

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-090

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

4 pages

(A)



Morini
580

Food and Drug Administration
Rockville MD 20857

JAN 18 1999

William E. Cusack, M.D.
Garrison Woman's Health Center
Doctor's Park
Dover, NH 03820

Dear Dr. Cusack:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol #092-002#) of CTR 99 and CTR 77 that you conducted for Organon.

From September 29 to October 10, 1999, Dr. Paraluman Leonin, representing the Food and Drug Administration (FDA), inspected the study identified above. This inspection is part of the FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Dr. Leonin presented her inspectional observations (i.e., Form FDA 483) and discussed these observations with you. From our evaluation of: (a) the inspection report; (b) copies of study records obtained during the inspection; (c) your letter of October 12, 1999 that you addressed to Dr. Leonin; and (d) your oral responses during the inspection to the inspectional observations, we conclude that you did not adhere to all the pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. In particular, we note that you failed to follow the protocol in that seven subjects were randomized into the study prior to completing all protocol mandated requirements.

Your letter of October 12, 1999, responds to the observations listed on the Form FDA 483 and addresses our concerns. We note your response to the observations and your assurance that corrective actions will be taken to prevent similar problems in your current and future studies. Your letter has been added to your file. If information is requested from your file in accordance with the Freedom of Information Act, our response will include the related correspondence in your file; this serves to give a more complete picture.

This Page
is Missing
from the
Original
Approval Package

Page 3 - William E. Cusack, M.D.

bcc:

HFA-224

HFD-580 Doc. Rm. NDA #21-090 and ~~_____~~

HFD-580 Review Div. Dir. Rarick

HFD-580 MO Davis

HFD-580 PM/CSO Mercier

HFD- 45 Reading File

HFD- 46 Chron File

HFD- 46 CIB File #1401

HFD- 46 Turner

HFR-NE-250 DIB Kraychuk

HFR-NE-252 BIMO MONITOR Kelley

HFR-NE-252 FIELD INVESTIGATOR Leonin

CFN: #1283575

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI no response required

3)VAI-R response requested

4)VAI-RR adequate response received prior to issuance of VAI-R letter

5)OAI-W warning letter

6)OAI NIDPOE letter

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted:

inadequate consent form

inadequate drug accountability

deviations from protocol

inadequate and/or inaccurate records

failure to report ADRs

other (specify)

O:\GDT/ Cusack

final:nlp/1/13/2000

~~_____~~



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 12 1999

Robert H. Friedman, M.D.
ReSearch for Health, Inc.
902 Frostwood, Suite 315
Houston, Texas 77024

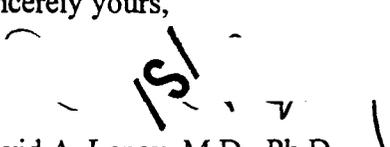
Dear Dr. Friedman:

Between November 16 and November 18, 1999, Mr. Patrick Stone, representing the Food and Drug Administration (FDA), inspected your conduct of a clinical study (protocol #092001) of the investigational drugs CTR 77 and CTR 99 (desogestrel and ethinyl estradiol) Tablets. You conducted this study for Organon, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to the Federal regulations and/or good clinical practices that govern the conduct of clinical studies and the protection of human subjects.

We appreciate the cooperation shown Mr. Stone during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,


David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research,
7520 Standish Place, Suite 103
Rockville, Maryland 20855

Food and Drug Administration
Rockville MD 20857Sidney A. Funk, M.D.
Hilltop Research
1100 Lake Hearn Dr., Ste. 360
Atlanta, GA 30342

OCT 29 1999

Dear Dr. Funk:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol # 092-001) of CTR 77 (desogestrel and ethinyl estradiol) that you conducted for Organon Inc.

Between October 10, 1999 and October 12, 1999, Ms. Leah M. Andrews, representing the Food and Drug Administration (Agency), inspected the study identified above. We reviewed the inspection report prepared by the Agency's inspector, and copies of study records obtained during the inspection. Based on our review, we conclude that you conducted your study in compliance with the Federal regulations that apply to clinical studies of investigational new drugs and with an acceptable standard of good clinical practices.

This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

ISL
Bette L. Barton, Ph.D., M.D.
Chief, Good Clinical Practices Branch 1 (HFD-46)
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 125
Rockville, MD 20855



Page 2 - Sidney A. Funk, M.D.

bcc:

HFA-224

HFD-580 Doc. Rm. NDA 21-090/IND

HFD-580 Review Div. Dir. Rar4ick

HFD-580 MO Davis

HFD-580 CSO/PM Mercier

HFD-45 Reading File

HFD-46 Chron File

HFD-46 CIB File #9360

HFD-46 Turner

HFD-46 Prager

HFR-SE-150 DIB Kline

HFR-SE-150 BIMO Monitor Todd

HFR-SE-150 Inspector Andrews

FIE: #3001237136

Field Classification: NAI

Headquarters Final Classification:

- 1)NAI
- 2)VAI no response required
- 3)VAI-R response requested
- 4)VAI-RR adequate response received before VAI-R ltr issued
- 5)OAI-W warning letter
- 6)OAI NIDPOE letter

If the Field and Headquarters classifications are different, explain why:

Deficiencies Noted:

- none
- inadequate consent form
- inadequate drug accountability
- deviations from protocol
- inadequate records
- failure to report ADRs
- other (specify)

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

2 pages

Mercioy

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: November 17, 1999	DUE DATE: January 7, 2000	OPDRA CONSULT #: 99-090
-------------------------------------	----------------------------------	--------------------------------

TO: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

PRODUCT NAME: Cyclessa™
(desogestrel and ethinyl estradiol tablets)

NDA #: 21-090

MANUFACTURER: Organon, Inc.
West Orange, NJ 07052

CASE REPORT NUMBER(S): Not applicable.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed proprietary name "Cyclessa™" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, we believe that the use of the proprietary name "Cyclessa" poses no significant safety risk and, therefore, we have no objections to the use of this proprietary name.

/s/ 1/7/2000

 Jerry Phillips, R.Ph.
 Associate Director for Medication Error Prevention
 Office of Post-Marketing Drug Risk Assessment
 Phone: (301) 827-3246
 Fax: (301) 480-8173

/s/ 1/7/00

 Peter Honig, M.D.
 Deputy Director
 Office of Post-Marketing Drug Risk Assessment
 Center for Drug Evaluation and Research
 Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 5, 2000

NDA NUMBER: 21-090

NAME OF DRUG: Cyclessa™ (desogestrel and ethinyl estradiol tablets)

NDA HOLDER: Organon, Incorporated
West Orange, NJ 07052

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the tradename Cyclessa™.

The name Cyclessa was submitted to the Labeling and Nomenclature Committee (LNC) on November 10, 1999 and was determined to be "acceptable" for this product.

