a satisfactory manufacturer response. It is normal practice for FDA to only respond to the manufacturer if the response is inadequate.

Enclosed please find the following documentation:

- Copy of ——— authorization letter (dated 8/21/00) to reference their DMF No. ——— for ———, as last updated on 1/3/00. Please note that ——— is owned by the parent company, ———. Therefore, the enclosed DMF letter is on ——— letterhead.

- Copy of the July 20, 1999 From FDA to ——— regarding the filing requirements.

An identical copy of this Amendment has been provided to the New York and Chicago District Offices. A document certification is attached.

If you have any questions concerning this Amendment, please contact Christine Mundkur by phone at 845-353-8432 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President,
Quality and Regulatory Counsel

Cc: ———
New York and Chicago District Office

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 5, 2001

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

BIOEQUIVALENCE AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250mg/0.035 mg – ——— 28 day regimens

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250mg/0.035 mg · ——— 28 day regimens.

Reference is also made to a January 4, 2001 bioequivalence letter submitted to companion ANDA 75-804 for Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg - ——— 28 day regimens. Even though we have not received a similar letter for this application, ANDA 75-808, we are submitting a bioequivalence amendment addressing the issues stated by FDA in their January 4, 2001 letter. This action was confirmed by Krista Scardina, Project Manager, Div. Of Bioequivalence, FDA in a February 2, 2001 phone conversation with Elisabeth Noble Gray, Barr Laboratories, Inc.

The January 4, 2001 bioequivalence letter addressed to ANDA 75-804 states:

Bioequivalency Comments:

Your proposed ——————————— dissolution method is not acceptable for the following:

1. Your argument that by using the 0.05% Tween-20 medium the dissolution rate *in vitro* does not reflect the actual dissolution rate *in vivo*, therefore, the method is not suitable. In the absence of a suitable verified *in vivo/in vitro* correlation this argument is not relevant. Furthermore, the *in vitro* dissolution testing for Norgestimate/Ethinyl Estradiol drug products serve mainly as a quality control specification for the manufacturing process.

2. The ——————————— dissolution method you proposed provided — % release of norgestimate in 15 minutes from Norgestimate/Ethinyl Estradiol Tablet 0.25 mg/0.035 mg. Therefore, this method is not suitable as a discriminatory tool for routine dissolution testing.

3. The 0.05% Tween-20 dissolution method recommended by the Agency and proposed by Pharmacopeial Forum (Vol. 26 (5) [Sept.-Oct. 2000] provided —% and —% release of norgestimate in 15 and 90 minutes, respectively, from Norgestimate/Ethinyl Estradiol Tablet, 0.25mg/0.035mg. Therefore, the method appears to be discriminatory for routine dissolution testing.

   The following dissolution testing will need to be incorporated intoyour stability and quality control programs:

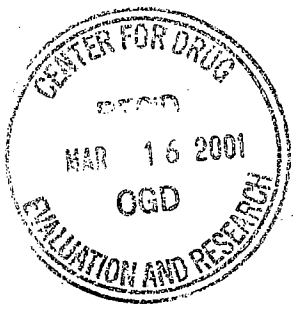
   The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37^0C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

   Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes.
   Not less than —% (Q) of the labeled amount of Ethinyl Estradiol is dissolved in 30 minutes.

Response:

Barr has adopted the Agency's above recommended dissolution testing procedure and specifications into their stability and quality control programs. Enclosed please find updated method validation report RD00-124B (**Attachment I**). System Suitability, Specificity (Sample Matrix Interference), Linearity, Precision, Ruggedness, Filtration Study and Sample and Standard Solution Stability studies were performed in order to provide assurance that the dissolution test procedure for Norgestimate and Ethinyl Estradiol is appropriate for testing the Barr product. Also enclosed please find Barr's updated In-Process and Finished Product Test Method, TM-461D and corresponding Analytical Specifications and Test Record and Marketed Product Stability Specifications and Test Records (**Attachment II**) which incorporate the Agency's recommended dissolution testing procedure and specifications.

This completes the bioequivalence amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.



Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 9, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/A C

AMENDMENT TO 2/1/01 AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg
—— 28 day regimens

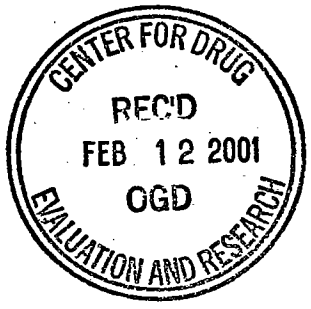
Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg) —— 28 day regimens.

Reference is also made to Barr's February 1, 2001 Amendment for a change in the manufacturing site of the ———— (supplied by ————) from ———— to ————

This Amendment is to correct the February 1, 2001 Amendment that incorrectly stated ———— new manufacturing site located in ———— as a site change. The new ———— site is an ALTERNATE site to ————'s existing ———— site. Therefore, the manufacturing sites for ———— ingredient are as follows:

Site 1:

Site 2:



In addition, the establishment attachment to the 356h form submitted with the February 1, 2001 Amendment has been corrected to include both manufacturing sites for ———— All documentation to support ————'s new, additional ———— site was submitted with the February 1, 2001.

REFERENCE: **ANDA # 75-808**
Norgestimate and Ethinyl Estradiol Tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250mg/0.035 mg
28 day regimens

An identical copy of this Amendment has been provided to the New York and Chicago District Offices. A document certification is attached.

If you have any questions concerning this Amendment, please contact Christine Mundkur by phone at 845-353-8432 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President,
Quality and Regulatory Counsel

Cc:
New York and Chicago District Office

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

3/9/2001 BARR LETTER

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 15, 2001

WAB

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

Attn:
Krista Scardina, Project Manager

Ms. Scardina,

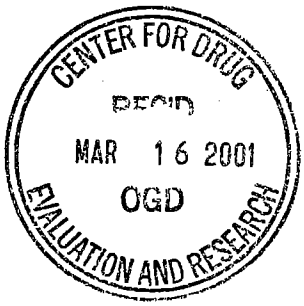
As we discussed in our phone conversation today, enclosed please find another copy of Barr's February 5, 2001 Bioequivalence Amendment.

