CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-873

CHEMISTRY REVIEW(S)

NDA 21-873

Yaz

Berlex Laboratories, Inc.

Donna F. Christner, Ph.D.
Division of Reproductive and Urologic Drug Products

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 5

The Executive Summary 11

I. Recommendations 11

A. Recommendation and Conclusion on Approvability 11

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 11

II. Summary of Chemistry Assessments 11

A. Description of the Drug Product(s) and Drug Substance(s) 11

B. Description of How the Drug Product is Intended to be Used 13

C. Basis for Approvability or Not-Approval Recommendation 13

III. Administrative 14

A. Reviewer's Signature 14

B. Endorsement Block 14

C. CC Block 14

Chemistry Assessment 15

I. DRUG SUBSTANCE 15

1. Description & Characterization 15

a. Description 15

b. Characterization / Proof Of Structure 15

2. Manufacturer 15

3. Synthesis / Method Of Manufacture 16

a. Starting Materials - Specs & Tests 16

b. Solvents, Reagents, etc. 16

c. Flow Chart 16
d. Detailed Description 16

4. Process Controls 16

a. Reaction Completion / Other In-Process Tests 16
b. Intermediate Specs & Tests 16

5. Reference Standard 16

a. Preparation 16
b. Specifications 17

6. Regulatory Specifications / Analytical Methods 17

a. Drug Substance Specifications & Tests 17
b. Purity Profile 19
c. Microbiology 19

7. Container/Closure System For Drug Substance Storage 19

8. Drug Substance Stability 19

II. DRUG PRODUCT 19

1. Components/Composition 19

2. Specifications & Methods For Drug Product Ingredients 20

a. Active Ingredient(s) 20
b. Inactive Ingredients 20

3. Manufacturer 21

4. Methods Of Manufacturing And Packaging 22

a. Production Operations 22
b. In-Process Controls & Tests 22
c. Reprocessing Operations 22

5. Regulatory Specifications And Methods For Drug Product 23

a. Sampling Procedures 23
b. Regulatory Specifications And Methods 23

6. Container/Closure System 24

7. Microbiology 25

8. Drug Product Stability 25

III. INVESTIGATIONAL FORMULATIONS 26

IV. ENVIRONMENTAL ASSESSMENT 26

V. METHODS VALIDATION 26

VI. LABELING 26

VII. ESTABLISHMENT INSPECTION 28

VIII. DRAFT DEFICIENCY LETTER 30

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 21-873

2. REVIEW #: 1

3. REVIEW DATE: 20-Sep-2005

4. REVIEWER: Donna F. Christner, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	22-Dec-2004
Amendment	23-Mar-2005
Amendment	23-Jun-2005
Amendment	14-Sep-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Berlex, Inc.
Address:	340 Changebridge Road PO Box 1000 Montville, NJ 07045-1000
Representative:	Nancy F. Velez
Telephone:	(973) 487-2305

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Yaz
b) Non-Proprietary Name (USAN): Drospirenone
Ethinyl estradiol
c) Code Name/# (ONDC only): ZK 30595 (Drospirenone)
ZK 227269 (Ethinyl estradiol-β-CC)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Oral Contraceptive **AND** Premenstrual Dysphoric Disorder

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: Drospirenone 3 mg/Ethinyl estradiol 0.02 mg

13. ROUTE OF ADMINISTRATION: Oral

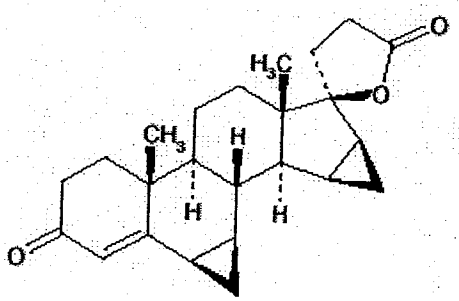
14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Drug Substance #1: Drospirenone



Drospirenone

Chemical Name(s):

IUPAC	6β, 7β; 15β, 16-Dimethylene-3-oxo-17α-pregn-4-ene-21, 17-carbolactone
CAS	6R-(6α,7α,8β,9α,10β,13β,14β,15α,16α,17β)1,3′,4′,6,7,8,9, E,10,11,12,13,14,15,16,20,21-Hexadecahydro-10,13-dimethylspiro-[17 H-dicyclopropa[6,7:15,16]cyclopental[a]phenanthrene-17,2′(5′H)-furan]-3,5′(2H)-dione
Other Names:	Dihydrospirorenone DRSP ZK 30595 (Schering AG Code No.)
CAS #:	67392-87-4
Molecular Formula:	$C_{24}H_{30}O_3$
Molecular Weight:	366.50
Stereochemistry:	Contains 10 asymmetric centers, corresponding to the stereochemistry of naturally occurring steroids at centers 8, 9, 10, 13 and 14.