Cyclessa is a triphasic oral contraceptive containing two active components, desogestrel (DSG) and ethinyl estradiol (EE). It is supplied in a 28-day treatment cycle pack with three active and one inactive dosing regimens: 7 tablets containing 0.1 mg DSG/0.025 mg EE, 7 tablets containing 0.125 mg DSG/0.025 mg EE, 7 tablets containing 0.15mg DSG/0.025 mg EE, and 7 inert tablets.

II. SAFETY AND RISK ASSESSMENT

A. Product name search, product availability and dosing comparison, and focus group

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which sound alike or look alike to Cyclessa™ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of

ⁱ MICROMEDEX Healthcare Intranet Series, 1999, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 1999).

ⁱⁱ American Drug Index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, Updated October 1999, Facts and Comparisons, St. Louis, MO.

^{iv} Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug and Generic Drug Approvals 1998-1999, and the electronic online version of the FDA Orange Book.

the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. An *internal focus group discussion* was conducted to review all findings from the searches.

A number of other products with look-alike or sound-alike proprietary or established names were identified: Alesse, cyclosporine, cyclacillin, cycloserine, Celexa, Zyprexa, and Cyclinex. Confusion of these products with Cyclessa seems unlikely, however, given the differences in dosage forms, available strengths, and usual dosing regimens of these products. Alesse is an oral contraceptive, contains ethinyl estradiol and levonorgestrel, is marketed by Wyeth Ayerst, and is supplied in 21- and 28-day treatment cycle packs. However, the visual and verbal similarity of the two product names was believed to be minimal.

B. Handwritten and verbal analysis of proposed names

A study was conducted within FDA employing a total of 46 health care professionals to evaluate potential errors in handwritten and verbal communications of the name Cyclessa. This exercise was conducted in an attempt to simulate usual clinical practice settings. One of the following prescriptions was communicated per each study participant. Each reviewer was then requested to provide an interpretation of this prescription via email.

HANDWRITTEN PRESCRIPTION (n=23)	VERBAL PRESCRIPTION (n=23)
Cyclessa, #1 month, u.d., 5 refills.	Cyclessa, dispense one month, take as directed, with 5 refills.

Results of this exercise are provided in Tables 2 and 3. We received responses from 16 of 23 (70%) surveyed with verbal prescriptions and 17 of 23 (74%) surveyed with written prescriptions. The majority of respondents provided misspelled variations of the drug name but these responses generally were phonetic variations of the name. However, one respondent to the written surveys expressed a concern for potential confusion with Orthocyclen. Another noted the similarity of the

Table 2: Verbal Prescriptions (16 of 23 response rate)

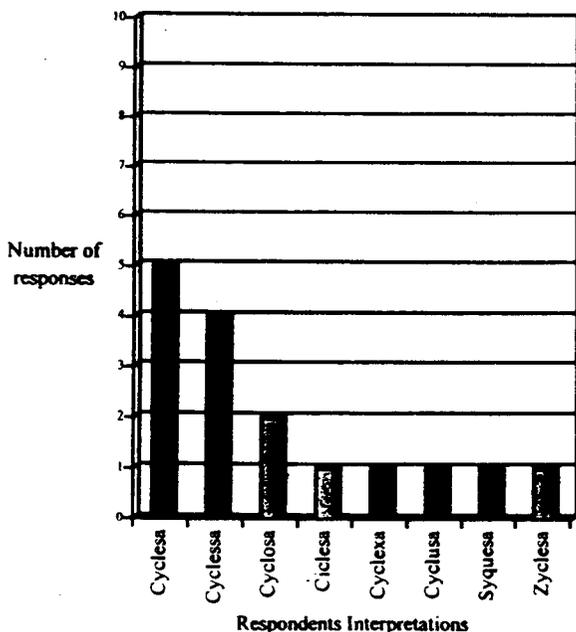
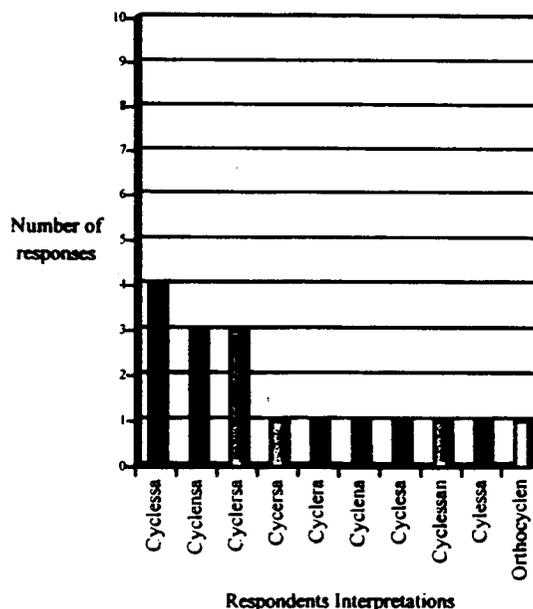


Table 3: Written Prescriptions (17 of 23 response rate)



^v WWW location <http://www.uspto.gov/tmdb/index.html>.

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1222 HFD# 580 PROPOSED PROPRIETARY NAME: PROPOSED ESTABLISHED NAME:
ATTENTION: David T. Lin Cyclessa desogestrel and ethinyl estradiol tablets
RE: NDA # 21-090

A. Look-alike/Sound-alike

Potential for confusion:

Low Medium High
 Low Medium High
 Low Medium High
 Low Medium High
 Low Medium High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

Satisfactory
 Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

ACCEPTABLE UNACCEPTABLE

F. Signature of Chair/Date

IS/ 8/11/99

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53 (c)(1)

- (i) **U.S. PATENT NO.** - 4,616,006
EXPIRATION DATE - October 7, 2003
- (ii) **TYPE OF PATENT** - Drug Product
- (iii) **NAME OF PATENT OWNER OF RECORD**

Ortho Pharmaceutical Corporation
Raritan, New Jersey

ORIGINAL DECLARATION

21 CFR §314.53(c)(2)

The undersigned declares that Patent No. 4,616,006 covers the formulation, composition and/or method of use of the product "CTR 77". This product is the subject of the application for which approval is being sought.

Patrick J. Osinski
Patrick J. Osinski
Vice President
Organon Inc.

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53 (c)(1)

- (i) U.S. PATENT NO. - 4,544,554
- EXPIRATION DATE - September 26, 2003
- (ii) TYPE OF PATENT - Method of Use
- (iii) NAME OF PATENT OWNER OF RECORD

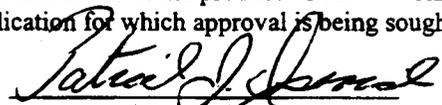
Ortho Pharmaceutical Corporation
Raritan, New Jersey

ORIGINAL DECLARATION

21 CFR §314.53(c)(2)

The undersigned declares that Patent No. 4,544,554 covers the formulation, composition and/or method of use of the product "CTR 77". This product is the subject of the application for which approval is being sought.

Yms



Patrick J. Osinski
Vice President
Organon Inc.