If you have any questions, please contact me by phone at (845) 353-8428 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Elisabeth Noble Gray
Technical Group Leader



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

Office of Generic Drugs

7500 STANDISH PLACE (HFD-600), ROCKVILLE, MD 20855

Phone: (301) 827-5763
Fax: (301) 594-0180

FAX TRANSMISSION COVER SHEET

Date:	March 28, 2001
To:	Christine Mundkur 845-353-8432
Fax:	845-353-3859
Re:	ANDA 75-808
Sender:	Ruby Yu, Project Manger

TOTAL NUMBER OF PAGES: __2___

Comment(s):

Bioequivalency comments provided.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75808 APPLICANT: Barr Laboratories

DRUG PRODUCT: Norgestimate/Ethinyl Estradiol Tablets
0.180mg/0.035 mg, 0.215mg/0.035 mg and
0.25mg/0.035mg- —— 28 day regimens

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes

Not less than —% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 minutes

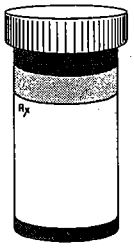
Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Christine Mundkur
Barr Laboratories, Inc.
Fax: 845-353-3859 **Phone:** 845-353-8432

From: Debra M. Catterson
Fax: 301-443-3847 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 3 **Date:** April 11, 2001

Comments:

Dear Ms. Mundkur,

Attached is the labeling review of your February 16, 2000 submission for ANDA 75-808 for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— 28 Day Regimens).

Please feel free to call me if you have any questions.

Sincerely,

Debra M. Catterson

FIRST GENERIC

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-808

Date of Submission: February 16, 2000 (Original draft labeling)

Applicant's Name: Barr Laboratories, Inc.

Established Name: Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (——— 28 day regimens)

Labeling Deficiencies:

1. **GENERAL COMMENT:**

   We believe that your proposed proprietary name "———" would be misleading as defined under 21 CFR 201.10(c)(5) since it sounds like or looks like the currently marketed oral contraceptives *Tri-Norinyl*, and *Tri-Levlen*. Please revise and/or comment.

2. **CONTAINER** (Fold-over blister dose card, ——— 28 Day):

   Satisfactory in draft.

3. **AUXILIARY LABEL**

   Satisfactory in draft.

4. ——— 28 Day):

   Satisfactory in draft.

5. **CARTON** (——— 6 x 28 Day):

   Satisfactory in draft.

6. **INSERT** (Physician Labeling, Detailed Patient Labeling, and Brief Summary Patient Labeling):

   a. GENERAL COMMENT:

   We note that you have modeled your labeling after the reference listed drug's labeling, Ortho Tri-Cyclen® by RW Johnson, revised May 1998. However, this labeling is not the most recently approved. 21 CFR 314.94(a)(8)(iv) requires that your labeling be the same as that approved for the reference listed drug. Please revise your physician insert labeling to be in accordance with the reference listed drug's labeling, revised January 2000 and approved June 5, 2000; and revise your Detailed Patient Labeling and Brief Summary Patient Labeling to be in accordance with the

reference listed drug's patient labeling, revised April 2000 and approved Jan. 16, 2001. Please refer to our fax dated April 6, 2001, concerning your ANDA 75-804, for a copy of the aforementioned reference listed drug labeling.

b. DESCRIPTION – (Physician Labeling only.):

Please correct the description of the contents of each gray, light blue, and blue tablet. For example, for the gray tablet, your labeling incorrectly states:

"Each gray tablet contains 0.180 mg [redacted] ...and 0.035 mg of the estrogenic compound, ethinyl estradiol...".

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

ANDA 75-808

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAY 14 2001

TO: APPLICANT: Barr Laboratories, Inc.

TEL: 845-353-8432

ATTN: Christine Mundkur

FAX: 845-353-3859

FROM: Ruby Yu
for: Paras Patel

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 18, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28 day regimens).

Reference is also made to your amendment(s) dated: November 28, 2000, February 1, 2001, February 9, 2001 and March 9, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Your labeling review is pending. Any comments found will be communicated in a separate letter.

CMC comments are attached.

P.M.P
5/14/01

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT MAY 14 2001

ANDA: 75-808

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— 28 day regimens)

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. [redacted]

2.

3.

4.

5.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your labeling review is pending. Any comments found will be communicated in a separate letter.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

June 1, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AF

Labeling Amendment

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg —— 28 day regimens

Reference is made to the pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg —— 28 day regimens.

Reference is also made to your facsimile letter dated April 11, 2001 regarding Barr's February 16, 2000 submission in which the following comments were made:

1. GENERAL COMMENTS:

We believe that your proposed proprietary name —— would be misleading as defined under 21 CFR 201.10c(5) since it sounds like or looks like the currently marketed oral contraceptives *Tri-Norinyl*, and *Tri-Levlen*. Please revise and/or comment.

2. CONTAINER (Fold-over blister dose card, —— 28 Day):

Satisfactory in draft.

3. AUXILIARY LABEL:

Satisfactory in draft.

4. —— 28 Day):

Satisfactory in draft.

CENTER FOR DRUG EVALUATION
JUN 04 2001

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg ——— 28 day regimens

5 **CARTON** (——— 6 x 28 Day)

Satisfactory in draft.

6. **INSERT** (Physician Labeling, Detailed Patient Lableing, and Brief Summary Patient Lableing):

a. GENERAL COMMENT:

We note that you have modeled your labeling after the reference listed drug's labeling, Ortho Tri-Cyclen® by RW Johnson, revised May 1998. However, this labeling is not the most recently approved. 21 CFR 314.94 (a)(8)(iv) requires that your labeling be the same as that approved for the reference listed drug. Please revise the physician insert labeling to be in accordance with the enclosed labeling for the reference listed drug, revised January 2000 and approved June 5, 2000; and revise your Detailed Patient Labeling and Brief Summary Patient Labeling in accordance with the reference listed drug's patient labeling, revised April 2000 and approved January 16, 2001. Please refer to our fax dated April 6, 2001 concerning your ANDA 75-804, for a copy of the aforementioned reference listed drug labeling.

b. DESCRIPTION – (Physician Labeling only):

Please correct the description of the contents of <u>each</u> gray, light blue, and blue tablet. For example, for the gray tablet, your labeling incorrectly states:

"Each gray tablet contains 0.180 mg ——————————————— ——————————— ...and 0.035 mg of the estrogenic compound, ethinyl estradiol..."

Please revise your labels and labeling, as instructed above and submit in final print.

RESPONSE:

Barr acknowledges your General Comment regarding our proposed proprietary name ——— ——— At this time we are submitting the following newly proposed trade names for submission to OPDRA:

1 ———
2 ———
3 ———
4 TRI-SPRINTEC™
5 ———

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg ——— 28 day regimens

Barr has updated it's Physician Insert, Detailed Patient Labeling, and Brief Summary Patient Labeling in accordance with the most recently approved labeling of RW Johnson for their Ortho Tri-Cyclen product as provided by FDA in their April 6, 2001 facsimile to Barr's ANDA 75-804. The Description in the Physician Labeling has also been corrected in response to your comment number 6b above.