1 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
12138	II	Schering AG	Drospirenone	3	Adequate	11-May-2004	NDA 21-098/ SCS010 by S.Tran
14960	II	Schering AG	Ethinylestradiol-β-cyclodextrin clathrate	3	Adequate	26-Jul-2004	NDA 21-676 by D. Christner
1985	II	Schering AG	Ethinyl estradiol	3	Adequate	09-Dec-2002	NDA ——by A. Mitra
	III			3	Adequate	28-May-2004	NDA 21-676 by D. Christner
	III			3	Adequate	02-Jun-2004	NDA 21-676 by D. Christner
	III			4	N/A		
	III			4	N/A		
	III			7	N/A	12-Mar-2001	
	IV			3	Adequate	28-May-2004	NDA 21-076 by D. Christner

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC Review #1	21-676	NDA CMC Review

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	31-Mar-2005	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Will be submitted		
DMETS/DDMAC	Yaz name not recommended; Labeling comments sent	18-Aug-2005	Laura Pincock, Ph.D.
EA	Categorical exclusion granted	28-May-2004	Donna F. Christner, Ph.D.
Microbiology	N/A		

The Chemistry Review for NDA 21-873

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be APPROVED from a CMC standpoint pending final acceptable labeling.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Yaz is indicated for use as an oral contraceptive and for treatment of premenstrual dysphoric disorder. It contains two drug substances: drospirenone and ethinyl estradiol as the β-cyclodextrin clathrate. Drospirenone is included at 3 mg/tablet and is in the approved drug product Yasmin. Ethinyl estradiol-β-cyclodextrin clathrate is included at 0.020 mg of ethinyl estradiol/tablet. Cyclodextrin is considered as an excipient and not part of the drug substance. Each drug substance is discussed below, followed by detailed information on the drug product.

The NDA sponsor is Berlex Labs. Both drug substances are manufactured by Schering AG and information is contained in DMFs 12138 and 14960. The drug product is also manufactured by Schering AG.

Drug Substances

Drosperinone

Complete information on drospirenone is contained in Schering AG's DMF # 12138. The most recent review of the DMF was done by S. Tran (Review # 10, dated 11-May-2004) and found **adequate**.

Basic information on the drug substance is provided in the NDA. Drospirenone is a white to off-white crystalline powder that is soluble in a number of organic solvents. Acceptance

criteria include [redacted]

[redacted]. Full release testing is performed at the Schering AG manufacturing site. Confirmatory Identification testing by IR is performed at the drug product manufacturing site. Stability data for up to [redacted] months is provided in the referenced DMF.

Ethinyl estradiol (as the β-cyclodextrin clathrate)

Complete information on ethinyl estradiol as the β-cyclodextrin clathrate is contained in Schering AG's DMF #14960, which was reviewed in conjunction with NDA 21-676 and found **adequate**. The referenced DMFs for ethinyl estradiol (DMF # 1985, reviewed by A. Mitra on 09-Dec-2002) and [redacted] (DMF [redacted] reviewed for NDA 21-676) are **adequate**.

Basic information is provided in the NDA. Ethinyl estradiol-B-cyclodextrin clathrate is a [redacted] white to off-white powder that is freely soluble in water. Data indicate that [redacted]

Acceptance criteria include [redacted]

[redacted]. Full release testing is performed at the Schering AG manufacturing site. Confirmatory Identification testing by IR is performed at the drug product manufacturing site. Stability data for up to [redacted] months is provided in the referenced DMF.

Drug Product

Yaz is indicated for use as an oral contraceptive **and** for treatment of premenstrual dysphoric disorder as a secondary indication. It is packaged in a blister-pack configuration containing 24 active tablets and 4 inert tablets. The active tablets contain drospirenone 3 mg and ethinyl estradiol 0.020 mg (as the β-cyclodextrin clathrate), and are film-coated, round, biconvex, 6 mm diameter tablets with a target weight of [redacted] mg, colored light pink and embossed with "DS" in a regular hexagon on one side. The inert tablets are film-coated, round, biconvex, 6 mm diameter tablets with a target weight of [redacted] mg, colored white and embossed with "DP" in a regular hexagon on one side. Both active and inert tablets contain Lactose monohydrate, Starch, and Magnesium stearate, with the inert tablets also containing Povidone. [redacted] Hypromellose, Talc, and Titanium dioxide, with the active tablets also containing Ferric Oxide, red.