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53 (c)(1)

- (i) U.S. PATENT NO. - 4,628,051
EXPIRATION DATE - September 26, 2003
- (ii) TYPE OF PATENT - Drug Product and Method of Use
- (iii) NAME OF PATENT OWNER OF RECORD

Ortho Pharmaceutical Corporation
Raritan, New Jersey

ORIGINAL DECLARATION

21 CFR §314.53(c)(2)

The undersigned declares that Patent No. 4,628,051 covers the formulation, composition and/or method of use of the product "CTR 77". This product is the subject of the application for which approval is being sought.

Patrick J. Osinski
Patrick J. Osinski
Vice President
Organon Inc.

NDA 21-090
Cyclessa™ (desogestrel/ethinyl estadiol)

Organon, Inc.

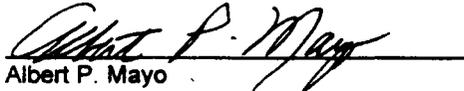
Exclusivity Checklist

N/A due to approvable action.

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned certifies that Organon Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with the New Drug Application for CTR 77 (desogestrel and ethinyl estradiol) Tablets, NDA 21-090.


Albert P. Mayo
Executive Director
Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**



FAX TRANSMISSION
REGULATORY AFFAIRS
ORGANON INC.
WEST ORANGE, NJ 07052
973-325-5285
FAX: 973-325-4769

To: Ms. Jennifer Mercier
Regulatory Project Manager

From: Ms. Giselle Rose
Regulatory Affairs

Fax #: 1-301-827-4267

Pages: 2, including this cover sheet

Date: December 20, 2000

Subject: NDA No. 21-090 Cyclessa™ [CTR 77] (desogestrel/ethinyl estradiol) Tablets

**APPEARS THIS WAY
ON ORIGINAL**



CONFIDENTIAL

Organon Inc.

December 20, 2000

Susan Allen, MD, Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-090
Cyclessa™ [CTR 77] (desogestrel/ethinyl estradiol)
Tablets
Response to FDA Fax of December 20, 2000

Dear Dr. Allen:

Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel/ethinyl estradiol) Tablets submitted on May 7, 1999, the approvable action letter dated March 7, 2000 with FDA requested changes to the product labeling, the FDA fax dated December 18, 2000 describing further labeling changes, and the FDA fax dated December 20, 2000 containing final labeling.

Organon accepts the labeling as specified in the December 20th fax (time stamp 16:20-16:33).

Organon Inc. considers this submission and all correspondence related thereto as confidential and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

If there are any questions regarding this submission, please feel free to contact the undersigned at (973) 325-4833 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,

Albert P. Mayo
Executive Director
Regulatory Affairs



GR/

Submitted in Duplicate
via Federal Express Airbill No. 819829305505

Organon Inc.
570 Mt Pleasant Rd
West Orange
New Jersey 07062
USA
Tel: (973) 325-4833



FAX TRANSMISSION
REGULATORY AFFAIRS
ORGANON INC.
WEST ORANGE, NJ 07052
973-325-5285
FAX: 973-325-4769

To: Ms. Jennifer Mercier
Regulatory Project Manager

From: Ms. Giselle Rose
Regulatory Affairs

Fax #: 1-301-827-4267

Pages: 6, including this cover sheet

Date: December 19, 2000

Subject: NDA No. 21-090 Cyclessa™ [CTR 77] (desogestrel/ethinyl estradiol) Tablets
Response to FDA Labeling Comments of December 18, 2000

**APPEARS THIS WAY
ON ORIGINAL**



CONFIDENTIAL

Organon Inc.

December 19, 2000

Susan Allen, MD, Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-090
Cyclessa™ [CTR 77] (desogestrel/ethinyl estradiol)
Tablets
Response to FDA Fax of December 18, 2000

Dear Dr. Allen:

Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel/ethinyl estradiol) Tablets submitted on May 7, 1999, the approvable action letter dated March 7, 2000 with FDA requested changes to the product labeling, and the FDA fax dated December 18, 2000 describing further labeling changes.

Organon is willing to accept the FDA-proposed changes specified in the December 18th correspondence except for the following:

**FDA REQUESTED CHANGE
PHYSICIAN PACKAGE INSERT
CLINICAL PHARMACOLOGY
Clinical Studies**

Strikeout entire "Clinical Studies" section including table and renumber all tables.

RESPONSE

Organon objects to the deletion of the "Clinical Studies" section as this provides important clinical information. The recently approved contraceptive drug product Lunelle® includes a "Clinical Studies" section and Organon requests similar consideration for Cyclessa™.

WJ

*safety concern
re: product*



Organon Inc.
575 Mt. Pleasant Ave.
West Orange
New Jersey 07062
USA
Tel: 1973-325-0500
Fax: 1973-325-4983

Number of Pages
Redacted 4 pages



Draft Labeling
(not releasable)



CONFIDENTIAL

Organon Inc.

November 1, 2000

ORIGINAL

Ms. Jennifer Mercier, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



NEW CORRESP

NIC

NDA No. 21-090
Cyclessa™ [CTR 77] (desogestrel/ethinyl
estradiol) Tablets
FDA Request for Information - Desk Copy of
Resubmission Dated October 20, 2000

Dear Ms. Mercier:

Reference is made to our Original New Drug Application NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel/ethinyl estradiol) Tablets submitted on May 7, 1999 and the Resubmission dated October 20, 2000. Reference is also made to your request in the telephone conversation of October 30, 2000 for two (2) desk copies of this submission. Enclosed herein please find the requested copies.

Should you require any additional information, please contact the undersigned at (973) 325-5285.

Sincerely,

Giselle Rose
Manager
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



Enclosures: 2 Copies

Submitted via Federal Express Airbill No. 8198 2930 5387

Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA

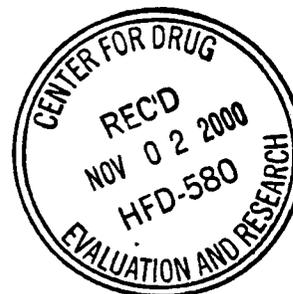
October 19, 2000



CONFIDENTIAL

Organon Inc.

Susan Allen, MD, Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 21-090
Cyclessa™ [CTR 77] (desogestrel/ethinyl estradiol)
Tablets
Resubmission

Dear Dr. Allen:

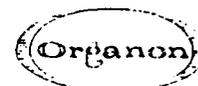
Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel/ethinyl estradiol) Tablets submitted on May 7, 1999 and the approvable action letter dated March 7, 2000 with FDA requested changes to the product labeling. Reference is also made to the FDA correspondence dated April 17, May 22, and August 11, 2000 for NDA No. 20-713 for Mircette® (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets and the FDA correspondence dated June 5, 2000 for Desogen® (desogestrel/ethinyl estradiol) Tablets.

