

**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**



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# 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

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original  
Amendment  
Amendment  
Amendment

Document Date

22-Dec-2004  
23-Mar-2005  
23-Jun-2005  
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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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- $\beta$ -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

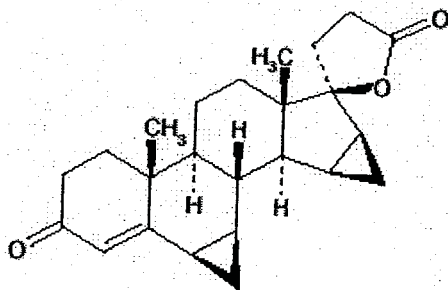
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**
**Drug Substance #1: Drospirenone**

**Drospirenone**

Chemical Name(s):

 IUPAC            6 $\beta$ , 7 $\beta$ ; 15 $\beta$ , 16-Dimethylene-3-oxo-17 $\alpha$ -pregn-4-ene-21, 17-carbolactone

 CAS                6R-(6 $\alpha$ ,7 $\alpha$ ,8 $\beta$ ,9 $\alpha$ ,10 $\beta$ ,13 $\beta$ ,14 $\beta$ ,15 $\alpha$ ,16 $\alpha$ ,17 $\beta$ )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<sub>24</sub>H<sub>30</sub>O<sub>3</sub>

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

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       § 552(b)(5) Deliberative Process



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	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

<sup>1</sup> 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")

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

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

**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  $\beta$ -cyclodextrin clathrate. Drospirenone is included at 3 mg/tablet and is in the approved drug product Yasmin. Ethinyl estradiol- $\beta$ -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

##### **Drospirenone**

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

Executive Summary Section

criteria include \_\_\_\_\_

\_\_\_\_\_. 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 \_\_\_\_\_ months is provided in the referenced DMF.

**Ethinyl estradiol (as the  $\beta$ -cyclodextrin clathrate)**

Complete information on ethinyl estradiol as the  $\beta$ -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 \_\_\_\_\_ (DMF \_\_\_\_\_ reviewed for NDA 21-676) are **adequate**.

Basic information is provided in the NDA. Ethinyl estradiol- $\beta$ -cyclodextrin clathrate is a \_\_\_\_\_ white to off-white powder that is freely soluble in water. Data indicate that \_\_\_\_\_

Acceptance criteria include \_\_\_\_\_

\_\_\_\_\_. 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 \_\_\_\_\_ 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  $\beta$ -cyclodextrin clathrate), and are film-coated, round, biconvex, 6 mm diameter tablets with a target weight of \_\_\_\_\_ 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 \_\_\_\_\_ 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. \_\_\_\_\_ Hypromellose, Talc, and Titanium dioxide, with the active tablets also containing Ferric Oxide, red.

The sponsor uses the ethinyl estradiol- $\beta$ -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

## CHEMISTRY REVIEW

### Executive Summary Section

estradiol to those using the ethinyl estradiol- $\beta$ -cyclodextrin clathrate. No significant change was seen when the tablets were stored at 25°C, but after 48 months at accelerated stability conditions, the assay for the ethinyl estradiol tablets dropped from 98% to 95%, with an increase in total degradation products from 1% to 2%, while the ethinyl estradiol- $\beta$ -cyclodextrin clathrate tablets showed a change in assay from 98% to 97%, with total degradation products increasing from 1% to 2%. 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 \_\_\_\_\_

Regulatory specifications for the tablets include Appearance, Identifications of ethinyl estradiol (TLC and HPLC), drospirenone (TLC and HPLC),  $\beta$ -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= 90% at 30 minutes to Q= 80% at 30 minutes for both APIs during review of NDA 21-676 to provide a more sensitive QC test.

Except for bioavailability 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  $\beta$ -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**

**Executive Summary Section**

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 referred 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- $\beta$ -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  $\beta$ -cyclodextrin.

The drug product is adequately controlled by the release specification. The manufacturing 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**

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Donna Christner  
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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

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

**For Carton/Container Labels:**



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/s/

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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.

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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