The sponsor uses the ethinyl estradiol-β-cyclodextrin clathrate to stabilize the low dose of ethinyl estradiol used in the tablets (0.020 mg compared to 0.030 mg used in the approved Yasmin). The sponsor submitted data comparing tablets manufactured using ethinyl

estradiol to those using the ethinyl estradiol-β-cyclodextrin clathrate. No significant change was seen when the tablets were stored at 25°C, but after [redacted] months at accelerated stability conditions, the assay for the ethinyl estradiol tablets dropped from [redacted]% to [redacted]%, with an increase in total degradation products from [redacted]% to [redacted], while the ethinyl estradiol-β-cyclodextrin clathrate tablets showed a change in assay from [redacted]% to [redacted], with total degradation products increasing from [redacted] to [redacted]%. The sponsor has submitted 48 month stability data to NDA 21-676 and requested an expiry of 48 months. Based on the submitted data, **an expiry of 48 months can be granted.**

Manufacturing involves [redacted]

Regulatory specifications for the tablets include Appearance, Identifications of ethinyl estradiol (TLC and HPLC), drospirenone (TLC and HPLC), β-cyclodextrin (TLC), ferric oxide, and titanium dioxide, Decomposition products, Dissolution, Content Uniformity and Mean content of ethinyl estradiol and drospirenone, and Microbial contamination. Dissolution specifications were tightened from Q= [redacted]% at 30 minutes to Q= [redacted]% at 30 minues for both APIs during review of NDA 21-676 to provide a more sensitive QC test.

Except for bioavailablity studies and some PK studies, clinical trials used the to-be-marketed formulation of the drug product. All clinical supplies were manufactured at the commercial manufacturing site.

B. Description of How the Drug Product is Intended to be Used

Yaz is packaged in a blister pack arranged in four rows of 7 tablets each. The pack contains 24 active tablets followed by 4 inert tablets, to be taken sequentially once daily. Each active pill contains drospirenone, 3 mg and ethinyl estradiol, 0.020 mg (as the β-cyclodextrin clathrate). Inert tablets contain no API.

Tablets are to be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F) with a 48-month expiry date

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-873 is a resubmission of NDA 21-676 for a different clinical indication. All CMC information for NDA 21-873 is referenced to NDA 21-676, except for the labeling information. Information in this review is taken from CMC Review #1 of NDA 21-676 or is refered to in this review. Recommendations are based on the initial evaluation of the data for NDA 21-676 and the additional stability data submitted during the review cycle.

Both drug substances are well characterized and controlled. Formation of the ethinyl estradiol-β-cyclodextrin clathrate helps to prevent degradation of the ethinyl estradiol in the dosage form as shown by stability studies of tablets with and without the β-cyclodextrin.

The drug product is adequately controlled by the release specification. The maufacturing process is robust.

The NDA can be APPROVED from a CMC standpoint pending final acceptable labeling.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

DChristner/20-Sep-2005
MRhee/20-Sep-2005
CWilliamson/20-Sep-2005

C. CC Block

21 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Donna Christner
9/30/2005 12:55:22 PM
CHEMIST

OC and PMDD indications

Moo-Jhong Rhee
9/30/2005 04:47:22 PM
CHEMIST
I concur

Addendum to CMC Review #1 of NDA 21-873

From: **Donna F. Christner, Ph.D.**
To: **NDA 21-873**
Date: **11-Dec-2005**
Subject: **Response to carton label comments,**
10-Nov-2005 Amendment
30-Nov-2005 Amendment

Recommendation and Conclusions on Approvability:

The original recommendation for NDA 21-873 was that the applications could be approved from a CMC standpoint pending acceptable labeling. Acceptable labeling has been submitted and both NDA 21-873 can be approved from a CMC standpoint

---

The sponsor has submitted the following information in the 10-Nov-2005response to our 14-Oct-2005 letter.

For Carton/Container Labels:

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Donna Christner
1/3/2006 02:30:32 PM
CHEMIST

I changed my review as per your instructions

Moo-Jhong Rhee
1/3/2006 02:38:28 PM
CHEMIST
Chief, Branch III

Addendum 2 to CMC Review #1 of NDA 21-873

From:	**Donna F. Christner, Ph.D.**
To:	**NDA 21-873**
Date:	**04-Aug-2006**
Subject:	**Review of updated Physician Insert, Amendments dated 01-Mar-2006 24-Mar-2006 28-Apr-2006**

Background

The original recommendation for NDA 21-873 was that the application could be approved from a CMC standpoint pending acceptable labeling. The cartons and labels were reviewed in the first Addendum to CMC Review #1 and found acceptable. The above Amendments include updated versions of the PI.

Recommendation and Conclusions on Approvability:

The **Description** and **How Supplied** sections are adequate. Acceptable labeling has been submitted and NDA 21-873 can be approved from a CMC standpoint.

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

/s/

Donna Christner
8/4/2006 09:08:15 AM
CHEMIST

Addendum on PI. Made changes as requested.

Moo-Jhong Rhee
8/4/2006 03:17:14 PM
CHEMIST
Chief, Branch III