In response to an OPDRA comment, Barr adjusted the PMS color bar with the generic product name by means of percentage variations to differentiate between the day regimens. To further provide differentiation between the day regimens, a background color box was added to the 28 day regimen labeling pieces.

In addition, Barr is changing the packaging configuration to include a foil pouch and wallet instead of a ———. The foil pouch will contain the same wording as the ——— except for the Barr logo (there is no logo on the pouch). Within the foil pouch will be the following components: blister card, fold-over dose card, unprinted wallet, PPI/Brief summary combination, and days of the week sticker. This change is being done for aesthetic purposes and is Annual Reportable in accordance to the Changes to an Approved NDA or ANDA Guidance, November 1999, Section IX.D.5. The new proposed package configuration (foil pouch/wallet) does not affect the primary packaging materials and provides the same or better protective properties as the old proposed package configuration (blister sleeve).

Attached please find the following documentation in support of this Labeling Amendment:

1. Side by side comparisons
   a. New versus previous fold-over dose cards
   b. New foil pouch versus previous
   c. New versus previous folding carton
   d. New versus previous PPI/brief summary combination
   e. New versus previous package brochure

2. Proposed labeling (4 archival and review copies)
   a. Fold-over dose cards
   b. Folding carton
   c. PPI/brief summary combination
   d. Package brochure

   Note that the "days of the week" sticker is not being included since it was approved in final print.

3. Documentation for the foil pouch
   a. Material Specification Sheet
   b. Engineering Diagram

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg - ——— 28 day regimens

Upon approval of one or more of these proposed trade names, Barr will submit final printed labeling to the Agency.

This completes the Labeling Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

APPEARS THIS WAY
ON ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

June 11, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg ——— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg ——— 28 day regimens.

Reference is also made to the Agencies' letter dated May 14, 2001 regarding Barr's November 28, 2000, January 2, 2001, February 1, 2001, February 9, 2001 and March 9, 2001 amendments in which the following deficiencies are stated:

SECTION A:
COMMENT 1:

Please note that the DMF ——— for ——————— remains inadequate. The DMF holder, ——— , has been notified of the deficiencies. Please do not respond to this MINOR amendment until you have been informed by the DMF holder stating that a satisfactory response has been submitted to Agency's DMF deficiency letter.

Response 1:

———————) responded to the Agency's Deficiency Letter on June 8, 2001.

COMMENT 2:

Proposed specification for the ———————————————
Please ———————————————

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 12 2001
OGD

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

6/11/2001 BARR LETTER

Enclosed as **Attachment III** please find the updated documentation: In-Process and Finished Product Test Method, TM-469D, corresponding Quality Control and Marketed Product Specifications and Test Records, and Marketed Product Stability Protocol.

SECTION B
COMMENT 1:

Your labeling review is pending. Any comments found will be communicated in a separate letter.

Response 1:

Barr acknowledges that labeling comments will be received under separate cover.

An identical copy of this Amendment has been provided to the New York and Chicago District Field Offices. A document certification is attached.

If you have any questions concerning this Amendment, please contact Christine Mundkur by phone at 845-353-8432 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President,
Quality and Regulatory Counsel

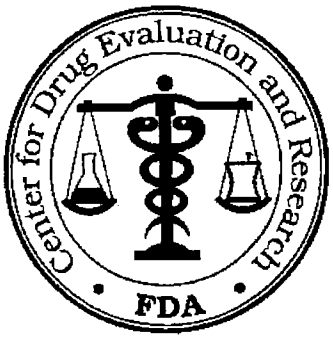
Cc: New York and Chicago District Office

MINOR AMENDMENT

ANDA 75-808

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL - 5 2001



TO: APPLICANT: Barr Laboratories

TEL: 845-353-8432

ATTN: Christine Mundkur

FAX: 845-353-3859

FROM: Ruby Yu

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.35 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg.

Reference is also made to your amendment(s) dated: June 11, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Labeling comments, if any, will be provided when the review is completed.

Ryu
7/5/01

JUL -5 2001

9. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-808

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (——— 28 day regimens)

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. Please note that the DMF ——— for ——————— remains deficient. The DMF holder, ———————, has been notified of the deficiencies. Please do not respond to this MINOR amendment until you have been informed by the DMF holder stating that a satisfactorily response has been submitted to Agency's DMF deficiency letter.

2. Please revise the specifications for ——————— ———————, according to manufacturer' current specifications, where applicable, and please provide a copy of your and manufacturer's updated specifications.

3. [redacted]

Sincerely yours,

Paul S. Lee

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 26, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/A M

MINOR AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg - ——— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg - ——— 28 day regimens.**

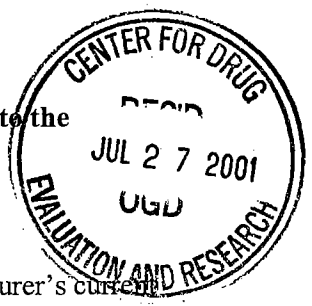
Reference is also made to FDA's July 5, 2001 deficiency letter in which the following is stated:

COMMENT A.1.

Please note that the DMF——— for ——————— remains deficient. The DMF holder, ———., has been notified of the deficiencies. Please do not respond to this MINOR amendment until you have been informed by the DMF holder stating that a satisfactory response has been submitted to Agency's DMF deficiency letter.

Response A.1.

——————. has informed Barr that on July 24, 2001 they submitted their response to the Agency's DMF deficiency letter.



COMMENT A.2.

Please revise the specifications for ————————————, according to manufacturer's current specifications, where applicable, and please provide a copy of your and manufacturer's updated specifications.

Response A.2.

——————— has not changed their specifications for the ———————————— (as stated in their July 24, 2001 DMF deficiency response letter). Therefore, there is no need for Barr to revise their specifications for the ————————————.

Barr Laboratories, Inc.

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg - [redacted] 28 day regimens.

COMMENT A.3.

[redacted]

Response A.3.

[redacted]

An identical copy of this Minor Amendment has been provided to the New York and Chicago District Offices. A document certification is attached.

If you have any questions concerning this Minor Amendment, please contact Christine Mundkur by phone at 845-353-8432 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President,
Quality and Regulatory Counsel

Cc: [redacted]
New York and Chicago District Offices

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

January 23, 2002

LABELING CORRESPONDENCE

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW CORRESP
NC

Via Fax 301-443-3847

RE: ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg ——— 28 Day Regimens

Dear Sir or Madam:

Reference is made to our pending Abbreviated New Drug Application for Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg ——— 28 Day Regimens.