Organon hereby provides a complete response to the deficiencies outline in the above-referenced action letter. Clinical studies with Cyclessa™ were completed in February 1996. There are no ongoing clinical studies at this time. Cyclessa™ has not been approved for marketing in any country nor has it been withdrawn or suspended from marketing in any country. All available information about the safety of Cyclessa™ was reported in the Integrated Summary of Safety in NDA No. 21-090. Therefore, in accordance with the "Guidance for Industry, Classifying Resubmissions in Response to Action Letters" and as this submission includes draft labeling, minor re-analysis of data previously submitted, and the revised drug product specifications agreed on March 2, 2000, Organon believes it should be considered a

For ease of review, each requested labeling change is listed and is followed by our response.

PHYSICIAN PACKAGE INSERT

SPONSOR CHANGE



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA

Number of Pages
Redacted 5 pages



Draft Labeling
(not releasable)

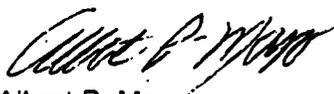
CONFIDENTIAL

Susan Allen, MD, Director (DRUDP)
October 19, 2000
Page 7

Organon Inc. considers this submission and all correspondence related thereto as confidential and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

If there are any questions regarding this submission, please feel free to contact the undersigned at (973) 325-4833 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,



Albert P. Mayo
Executive Director
Regulatory Affairs

GR/cs

Submitted in Triplicate
via Federal Express Airbill No. 8198-2930-6615

**APPEARS THIS WAY
ON ORIGINAL**

0007

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Organon Inc.	DATE OF SUBMISSION October 19, 2000
TELEPHONE NO. (Include Area Code) 973-325-4833	FACSIMILE (FAX) Number (Include Area Code) 973-325-4769
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 375 Mount Pleasant Avenue West Orange, New Jersey 07052	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Organon Inc. 375 Mt. Pleasant Avenue West Orange, New Jersey 07052 973-325-4833 (Phone) / 973-325-4769 (Fax)

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-090	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) desogestrel (DSG) and ethinyl estradiol (EE)	PROPRIETARY NAME (trade name) IF ANY Cyclessa
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) DSG: 13-ethyl-11-methylene-18, 19-dinor-17 α -pregn-4-en-20-yn-17-ol EE: 19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol	CODE NAME (if any) CTR 77
DOSAGE FORM: Tablets	STRENGTHS: 100 μ g DSG/25 μ g EE; 125 μ g DSG/25 μ g EE; 150 μ g DSG/25 μ g EE, placebo
ROUTE OF ADMINISTRATION: Oral	

(PROPOSED) INDICATION(S) FOR USE:

Prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception

CLASSIFICATION INFORMATION

CLASSIFICATION TYPE

(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b) (1) 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: _____ Holder of Approved Application: _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
Resubmission

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-071 Desogen (desogestrel and ethinyl estradiol) Tablets
NDA 20-713 Mircette (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets

This application contains the following items: (Check all that apply)

X	1. Index
X	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
X	8. Clinical data section (e.g., 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case reports forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

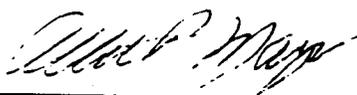
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Albert P. Mayo Executive Director Regulatory Affairs	DATE 10-19-2000
---	--	--------------------

ADDRESS (Street, City, State, and ZIP Code) 375 Mount Pleasant Avenue West Orange, New Jersey 07052	Telephone Number (973) 325-4833
---	------------------------------------

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

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**APPEARS THIS WAY
ON ORIGINAL**



FAX TRANSMISSION
REGULATORY AFFAIRS
ORGANON INC.
WEST ORANGE, NJ 07052
973-325-5285
FAX: 973-325-4769

To: Ms. Jennifer Mercier **From:** Ms. Giselle Rose
Regulatory Project Manager Regulatory Affairs
Fax #: 1-301-827-~~4267~~ *4267* **Pages:** 3, including this cover sheet
Date: March 2, 2000
Subject: NDA No. 21-090 Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets

Jen,

As discussed in this morning's teleconference. The original will be submitted to the Document Room.

Regards,
Giselle

**APPEARS THIS WAY
ON ORIGINAL**

**CONFIDENTIAL**

Organon Inc.

March 2, 2000

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

**NDA No. 21-090 Cyclessa™ [CTR 77]
(desogestrel and ethinyl-estradiol) Tablets
Response to FDA Request for Information**

Dear Dr. Allen:

Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel [DSG] and ethinyl estradiol [EE]) Tablets submitted on May 7, 1999, and to the following FDA/Organon communication: the FDA Information Review (IR) letter dated January 5, 2000; Organon's response to the IR letter dated January 24, 2000; the FDA-Organon teleconference held on February 10, 2000; the additional data provided on February 16, 2000; the telephone conversation with Dr. S. Madani, Dr. M-J Rhee, Ms. J. Mercier, the undersigned, and Ms. G. Rose on February 23, 2000, in which the Division requested the dissolution specification to be "Not less than ~~Q~~ (Q) of the labeled amount in 15 minutes;" the response dated February 25, 2000; the telephone conversation with Dr. M-J Rhee, and Ms. G. Rose of February 28, 2000, the response dated February 29, 2000, and finally, to the teleconference on March 2, 2000.

As discussed during the March 2nd teleconference, Organon agrees to FDA's proposed specification of Q ~~—~~ after 15 minutes for the release specification and the specification of Q ~~—~~ after 30 minutes for the stability specification, with the Phase 4 commitment to perform dissolution testing at 15 and 30 minutes on the first 3 commercial batches of each strength of CTR 77 product at 40°C/75% RH up to 6 months and 25°C/60% RH up to 12 months. Data are to be submitted to the Division when 12 months dissolution data are available, at which time an evaluation of the specification will be made.

Additionally, the participants from Organon follow:

Dr. Gertjan Hartholt, Manufacturing Technology (Oss)
Ms. Erma Hoebergen, Manufacturing Technology (Oss)
Dr. Stanley Kline, Analytical Methods Development (West Orange)
Mr. Herman Kolman, Regulatory Affairs (Oss)
Dr. Henk Koops, Regulatory Affairs (West Orange)
Dr. Thomas Pituk, Regulatory Affairs (West Orange)
Dr. Jay Rehingold, Pharmaceutical Development (West Orange)
Ms. Giselle Rose, Regulatory Affairs (West Orange)
Dr. Chris Vermont, Quality Assurance (Oss)



CONFIDENTIAL

Susan Allen, MD, Acting Director (DRUDP)

March 2, 2000

Page 2

Organon Inc. considers this submission and all correspondence related thereto as confidential and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

If there are any questions regarding this submission, please feel free to contact the undersigned at (973) 325-4830 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,



Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

GR/HPM

Form 356h
Submitted in Duplicate
via Federal Express Airbill No. 810494767809

**APPEARS THIS WAY
ON ORIGINAL**

CONFIDENTIAL

Susan Allen, MD, Acting Director (DRUDP)
March 1, 2000
Page 2

Intra-assay precision and accuracy information for Studies 013007 and 013008 were submitted in _____ (Study 013007, Appendix D, Vol. 1.28, pages 0171-0286 and Study 013008 Appendix C, Vol. 1.31, pages 0146-0261) but have been provided again for your convenience (013007 Appendix D.pdf and 013008 Appendix C.pdf).