At this time, Barr would like to propose the Trade name '———' for the Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215mg/0.035 mg, and 0.250 mg/0.035 mg in ——— ——— 28 Day Regimens.

Please note that we would like to keep the already approved "Tri-Sprintec" tradename available in the event the proposed tradename '———' is denied by DMETS.

Upon approval of the proposed trade name, we will amend our application and submit final printed labeling to the Agency.

This completes the Labeling Correspondence. If you have any questions, please contact me by phone at (845) 348-6894 or by fax at (845) 353-3859.

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 25 2002

Sincerely,

BARR LABORATORIES, INC.

Salvatore P. Peritore, M.S., R.Ph.
Associate Director, Regulatory Affairs

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 29, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, USP
0.18/0.035mg, 0.215/0.035 mg and 0.25/0.035 mg)
——— 28 day regimens.

TELEPHONE AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, USP 0.18/0.035 mg, 0.215/0.035 mg, 0.25/0.035 mg - ——— 28 day regimens.

Reference is also made to a March 27, 2002 phone conversation among Ruby Wu, Dr. David Grill, and Neeru Takiar, OGD, FDA and Christine Mundkur, ——————— ——————— and Elisabeth Noble Gray, Barr Laboratories, Inc. regarding the following changes/clarifications.

———————

Barr Laboratories, Inc. has updated the Raw Material Test Method along with the corresponding Raw Material Specification and Test Record for the ——————— ——— to incorporate the manufacturer's specifications for ———————, and Melting Point. The updated Raw Material Specification and Test Record can be found in Attachment I.

RECEIVED
APR 0 1 2002
OGD / CDER

Packaging - Secondary Pouch Material

As stated in Barr's April 20, 2001 Labeling Amendment, we are changing our packaging configuration to include an aluminum foil pouch and wallet instead of a ———. Sprintec™ will be packaged in blisters of——— 28 tablets as follows: the blisters will be placed within a fold over card, the dose cards will be packaged in aluminum foil pouches along with a days of the week sticker, combination detailed patient labeling, brief summary, and non-printed vinyl wallet. This change is being done for esthetic reasons only.

The new proposed package configuration (foil pouch/wallet) does not affect the primary packaging materials and provides the same or better protective properties as the old proposed package configuration ———.

The following information concerning the aluminum foil pouch can be found in Attachment II.

- DMF Authorization Letter (DMF-——— from ———
- ——— Material Specification
- Pouch Diagram
- ——— Material Specification
- ——— Certification of Compliance (representative Lot # 7-43614)

Finished Product Analytical Specification and Test Record and Test Method

FDA requested that Barr Laboratories, Inc. update their current In-Process and Finished Product Test Method and Analytical Specifications and Test Record to incorporate the ——— assay specification of ——— % for ——— testing and to tighten the impurity specification for ——— for release purposes.

[redacted]

See Attachment III for our "Justification for the proposed impurities testing requirements for the Norgestimate and Ethinyl Estradiol Tablets.

A copy of the updated In-Process and Finished Product Test Method and Analytical Specifications and Test Record are provided in Attachment IV.

Stability Report/Dissolution Testing

Please find as Attachment V a copy of the updated stability report. Note that the last two time points (18 months and 25 months) were tested under the new dissolution method and specifications (NLT — % (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes. NLT — % (Q) of the labeled amount of Ethinyl Estradiol is dissolved in 30 minutes). Also note that the submission batches were re-accelerated and tested with the updated dissolution method. Results of this "experimental study" are also provided in Attachment V.

A similar Telephone Amendment is being submitted under separate cover to Barr's Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035mg application, ANDA 75-804.

An identical copy of this Telephone Amendment has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

May 15, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, USP
0.18/0.035mg, 0.215/0.035 mg and 0.25/0.035 mg)
——— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, USP 0.18/0.035mg, 0.215/0.035 mg, and 0.25/0.035 mg ——— 28 day regimens.

Reference is also made to our March 29, 2002 Telephone Amendment and a May 5, 2002 phone conversation between Ruby Wu and Neeru Takiar, Ph.D., FDA and Christine Mundkur, Barr Laboratories, Inc. In the phone conversation Dr. Takiar requested that the following additional information be submitted in a Telephone Amendment.

Explanation on why leeching studies were not conducted

Barr Laboratories, Inc. has looked into the possibility of printing ink leeching and permeating through the pouch and dose card into the blisters. All printed materials are imprinted on the outer side of the secondary packaging component. Any leeching of ink is therefore not feasible; thus no further leeching studies will be necessary.

RECEIVED
MAY 16 2002
OGD/CDER

Redacted 4 page(s)

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confidential commercial

information from

5/15/2002 BARR LETTER

Barr Laboratories, Inc.

6.1

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

June 10, 2002

ORIG AMENDMENT
N/Am

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Via facsimile 301-594-0181

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, USP 0.180/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035mg
——— 28 day regimens

TELEPHONE AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol tablets, USP 0.180mg/0.035 mg, 0.215mg/0.035mg, and 0.25mg/0.035 mg ——— 28 day regimens.

Reference is also made to a June 10, 2002 phone conversation between Neeru Takiar, Ph.D., FDA and Christine Mundkur, Barr Laboratories, Inc., in which Dr. Takiar requested we submit an updated raw material specifications & test record and test method for ———————————————————————————————. Dr. Takiar requested that the information be submitted in a Telephone Amendment.

Accordingly, attached please find the following documents:

- Quality Control Raw Material Specifications & Test Record for ———————, ———————, Revision 13
- Raw Material Test Method for ———————————————, Version 2.0

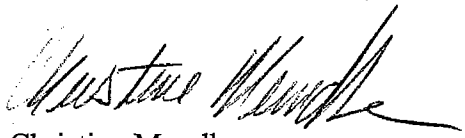
RECEIVED
JUN 11 2002
OGD / CDER

NW 6-18-02

A similar Telephone Amendment is being submitted under separate cover to Barr's Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035mg) application, ANDA 75-804.

An identical copy of this Telephone Amendment has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this Telephone Amendment, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.



Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

ANDA 75-808

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL -3 2002

TO: APPLICANT: Barr Laboratories, Inc. TEL: 845-353-8432

ATTN: Christine Mundkur FAX: 845-353-3859

FROM: Ruby Wu PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.18/0.035 mg, 0.215/0.035 mg, and 0.25/0.035 mg.

Reference is also made to your amendment(s) dated: July 26, 2001; March 29, May 15, and June 10, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Labeling comments, if any, will be provided under separate cover.

7/03/02

JUL 3 2002

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

NDA: 75-808

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. [redacted]

2.

3.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

A review of the labels and labeling is pending. Any deficiencies found will be sent to you under separate cover.

Sincerely yours,

Paul Schwetz for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 9, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.18mg/0.035 mg,
0.215mg/0.035 mg, and 0.250mg/0.035 mg
———28 day regimens

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.18mg/0.035 mg, 0.215mg/0.035 mg, and 0.250mg/0.035 mg - ——28 day regimens.

Reference is also made to the Agency's letter dated July 3, 2002 and a conference call on July 8, 2002, between Linda O'Dea, Nicholas Tantillo, and Christine Mundkur from Barr Laboratories, Inc. and Ruby Wu, Paul Schwartz, Dave Gill, Neeru Takiar, and Sarah Kim from OGD in which the following deficiencies were discussed:

COMMENT 1:

[ ]

Response 1:

As discussed in the conference call on July 8, 2002, Barr Laboratories, Inc. commits to working with the manufacturers of the———— specifications based on the data that is available and submit these revised specifications post-approval in a Changes Being Effected Supplement.

COMMENT 2:

[ ]

JUL 10 2002
OGD / CDER

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

7/9/2002 BARR LETTER

A similar Minor Amendment is being submitted under separate cover to Barr's Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035mg application, ANDA 75-804.

An identical copy of this Amendment has been provided to the New York and Chicago District Field Offices. A document certification is attached.

If you have any questions concerning this Amendment, please contact Nicholas Tantillo by phone at 845-348-8051 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Nicholas C. Tantillo
Sr. Director Regulatory Affairs

Cc: New York and Chicago District Office

APPEARS THIS WAY
ON ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

6.1

July 17, 2002

NEW CORRESP

NC

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW IMFORMATION CORRESPONDENCE

REFERENCE: ANDA 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg,
0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
——— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— 28 day regimens.

Reference is also made to a telephone conversation between Nicholas Tantillo, of Barr Laboratories, Inc. and Sara Kim, of FDA in which Ms. Kim requested that Barr restate our commitment to method validation post-approval. Ms. Kim requested that this information be submitted in a New Information Correspondence.

Accordingly please see method validation commitment below:

All has been found to be acceptable 12/18/02

Barr commits to resolve any issues identified in the methods validation process after approval.

Please be advised that identical copies of this Correspondence have been provided to the New York and Chicago District Offices. Document certifications are attached.

A similar New Information Correspondence is being submitted under separate cover to Barr's Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035mg) application, ANDA 75-804.

An identical copy of this New Information Correspondence has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this New Information Correspondence, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

Nicholas C. Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JUL 18 2002
OGD / CDER

Barr Laboratories, Inc.

6.1

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 22, 2002

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW IMFORMATION CORRESPONDENCE

REFERENCE: ANDA 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg —— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg —— 28 day regimens.

Reference is also made to a telephone conversation between Nicholas Tantillo, of Barr Laboratories, Inc. and Sara Kim, of FDA in which Ms. Kim requested information on the status of Barr's Patent Challenge. Ms. Kim requested that this information be submitted in a New Information Correspondence.

Barr Laboratories, Inc. was notified that on June 6, 2000, a formal complaint was filed by Ortho Pharmaceutical Corp. against Barr Laboratories, Inc. in the United States District Court of New Jersey. Their has been no trial date set to this date however, Barr Laboratories, Inc. will notify the Agency of an updates as they become available.

Please be advised that identical copies of this Correspondence have been provided to the New York and Chicago District Offices. Document certifications are attached.

If you have any questions concerning this New Information Correspondence, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

Nicholas C. Tantillo
Senior Director, Regulatory Affairs

RECEIVED
JUL 23 2002
OGD / CDER

7/25/02

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 30, 2002

LABELING AMENDMENT

Office of Generic Drugs
CDER/Food and Drug Administration
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AF

REFERENCE: ANDA # 75-808
Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg - ——— 28 Day Regimens

Ladies and Gentlemen:

We refer to our pending Abbreviated New Drug Application for Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg ——— 28 Day Regimens.

At this time, we are submitting draft labeling using the proprietary name Tri-Sprintec on the labeling. This name was approved by OPDRA and a fax informing us of this approval was sent on August 17, 2001 by Debra Catterson of the Label Review Branch.

Specifically, we are submitting four copies of draft labeling containing our proprietary name on the following pieces:

Package insert labeling (rev. July 2002)
Patient labeling (rev. July 2002)
Printed cartons, for ——————— 28-day regimens (versions R7-02)
Printed foil pouches for ——————— 28-day regimens (versions R7-02)
Blister cards for ——————— 28-day regimens (versions R7-02)

Please note that the text on the above labeling pieces has not changed except for addition of the proprietary name. The text was submitted in a June 1, 2001 response to the agency.

If you have any questions, please contact me by phone at (845) 348-6894 or by fax at (845) 353-3859.

Sincerely,

RECEIVED
JUL 3 1 2002
OGD / CDER

Salvatore P. Peritore, M.S., R.Ph.
Associate Director, Regulatory Affairs

Emily Thomas NTT 8/21/02

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 14, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW CORRESP
NC

NEW INFORMATION CORRESPONDENCE

REFERENCE: ANDA 75-808
Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
——— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— 28 day regimens.

Reference is also made to a telephone conversation between Nicholas Tantillo, of Barr Laboratories, Inc. and Sara Kim, of FDA in which Ms. Kim requested information on the status of Barr's Patent Challenge. Ms. Kim requested that this information be submitted in a New Information Correspondence.

→ 30 MO 12/9/02 (being no rr date provided)

Barr Laboratories, Inc. was notified that on June 9, 2000, a formal complaint was filed by Ortho Pharmaceutical Corp. against Barr Laboratories, Inc. in the United States District Court of New Jersey, Civil Action number 00-CV-0205 (GEB). There has been no trial date set to this date however, Barr Laboratories, Inc. will notify the Agency of an updates as they become available.

If you have any questions concerning this New Information Correspondence, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

(for)

Nicholas C. Tantillo
Senior Director, Regulatory Affairs

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AUG 15 2002
OGD / CDER

* return receipts in earlier volume w/ rr date of 4/28/00 – 30 mos exp. 10/29/02 7.1

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1300

No rr date
30 mo stands
@ 12/9/02
generic name
NAI 8/21/02 ST
NAI Sara Kim 8/21/02

August 16, 2002

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW INFORMATION CORRESPONDENCE

REFERENCE: ANDA 75-808
Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
—— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg - —— 28 day regimens.