Should you require additional information, please do not hesitate to contact the undersigned at (973) 325-4830 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,



Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

JR/cjw

Form FDA 356h
Desk Copy to Ms. Jennifer Mercier, HFD-580

Sent in Duplicate
via Federal Express Airbill No. 810494769948

**APPEARS THIS WAY
ON ORIGINAL**



Organon Inc.

February 25, 2000

CONFIDENTIAL

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

**NDA No. 21-090 Cyclessa™ [CTR 77]
(desogestrel and ethinyl estradiol) Tablets
Response to FDA Request for Information**

Dear Dr. Allen:

Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets submitted on May 7, 1999, to the FDA Information Review (IR) letter dated January 5, 2000, to Organon's response to the IR letter dated January 24, 2000, to the FDA-Organon teleconference held on February 10, 2000, to the additional data provided on February 16, 2000 and to the telephone conversation with Dr. S. Madani and Dr. M-J Rhee and the undersigned and Ms. G. Rose on February 23, 2000, in which the Division requested the dissolution specification to be "Not less than $\frac{1}{2}$ (Q) of the labeled amount in 15 minutes."

As stated in our response of February 16th, we strongly disagree with the FDA approach of setting a specification that would result in a percentage of failures, in order to establish the sensitivity of a test. We had already noted in discussions with FDA that this product demonstrates excellent bioavailability, and the proposed dissolution specifications are well within the range acceptable relative to bioavailability; therefore, safety and efficacy are not the issue. In this regard, specifications that result in unnecessary retesting, and potential rejection, of commercial batches that are otherwise acceptable would be considered unnecessarily tight.

The dissolution specification should have an ~~unacceptable~~ $\frac{1}{2}$ The batches that do not pass should be considered as deviating. From the standpoint of current industry practice, a percentage of failures, therefore, would indicate a problem with the quality of the product. The argument that the specifications could be relaxed at a later time, following a prior approval supplemental NDA, implies that a significant number of batches would have to fail dissolution testing to justify such a consideration. However, dissolution failures occurring during commercial stability would result in the possibility of potential recall of batches, without relevance to product safety and efficacy. From both a practical and a GMP perspective, it would be difficult to release a product with the understanding that a relatively high percentage of product would be at risk for recall.



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500
Fax: (973)-325-4589

CONFIDENTIAL

Susan Allen, MD, Acting Director (DRUDP)
February 25, 2000
Page 2

Although we disagree with the FDA approach, the limited release data available for Cyclessa pilot/validation batches show that a specification of $Q=$ after 15 minutes would result in an S1 failure rate of 3 out of 21 batches (14%) while a specification of $Q=$ after 30 minutes would result in an S1 failure rate of 1 out of 21 batches (5%), a reasonable percentage of S1 failures. Also, as stated in the February 16th response, zero time dissolution profile data for the stability batches show an S1 failure rate for 2 of the 9 batches (22%) using a specification of $Q=$ after 15 minutes. No 15 minutes dissolution data during the stability studies are available; therefore, it is impossible to conclude that a 15 minute specification could be met. Using the proposed specification $Q=$ after 30 minutes, during the stability study 4 out of 12 batches showed S1 failure, indicating that the specification is already sufficiently tight.

Testing at 15 minutes introduces relatively more experimental variability than testing at 30 minutes. For example, slight variations in time have greater impact at 15 minutes than at 30 minutes. Also similarly slight variations in experimental method (e.g., the position of the tablet in the dissolution vessel resulting in variations in disintegration of the tablet) would have greater effect on results at 15 minutes than at 30 minutes. Therefore, there is a greater chance of failure due to small, inconsequential variations when the product is tested at 15 minutes rather than after longer periods (e.g., 30 minutes).

The current FDA approach is not in line with current global practice for all product specifications as generally accepted within pharmaceutical industry and within ICH working groups. Also as stated in our previous correspondence, elimination of Stage 3 testing, as proposed within Ph.Eur./ICH, would further increase the risk of unnecessary rejection of batches. In addition, a current proposal is being evaluated by USP for a DSG/EE monograph dissolution specification of NLT (Q) DSG and NLT (Q) EE for 60 minutes.

Based on the above rationale, we can not accept the FDA proposed dissolution specification for this product of $Q=$ after 15 minutes. We believe that our originally proposed specification of $Q=$ after 30 minutes is sufficiently tight to serve the intended alert function, and we respectfully request that FDA reconsider this proposal.

Organon Inc. considers this submission and all correspondence related thereto as confidential and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

CONFIDENTIAL

Susan Allen, MD, Acting Director (DRUDP)
February 25, 2000
Page 3

If there are any questions regarding this submission, please feel free to contact the undersigned at (973) 325-4830 or Ms. Giselle Rose at (973) (325-5285).

Sincerely,



Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

GR/cjw

Submitted in Duplicate
via Federal Express Airbill No. 810494769959

**APPEARS THIS WAY
ON ORIGINAL**



Organon Inc.

CONFIDENTIAL

March 1, 2000

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

**NDA No. 21-090 Cyclessa™ [CTR 77]
(desogestrel and ethinyl estradiol) Tablets**

Response to FDA Request for Information

Dear Dr. Allen:

Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets submitted on May 7, 1999 and

to the request from Dr. S. Madani, Biopharmaceutics Reviewer, for information on the Human Pharmacokinetics and Bioavailability studies in the NDAs. Finally, reference is made to the submission dated February 7, 2000 which provided the location of inter-assay precision and accuracy validation information for the RIA assays used in these studies.

Enclosed herein are the method validation reports for the RIA analysis of EE, ENG and SHBG used in Studies 092003, 092004, 092005 and 092006 which provide intra-assay precision and accuracy information as well as cross reactivity information. These reports have been provided in pdf format on CD-ROM (Attachment 1). The location of the information within the reports is provided in the following table:

File Name	Report Page
EE Validation.pdf	
Intra-assay precision and accuracy	12
% Cross reactivity	18
ENG Validation.pdf	
Intra-assay precision and accuracy	11
% Cross reactivity	17
SHBG Validation.pdf	
Intra-assay precision and accuracy	12
% Cross reactivity	7



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA

ORIGINAL



CONFIDENTIAL

Organon Inc.

February 16, 2000

NEW CORRESP

NIC

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



**NDA No. 21-090 Cyclessa™ [CTR 77]
(desogestrel and ethinyl estradiol) Tablets**

**Response to FDA Request for Information
General Correspondence: Sponsor Prepared
Minutes of FDA-Organon Teleconference of
February 10, 2000**

Dear Dr. Allen:

Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets submitted on May 7, 1999 and NDA No. _____

Reference is also made to the FDA-Organon teleconference held on February 10, 2000 at the request of the Division to discuss Organon's response dated January 24, 2000 to the Information Review (IR) letters for the above-referenced NDAs.

We herewith submit the minutes which reflect our understanding of the discussions and agreements reached during the teleconference (Attachment 1). As agreed, we hereby provide data to support a revised specifications for impurity (Attachment 2) and to support the current proposed dissolution specifications (Attachment 3) for both NDAs.

Finally, we request a copy of the Agency prepared minutes of this meeting.

Organon, Inc. considers this submission and all correspondence related thereto as confidential and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.



*Reviewed
remit See Review # 2
J. H. Boal*

REVIEWS COMPLETED
CSO ACTION

Organon Inc.
375 Mt. Pleasant Avenue
West Orange

Attachment 1



CONFIDENTIAL

Organon Inc.

January 31, 2000

Ms. Jennifer Mercier, Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

ORIGINAL

**NDA No. 21-090 Cyclessa™ [CTR 77]
(desogestrel and ethinyl estradiol) Tablets**

Response to FDA Request for Information - Desk Copy

Dear Ms. Mercier:

NC

Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets submitted on May 7, 1999 and

Reference is also made to the request from Dr. S. Slaughter on January 27, 2000 for desk copies. Enclosed please find the following volumes:

NDA No. 21-090, Vol. 97 Integrated Summary of Efficacy
NDA No. 21-090, Vol. 98 Integrated Summary of Safety

Should you require any additional information, please contact Ms. Giselle Rose at (973) 325-5285.

Sincerely,

Thomas L. Pituk
Associate Director, Regulatory Affairs

REVIEWS COMPLETED		
CSO ACTION:		
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.	<input type="checkbox"/> MEMO
CSO INITIALS	<i>[Signature]</i>	DATE
		2/18/00



Enclosures

Submitted via Federal Express Airbill No. 810494767717

Organon Inc
575 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel (973) 325-4500
Fax (973) 325-4589



CONFIDENTIAL

Organon Inc.

January 24, 2000

ORIGINAL

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT
BC



**NDA No. 21-090 Cyclessa™ [CTR 77]
(desogestrel and ethinyl estradiol) Tablets
Response to FDA Information Review Letter
Dated January 7, 2000**

Dear Dr. Allen:

Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets submitted on May 7, 1999 and to the Information Review (IR) letter dated January 7, 2000 with respect to Chemistry, Manufacturing and Controls Information. We hereby provide responses to those requests in the same order as presented in your correspondence.

FDA Query 1:

Please indicate whether there is additional acceptance testing performed on the incoming batches of drug substance.

Response 1:

The drug substances desogestrel and ethinyl estradiol are fully tested and released by N.V. Organon, Oss, the Netherlands, before they are used in the manufacture of Cyclessa tablets at N.V. Organon. For

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> MAIL <input type="checkbox"/> MEMO
CSO INITIALS	DATE



Organon Inc.
375 Mt. Pleasant Ave.
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500

CONFIDENTIAL

Susan Allen, MD, Acting Director (DRUDP)
January 24, 2000
Page 2

FDA Query 2:

Please tighten your stability specifications for related steroids to NMT 1% for individual impurity and NMT 1% for total impurities.

Response 2:

The proposed specifications (release and shelf-life) for Cyclessa tablets are based on and are identical to the approved specifications in NDA No. 20-071 for Desogen® (desogestrel and ethinyl estradiol) Tablets and in NDA No. 20-713 for Mircette™ (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets. For these marketed products these limits for related steroids were considered acceptable in view of the results obtained as well as the fact that both desogestrel (DSG) and ethinyl estradiol (EE) are well-known, pharmacopoeial drug substances used in many products and consequently the degradation products are considered qualified in view of the extensive clinical and market experience with products containing these drug substances. Both are human metabolites of desogestrel and therefore need no further qualification.

It is noted that for the Cyclessa tablets strengths (100/25, 125/25, and 150/25 DSG/EE) the total drug substance content is less than in Desogen (150/30 DSG/EE), resulting in lower absolute amounts of related steroids.

It is concluded that it is preferred to maintain the current approved specifications for Desogen and Mircette for the entire range of DSG/EE tablets including Cyclessa.

FDA Query 3:

Regarding the expiration period, based on the available real time stability data, we recommend a tentative expiration date of at 25°C/60% RH.

Response 3:

Enclosed herein in Attachment 1 are an update of the stability reports submitted in NDA No. 21-090 (Volume 10, pages 0162-0240) which now provide primary stability data up to 36 months for Cyclessa tablets (three batches of each strength, total 9 batches). These data support an expiration date of 36 months for this product.

CONFIDENTIAL

Susan Allen, MD, Acting Director (DRUDP)
January 24, 2000
Page 3

FDA Query 4:

Please revise the stability commitment to include the following statement: "The extension of the expiration date will be based on the real time data from the first three commercial production batches".

Response 4:

In view of the response to Query 2, revision of the stability commitment is not needed as Organon proposes an expiry date of 36 months.

FDA Query 5:

Please note that the immediate container should have the following information:

- a. Company name
- b. Expiration date
- c. a Lot number

Response 5:

The company name, expiration date, and lot number will be included on the final printed labeling (FPL) for the blister pack lidding foil for the trade, clinic and professional sample presentations.

Should you require additional information, please do not hesitate to contact the undersigned at (973) 325-4830 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,



Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

GR/hpm

Sent in Duplicate
Form FDA 356h
Attachments

via Federal Express Airbill No. 810494765839



AKZO NOBEL

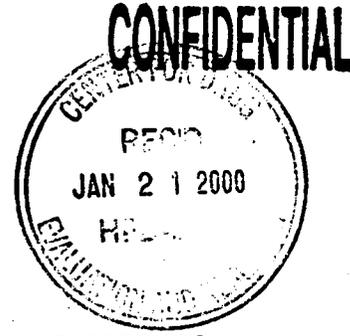
ORIGINAL

Organon Inc.

January 20, 2000

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT



BM

**██████████ Cyclessa™ [CTR 77]
(desogestrel and ethinyl estradiol) Tablets**

Response to FDA Request for Information

Dear Dr. Allen:

Reference is made to NDA No. 21-090 for Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets submitted on May 7, 1999 and NDA No. ██████████

Reference is also made to the Medical Officer's request on December 7, 1999 for a copy of labeling for Marvelon® and Mercilon®. We hereby provide the following in response to the request:

- For Marvelon, the Irish Pharmaceutical Healthcare Association Data Sheet and Summaries of Product Characteristics Compendium 1999-2000 (for Marviol) and the Swedish Summary of the Product Characteristics (for Desolett) are provided in Attachments 1 and 2, respectively. An English translation has been provided for the latter.
- For Mercilon, the Irish Pharmaceutical Healthcare Association Data Sheet and Summaries of Product Characteristics Compendium 1999-2000 and the Swedish Summary of the Product Characteristics are provided in Attachments 3 and 4, respectively. An English translation has been provided for the latter.

Should you require additional information, please do not hesitate to contact the undersigned at (973) 325-4830 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,

Giselle Rose for

Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

GR/cjw

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS DATE

NAI - @ 1/31/00



Attachments
Form FDA 356h
Desk Copy to Ms. Jennifer Mercier, HFD-580

Sent in Duplicate

Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA

014231



CONFIDENTIAL

Organon Inc.

January 7, 2000

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857



**NDA 21-090 Cyclessa™ (desogestrel and ethinyl estradiol)
[CTR 77] Tablets**

120-Day Safety Update

Dear Dr. Rarick:

~~ORIGINAL~~

SU

Reference is made to our pending New Drug Applications NDA 21-090 for Cyclessa™ (desogestrel and ethinyl estradiol) [CTR 77] Tablets submitted on May 7, 1999 and _____

Reference is also made to the 120-day safety update submitted on September 2, 1999. Finally, reference is made to the telephone conversation of November 19, 1999 between Ms. Jennifer Mercier, Project Manager, of your Division and Ms. Giselle Rose, Organon Regulatory Affairs, regarding the format, content, and timing of the second safety update.

In accordance with 21 CFR §314.50(d)(5)(vi)(b)(1), we herewith submit the second update of safety data. As previously agreed with FDA, this update consists of one safety update for both NDAs consisting of a cross-reference to our other marketed oral contraceptive products, Mircette™ and Desogen®. Clinical studies with CTR 77 and CTR 99 Tablets were completed in February 1996. There are no ongoing clinical studies at this time. All available information about the safety of these products was reported in the Integrated Summary of Safety in the respective NDAs. Therefore, we hereby authorize the Agency to refer to NDA 20-713 for Mircette™ (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets and to NDA 20-071 for Desogen® (desogestrel and ethinyl estradiol) Tablets specifically for the review of relevant safety information.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential proprietary and trade secret information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions regarding this submission, please contact the undersigned at (973) 325-4830 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,

Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

GRhpm

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REVIEWS COMPLETED		
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Organon Inc.
375 Mt. Pleasant Avenue
West Orange

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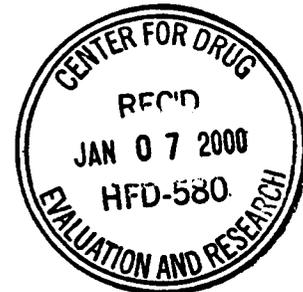
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January 6, 2000

ORIG AMENDMENT

B2

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857



Organon Inc

revised
see NDA 2109
NDA 21090
IS!
1/11/00

Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets

Response to FDA Request for Information

Dear Dr. Rarick:

Reference is made to NDA 21-090 for Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets submitted on May 7, 1999 and

Reference is also made to the requests of Dr. Brenda Gierhart, Medical Officer, on December 8, 1999 and Dr. Soraya Madani, Biopharmaceutics Reviewer, on December 16, 1999 to provide the following information. Finally, reference is made to the conversation with Ms. Jennifer Mercier on January 5, 2000 with respect to Dr. Gierhart's request for patient information.

- 1) For Study 092002 CTR 99 Patient #09069, provide a) hospital admission history, physical and discharge summaries for 11/07/95 admission from and b) additional information regarding patient from the Principle Investigator,

As discussed with Ms. Mercier on January 5th, admission history, physical and discharge summaries from are still outstanding. Every effort is being made to contact the patient to obtain authorization to release the medical records to Organon. In order to facilitate the review, we hereby provide information received from the investigator in Attachment 1: a consultation report, ambulatory care visit report and discharge summary. Information from will be forwarded as soon as it becomes available.

- 2) For the in vitro dissolution data for both NDAs, provide the tables and plots on a CD-ROM. As the plots only represent mean values, regenerate the plots with standard deviation included in the plots (and not % standard deviation or standard error).



REVIEWS COMPLETED
CSO ACTION:
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2/4/00 NAI
Has the chemist seen this??
Should be seen
IS!
Organon Inc
375 Mt. Pleasant Ave
West Orange
New Jersey 07062

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Lisa Rarick, MD, Director (DRUDP)
January 6, 2000
Page 2

The tables and plots of in vitro dissolution data in NDA No. 21-090, Vol. 16, Appendix A, Comparative Dissolution Report SDG RR 5090 (SDGRR 5090.doc) and NDA No. 21-091, Vol. 21, Appendix A, Comparative Dissolution Report PDR-522 (PDR522.doc) are located on the CD-ROM in Attachment 2. Additionally, the tables have been regenerated to include standard deviation (SDGRR 5090 with SD.doc and PDR522 with SD.doc) and the plots have been regenerated to include standard deviation (SDGRR 5090 plots.pdf and PDR522 plots.pdf). Please note that the plots were generated with the SigmaPlot program and have been provided electronically in pdf format. A hard copy of these files is located in Attachment 3.

Should you require additional information, please do not hesitate to contact the undersigned at (973) 325-4830 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,



Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

GR/hpm

Sent in Duplicate
Desk Copy to Ms. Jennifer Mercier, HFD-580
Form FDA 356h
Attachments

via Federal Express Airbill No. 810494765519

**APPEARS THIS WAY
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Revised

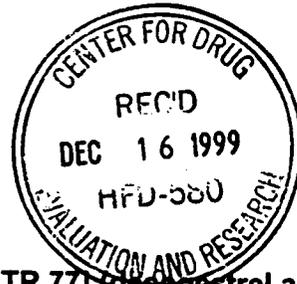
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Organon Inc.

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December 15, 1999

ORIG AMENDMENT
BB

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 21-090 CyclessaTM [CTR 77] (desogestrel and ethinyl estradiol) Tablets

Response to FDA Request for Information

Dear Dr. Rarick:

Reference is made to NDA No. 21-090 for CyclessaTM (desogestrel and ethinyl estradiol [CTR 77]) Tablets submitted on May 7, 1999 and

Reference is also made to the teleconference with Ms. Jennifer Mercier, Project Manager, and Dr. Soraya Madani, Biopharmaceutics Reviewer, of your Division and Ms. Giselle Rose, Regulatory Affairs, on November 30, 1999 requesting information. Finally, reference is made to Ms. Mercier's request on December 7, 1999 for additional information to facilitate the review of the above-referenced NDAs. We hereby submit the following in response to the above requests:

- 1) In NDA No. 21-090, Vol. 17, Study 092004, page 0059, Tables 5 and 6, SHBG and testosterone measurements were presented as Mean \pm SEM. However, it is not clear what the mean represents. This applies to as well.

For individual patients, serum SHBG and testosterone were measured from the 0 hour blood samples on Days 1, 7, 14, and 21. SHBG and testosterone sample results used in the calculation of the mean for these days are listed in NDA No. 21-090, Vol. 21, Study 092004, Appendix B.1, Bioanalysis Subreport, pages 0011-0013 and pages 0091-0093, respectively; and

- 2) In NDA No. 21-090, Vol. 17, Study 092004, pages 0045-0046, there is a description (in the Statistical and Analytical Methods Section of the report) of serum concentration plots. However, plots were not provided (in the Results Section). This applies to as well.

Serum concentrations plots were provided in a Pharmacokinetics Subreport. For NDA No. 21-090, Study 092004, Appendix B.2, Pharmacokinetics Subreport was inadvertently omitted from the original submission and is provided herein in Attachment 1. Serum concentrations plots are provided in



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
TEL: (973) 225-1500

Lisa Rarick, MD, Director (DRUDP)
December 15, 1999
Page 2

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- 3) In NDA No. 21-090, Vol. 16, page 0027, Table 7, explain why the half-life for EE in the multiple dose study was almost twice that of the single dose studies.

The longer half-life for EE in the multiple-dose study (092004: mean $t_{1/2}$ = 28.23 h, median $t_{1/2}$ = 23.96 h) compared to the single-dose studies (092005: mean $t_{1/2}$ = 14.90 h, median $t_{1/2}$ = 14.47 h; 092006: mean $t_{1/2}$ = 16.37 h, median mean $t_{1/2}$ = 14.81 h) is due to the longer measurable EE concentrations for the multiple-dose study (up to approximately 72 h after dosing) in comparison with the single-dose study (up to approximately 54 h after dosing). This implies that the half-life could be estimated over a longer time interval in the case of the multiple dose study compared to that of the single dose study.

- 4) FDA Form 483 for Site 12 (Dr. Fordyce)

Form FDA 483 for Site 12, Nancy H. Fordyce, MD, Principal Investigator, is provided in Attachment 2. Dr. Fordyce was replaced by Frances M. Fisk, MD. Dr. Fisk's response to the 483 has also been provided.

Should you require additional information, please do not hesitate to contact the undersigned at (973) 325-4830 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,



Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

REVIEWS COMPLETED	
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GR/cjw

Sent in Duplicate:
Desk Copy to Ms. Jennifer Mercier, HFD-580

Form FDA 356h
Attachments

via Federal Express Airbill No. 810494768194



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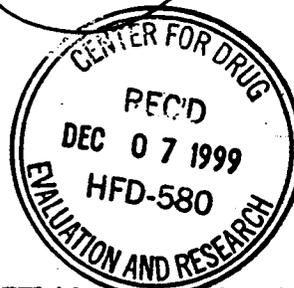
Organon Inc.

December 6, 1999

ORIG AMENDMENT

Handwritten: NDA 21-090
12/31/99
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Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857



NDA 21-090 Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets

Response to FDA Request for Information

Dear Dr. Rarick:

Handwritten: BM

Reference is made to NDA 21-090 for Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets submitted on May 7, 1999 and !

Reference is also made to the request from Ms. Jennifer Mercier of your Division on November 8, 1999 for information to facilitate the review of the above-referenced NDAs. Finally, reference is made to the telephone conversation between Ms. Mercier and Ms. Giselle Rose, Regulatory Affairs, on December 2, 1999, with respect to information pending for one patient. We hereby provide the following information:

1) A copy of all available medical records on the following four patients who had vascular adverse events:

CTR 77, Study 092-002, Patient #20029*

CTR 99, Study 092-001, Patient #09035

CTR 99, Study 092-002, Patient #09069*

CTR 99, Study 092-002, Patient #49052*

* including hospital admission history, physical, and discharge summaries

The Case Report Forms (CRFs) including hospital admission history, physical, and discharge summaries where applicable for the above-referenced patients are provided in Attachments 1 through 4, respectively. As discussed with Ms. Mercier on December 2nd, for Patient 49052 hospital discharge information is available, however, admission information was never received. Attempts are being made to obtain the medical records (via authorization from the patient) from the hospital. The admission information will be forwarded under separate cover as soon as it becomes available.



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA

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Lisa Rarick, MD, Director (DRUDP)
December 6, 1999
Page 2

2) A copy of Volume 1.1, the Integrated Summary of Efficacy, and the Integrated Summary of Safety for both NDAs.

Enclosed please find the following volumes:

NDA 21-090 Volume 1.1 21 CFR §314.50(b) Index
NDA 21-090 Volume 1.97 21 CFR §314.50(d)(5)(v) Integrated Summary of Efficacy
NDA 21-090 Volume 1.98 21 CFR §314.50(d)(5)(vi) Integrated Summary of Safety

Should you require additional information, please do not hesitate to contact the undersigned at (973) 325-4830 or Ms. Giselle Rose at (973) 325-5285.

Sincerely,



Thomas L. Pituk, PhD
Associate Director, Regulatory Affairs

GR/cjw

Sent in Duplicate:
Archival Copy
Desk Copy to Ms. Jennifer Mercier, HFD-580

Form FDA 356h
Attachments

via Federal Express Airbill No. 810494768530

(12/10/99)
Reviewed
NAI - under
NDA Review
BSG

REVIEWS COMPLETED	
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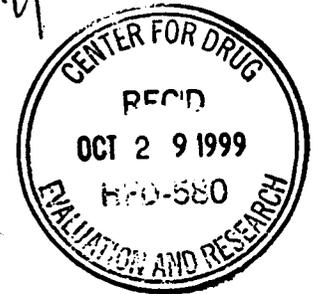
ORIG AMENDMENT
BB

Organon Inc.

October 28, 1999

*Inadequate
see review
2/2/00*
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Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857



NDA 21-090 Cyclessa™ [CTR 77] (desogestrel and ethinyl estradiol) Tablets

Response to FDA Request for Information

Dear Dr. Rarick:

Reference is made to NDA 21-090 for CTR 77 (desogestrel and ethinyl estradiol) Tablets submitted on May 7, 1999 and

Reference is also made to the telephone conversations between Ms. Jennifer Mercier and the undersigned on October 22 and 26, 1999 requesting the following information to be submitted to facilitate the Biopharmaceutics Review of the above referenced NDAs.

- 1) **Package insert for both CTR 77 in Word format.**
- 2) **Report synopses, tables, and graphs for CTR 77 PK Studies 092004, 092005, and 092006; CTR 99 PK Studies 092003, 013007, and 013008, in Word format.**

As discussed with Ms. Mercier, complete reports which include synopses, tables, and graphs will be provided. Studies 092003, 092004, 092005 and 092006 are WordPerfect documents; Studies 013007 and 013008 are only available in PDF format. All PK reports in PDF format were previously submitted on July 1, 1999 in response to an FDA request. Therefore, Studies 013007 and 013008 need not be provided again.

Enclosed please find the following Word and WordPerfect files provided on one (1) zip disk in Attachment 1 for Cyclessa [CTR 77] Tablets:

- Brief Summary Patient Package Insert.doc
- Detailed Patient Package Insert.doc
- Package Insert.doc
- 092004.wpd
- 092005.wpd
- 092006.wpd

NAI - 11/5 - ^ ^ 151

REVIEWS COMPLETED

USC ACTION:
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Organon Inc
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500
Fax: (973) 325-4589