Reference is also made to a telephone conversation between Nicholas Tantillo, of Barr Laboratories, Inc. and Sara Kim, of FDA in which Ms. Kim requested information on the complaint filed by Ortho-McNeil Pharmaceutical, Inc. against Barr Laboratories, Inc.. Ms. Kim requested that this information be submitted in a New Information Correspondence.

Barr Laboratories, Inc. was notified that on June 9, 2000, a formal complaint was filed by Ortho Pharmaceutical Corp. against Barr Laboratories, Inc. in the United States District Court of New Jersey, Civil Action number 00-CV-0205 (GEB). Please find attached a copy of the complaint letter filed in United States District Court for the District of New Jersey by Ortho-McNeil Pharmaceutical, Inc. for patents 4,530,839, 4,544,554 and 4,616,006. Barr also submitted a Paragraph IV Patent Certification with respect to U.S. Patent No. 4,628,051. A complaint was not filed within the 45 day time limit.

If you have any questions concerning this New Information Correspondence, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

(for)

Nicholas C. Tantillo
Senior Director, Regulatory Affairs

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AUG 19 2002
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Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 13, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
Ne

General Correspondence

REFERENCE: **ANDA 75-808**
Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg)
[redacted] **Tri-Sprintec ™** 28 day regimens.

Reference is made to Barr Laboratories, Inc.'s ("Barr") pending Abbreviated New Drug Application ("ANDA"), dated February 16, 2000 submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for **Tri-Sprintec ™** (norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg) [redacted] **Tri-Sprintec™** 28 day regimens.

Reference also is made to the telephone conversation between Christine Mundkur of Barr and Peter Rickman of OGD on September 4, 2002.

As discussed with the Agency, Barr Laboratories, Inc. is hereby withdrawing information that pertains to [redacted] from this application. Barr expects to submit [redacted] reflecting this change as soon as it becomes available.

Barr has submitted an identical copy of this General Correspondence to the Chicago and New York District Office. A document certification is attached.

If you have any questions concerning this application, please contact me by telephone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Sr. Director Regulatory Affairs

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SEP 16 2002
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Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

9/24/2002 BARR LETTER

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

7.1

October 25, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW CORRESP
NC

NEW INFORMATION CORRESPONDENCE

REFERENCE: ANDA 75-808
Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg - 28 day regimen.

Reference is also made to an October 25, 2002 telephone conversation between Sara Kim, of FDA and Nicholas Tantillo, of Barr Laboratories, Inc. and a subsequent telephone conversation on the same date between Elisabeth Noble-Gray, of Barr Laboratories, Inc. and Ms. Kim. Ms. Kim noted the inconsistency between the Civil Action Number stated in Barr's August 16, 2002 New Information Correspondence Cover Letter (00-CV-0205) and the number stated in the attachment (00-CV-2805). Ms. Kim requested Barr look into the matter and submit an updated cover letter as a New Information Correspondence.

Barr Laboratories, Inc. stated in the New Information Correspondence that the Civil Action number was 00-CV-0205 (GEB), however this was a typographical error. The correct Civil Action number was 00-CV-2805 (GEB). Barr Laboratories, Inc. apologizes for any inconvenience that this may have caused the Agency.

If you have any questions concerning this New Information Correspondence, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

(for)

Nicholas C. Tantillo
Senior Director, Regulatory Affairs

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8/8/03 NAT P.N.P

Barr Laboratories, Inc.

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NEW CORRESP
NC

July 31, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **ANDA 75-808**
Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets, USP 0.180mg/0.035 mg, 0.215mg/0.035 mg, and 0.250mg/0.035 mg) - 28 day regimens

PATENT CORRESPONDENCE

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets USP, 0.180mg/0.035 mg, 0.215mg/0.035 mg, and 0.250 mg/0.035 mg) - 28 Day Regimen.

As per the telephone conversation between Linda O'Dea and Christine Mundkur, Barr Laboratories Inc., and Gregg Davis, FDA, Barr is hereby submitting this Patent Correspondence regarding a settlement in the court proceeding Ortho McNeil Pharmaceutical, Inc. and Barr Laboratories, Inc. Civil Action Number 00-CV-02805 (GEB) on patent numbers 4,544,554 (the '554 Patent) and 4,616,006 (the '006 Patent).

In the Consent Judgment and Order, Barr acknowledges that the '554 and '006 patents are valid and enforceable. Therefore, Barr is hereby updating our Abbreviated New Drug Application to a Paragraph III Patent Certification from the previously submitted Paragraph IV Patent Certification for these two patents. Please find enclosed in Section III, Patent Certification and Exclusivity Statement, a copy of the updated Paragraph III Certification and a copy of the Consent Judgment and Order.

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Additionally, with respect to Patent Number 4,530,839 ('839 Patent) Ortho-McNeil Pharmaceuticals and Barr Laboratories, Inc. agreed to dismiss the on going litigation regarding this patent. Please find enclosed in Section III, Patent Certification and Exclusivity Statement, a copy of the Stipulation of Dismissal. In regards to Patent Number 4,628,051 as Barr has previously informed the Agency, Ortho McNeil Pharmaceutical Inc. did not sue Barr on this listed patent.

An identical copy of this Patent Correspondence has been provided to the New York District Office. A document certification is attached.

This completes Barr's Patent Certification. If you have any questions concerning this submission, please contact me by phone at (201) 930-3600 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

(for)
Nicholas Tantillo
Senior Director,
Regulatory Affairs

cc: New York District Office

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 1, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
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Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
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MINOR AMENDMENT FOR FINAL APPROVAL

REFERENCE: **ANDA 75-808**
Tri-Sprintec (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) – 28 Day Regimen

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Tri-Sprintec (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) – 28 day Regimen.**

Reference is also made to Barr's July 31, 2003, Patent Correspondence, in which the status of all four patents are summarized.

Barr is requesting final approval for ANDA 75-808 for Tri-Sprintec (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) – 28 day Regimen. This Minor Amendment is being filed in response to the agreement reached in the Ortho McNeil Pharmaceutical, Inc. v. Barr Laboratories, Inc, Civil Action No. 00-CV-02805 (GEB), on July 30, 2003.

Barr is requesting Final Approval on September 26, 2003, upon expiration of the listed patents. Additionally, Barr recognizes that a written request for pediatric studies has been issued by the Agency for the reference listed drug.

Reference is also made to the July 31, 2003 telephone conversation between Linda O'Dea and Christine Mundkur, Barr Laboratories, Inc., and Gregg Davis, FDA, regarding the pending supplements. Barr is requesting that the following supplements be converted to amendments:

- March 28, 2003 – Special Supplement - Changes Being Effected in 30 days (Alternate packaging sites (Ohio and ———) and Alternate Norgestimate, USP manufacturing site)
- April 14, 2003 – Special Supplement - Changes Being Effected in 30 days ———

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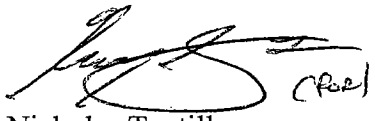
- July 24, 2003 – Special Supplement - Changes Being Effected

- May 1, 2003 – Labeling Submission ("Post Tentative Approval" labeling revisions)

An identical copy of this Minor Amendment has been provided to the New York District Office. A document certification is attached.

If you have any questions regarding this submission, please contact me by fax at 201-930-3318 or by phone at 201-930-3650.

Sincerely,
BARR LABORATORIES, INC.



Nicholas Tantillo
Senior Director Regulatory Affairs

cc: New York District Office

APPEARS THIS WAY
ON ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

NDA SUPP AMEND
SCB-001-WD
SCB-002-WD
SCB-003-WD
SCB-004-WD
SCA-008-WD
SCF-006-WD
SCR-007-WD
SL-005-WD
NC - WD

August 14, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
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Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

WITHDRAWAL OF PENDING SUPPLEMENTS AND AMENDMENT FOR FINAL APPROVAL

REFERENCE: **ANDA 75-808**
Tri-Sprintec (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) – 28 Day Regimen

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Tri-Sprintec (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) – 28 day Regimen.**

Reference is also made to Barr's July 31, 2003, Patent Certification Amendment.

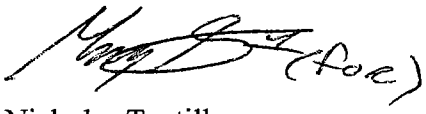
Reference is also made to the August 14, 2003 telephone conversation between Nicholas C. Tantillo, Barr Laboratories, Inc., and Sarah Kim, FDA, regarding the pending supplements. Barr is hereby withdrawing the August 1, 2003 Amendment for Final Approval and the following Supplements without prejudice to future filing.

- March 28, 2003 – Special Supplement - Changes Being Effected in 30 days (Alternate packaging sites (Ohio and ——— and Alternate Norgestimate; USP manufacturing site)
- April 14, 2003 – Special Supplement - Changes Being Effected in 30 days (———)
- July 24, 2003 – Special Supplement - Changes Being Effected (———)
- May 1, 2003 – Labeling Submission ("Post Tentative Approval" labeling revisions)
- August 1, 2003 – Amendment Requesting Final Approval (Requesting that all Supplements be changed to Amendments)

An identical copy of this Withdrawal of Pending Supplements and Amendments has been provided to the New York District Office. A document certification is attached.

If you have any questions regarding this submission, please contact me by fax at 201-930-3318 or by phone at 201-930-3650.

Sincerely,
BARR LABORATORIES, INC.



Nicholas Tantillo
Senior Director Regulatory Affairs

cc: New York District Office

APPEARS THIS WAY
ON ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

SENT BY FEDERAL EXPRESS, AND BY FACSIMILE AT (301) 594-0183

August 21, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT

N/am

FPL

AMENDMENT FOR FINAL APPROVAL

REFERENCE: **ANDA 75-808**
Tri-Sprintec (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) – 28 Day Regimen

Reference is made to our Abbreviated New Drug Application dated February 16, 2000 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Tri-Sprintec (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) – 28 day Regimen.** This application was approved on December 18, 2002 at the termination of the 30-month stay.

Final approval was granted on 12/18/02

Reference is also made to your August 20, 2003 letter informing Barr Laboratories, Inc., that the final approval of this ANDA is rescinded and that the application is tentatively approved.

We are hereby amending this application to receive final approval. We request that approval be made effective when U.S. Patent No. 4,544,554 and U.S. Patent No. 4,616,006 expire on September 26, 2003.

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With this amendment we are resubmitting the final printed labeling that Barr originally submitted on May 1, 2003. Enclosed are 12 copies each of the final printed Folding Cartons (dated R11-02), Package Brochure (dated November 2002), and the Combination Detailed Patient Labeling Brief Summary (dated November 2002).

Because this application was given final approval on December 18, 2000, the following CMC changes made after approval were submitted as supplements to the approved application:

- March 28, 2003 – Special Supplement - Changes Being Effected in 30 days (Alternate packaging sites (Ohio and ———) and Alternate Norgestimate, USP manufacturing site – same manufacturer)
- April 14, 2003 – Special Supplement - Changes Being Effected in 30 days (————————)
- July 24, 2003 – Special Supplement - Changes Being Effected (———— ————————)

We acknowledge that these supplements are now considered to be withdrawn.

Upon receipt of final approval on September 26, 2003, Barr will immediately submit a "Supplement - Changes Being Effected" (CBE-0) for the changes described in the March 28, 2003, April 14, 2003, and July 24, 2003 previously submitted CMC supplemental applications listed above.

It is Barr's intent that product made with these changes will enter commercial distribution as soon as the ANDA is approved.

The rationale for submitting these changes in a CBE-0 is as follows:

1. The CMC changes were properly submitted and implemented during the approximately 8 months since the ANDA was given final approval. In the course of accepting the CBE-30 applications listed above, OGD has already applied the 30-day waiting period required of a CBE-30.

   With respect to the withdrawn March 28, 2003 Supplement - Changes Being Effected in 30 Days which provides for the addition of an alternate manufacturing site (———— in addition to ———— facility at ————) for the API, Norgestimate USP, plus two alternate packaging sites, Barr's Ohio facility and the contract packager ————, OGD has already applied the 30-day waiting period and has determined that the change is not a major change. Therefore, the change has already received the acceptance of the Deputy Division Director as a CBE-30 and a compliance read was requested and was deemed to be acceptable. Otherwise, the OGD would have contacted Barr within the 30-day period following receipt of Barr's March 28, 2003 CBE-30 and instructed that the change should not be implemented. This did not happen.

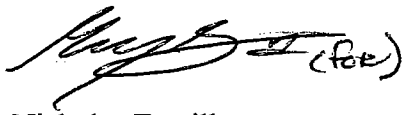
Therefore, we see no reason why in this unusual situation that a second 30-day waiting period should be applied when the same supplement is resubmitted on the day of final approval. OGD should allow this change in this situation, as a CBE-0.

2. The Norgestimate alternate manufacturing site (same manufacturer) change contained in the March 28, 2003 CBE-30 has already been submitted and approved in a related ANDA: The finished product batch information (batch 209872001T) submitted in the March 28, 2003 CBE-30 for ANDA 75-808 is the same as the information submitted in ANDA 75-804 for Sprintec in a CBE-30 dated October 17, 2002 and subsequent Amendment dated March 26, 2003. That supplement was approved May 29, 2003. Both Sprintec and Tri Sprintec products share one strength of product and batches of this strength can be used for either product.

3. The approved October 17, 2002 CBE-30 for ANDA 75-804 also included Barr Ohio as an alternate packaging site. The CBE-30 for ——— as alternate packaging site was submitted March 26, 2003 for ANDA 75-804, and has become effective.

We look forward to final approval of this application on September 26, 2003. If you have any questions, please contact Nicholas Tantillo by telephone at (201) 930-3650, or by facsimile at (201) 930-3318. Thank you for your consideration in this matter.

Sincerely,



Nicholas Tantillo
Senior Director, Regulatory Affairs

cc: New York District Office

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 11, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

CMC AMENDMENT
N/AF

Labeling Amendment

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 75-808
Tri-Sprintec™ (Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg) - 28 day regimen

Reference is made to the tentatively approved Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Tri-Sprintec™ (Norgestimate and Ethinyl Estradiol Tablets, 0.180mg/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035 mg)- 28 day regimen.

Reference is also made to a telephone message to Nancy Westcott, Barr Laboratories Inc., from Debra Catterson, OGD on September 11, 2003 in which Ms. Catterson requested the final printed labeling of the Pouch Foil and the fold over blister card.

Please find enclosed in Section V, Labeling, 12 copies of both the final printed labeling of the Pouch, Part Code 901801 Revision R9-02, and fold over blister card, Part Code 2169018580101 Revision R9-02. Please note that the fold over card and Pouch foil are the same revisions as those previously submitted

This completes the Labeling Amendment. If you have any questions, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

(for)
Nicholas Tantillo
Senior Director,
Regulatory Affairs

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SEP 12 2003
OGD/CDER

Cc: D. Catterson (desk copy)

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 19, 2003

NEW CORRESP

NC.

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

LABELING CORRESPONDENCE

REFERENCE: ANDA 75-808
Tri-Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
——— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Tri-Sprintec™ (norgestimate and ethinyl estradiol Tablets, 0.18 mg/0.035mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg) - 28 day regimen.

Reference is also made to a Labeling Correspondence dated September 16, 2003 for "post-approval" labeling revisions, which can be made at the time of next printing and submitted in an annual report.

Barr Laboratories, Inc. acknowledges the Agency's comments and commits to making these labeling revisions at the time of next printing. Barr will submit the updated labeling in the Annual Report with the changes described in full.

If you have any questions concerning this Labeling Correspondence, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC

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SEP 2 2 2003
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Nicholas C. Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

October 20, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
(N/AM)

MINOR AMENDMENT - FINAL APPROVAL REQUESTED

REFERENCE: **ANDA 75-808**
Tri-Sprintec® (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) – 28 Day Regimen

Reference is made to our Abbreviated New Drug Application dated February 16, 2000 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Tri-Sprintec Tablets (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) packaged in a 28-day cycle regimen.**

Reference is also made to the tentative approval letter dated September 26, 2003 stating that the agency is unable to grant final approval at this time because Ortho-McNeil Pharmaceuticals, Inc. has submitted data to their NDA (the "Ortho data submission") to provide for the use of the reference product, Ortho Tri-Cyclen in the pediatric population.

Additionally, reference is made to our July 31, 2003 patent correspondence regarding the settlement agreement in the court proceeding Ortho-McNeil Pharmaceutical, Inc. and Barr Laboratories, Inc. Civil Action Number 00-CV-02805 (GEB) relating to U.S. Patent No. 4,544,554 and U. S. Patent No. 4,616,006.

In connection with this settlement agreement, the recent Ortho data submission raises new circumstances that will affect the effective date of final approval of this application. One of the conditions of the settlement agreement is that if Ortho-McNeil obtains pediatric exclusivity for Ortho Tri-Cyclen, Ortho-McNeil will waive the pediatric exclusivity as to Barr's ANDA 75-808 on the earlier of: (a) December 29, 2003, or (b) the date on which a third-party is allowed to enter the market with the Ortho-McNeil product or a generic version thereof. Ortho-McNeil will also provide Barr with 30 days written notice prior to the date on which a third-party would be authorized by Ortho-McNeil to enter the market with Ortho Tri-Cyclen or a generic version thereof.

RECEIVED
OCT 21 2003
OGD/CDER

Barr Laboratories, Inc.

ANDA 75-808
Tri-Sprintec® (Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg, and 0.250/0.035 mg) – 28 Day Regimen

In the event that Ortho McNeil obtains pediatric exclusivity for Ortho Tri-Cyclen, the settlement agreement gives Barr the right to launch Tri-Sprintec at least three months earlier than would otherwise be permitted. In order to be ready, we are amending this application because ANDA 75-808 may now be considered for final approval. At this time, we request that approval be made effective on December 29, 2003.

Under the settlement agreement, an alternative to the December 29, 2003 date is the date on which Ortho-McNeil authorizes a third-party to enter the market with the Ortho-McNeil product or a generic version thereof. Ortho-McNeil will provide Barr with 30 days written notice prior to that date. Because this can happen at any time prior to December 29, 2003, we may have to amend this application in the future to request final approval effective before December 29, 2003.

Finally, Barr's application could be approved prior to December 29, 2003 if the Agency determines that Ortho's submission does not meet the requirements for a pediatric extension.

As noted in our August 21, 2003 amendment for final approval, because this application was given final approval on December 18, 2000 [which was rescinded on August 20, 2003], changes made after approval were submitted as supplements to the approved application. Upon receipt of final approval on or before December 29, 2003 Barr will immediately submit a "Supplement – Changes Being Effected " (CBE-0) for the changes described in the August 21, 2003 amendment.

Also, as noted in our September 19, 2003 labeling correspondence, we acknowledge the labeling comments made in your September 16, 2003 correspondence. We commit to making these labeling revisions at the time of next printing and to submit the updated labeling in the Annual Report.

If you have any questions regarding this submission, please contact me by fax at 201-930-3318 or by phone at 201-930-3650.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs