CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-676

CHEMISTRY REVIEW(S)

Addendum to CMC Review # 2 of NDA 21-676

From:	**Donna F. Christner, Ph.D.**
To:	**NDA 21-676**
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 21-676 was that the applications could be approved from a CMC standpoint pending acceptable labeling. Acceptable labeling has been submitted and NDA 21-676 can be approved from a CMC standpoint

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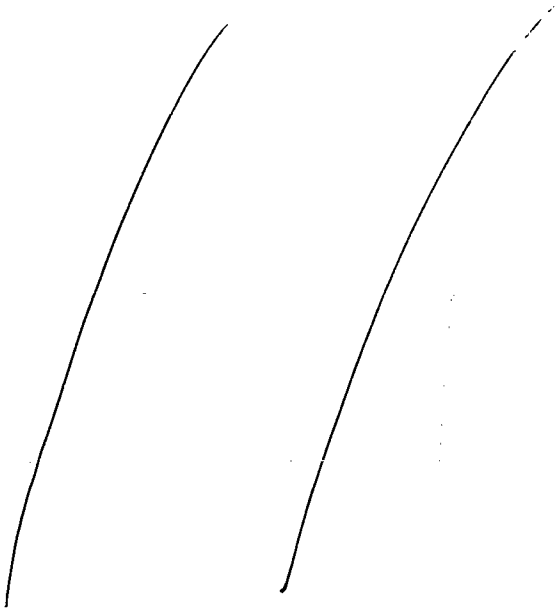
The sponsor has submitted the following information in the 10-Nov-2005response to our 14-Oct-2005 letter.

For Carton/Container Labels:



2 Page(s) Withheld

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/ Draft Labeling

_____ 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 02:27:50 PM
CHEMIST

I changed the review as per your suggestion

Moo-Jhong Rhee
1/3/2006 02:32:25 PM
CHEMIST
Chief, Branch III

NDA 21-676

Yaz

Berlex Laboratories, Inc.

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-676

2. REVIEW #: 2

3. REVIEW DATE: 20-Sep-2005

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	16-Oct-2003
Amendment	25-Nov-2003
Amendment	29-Jan-2004
Amendment	16-Apr-2004
Amendment	26-Apr-2004
Amendment	28-Apr-2004
Amendment	06-May-2004
Amendment	09-Jun-2004
Amendment	11-Jun-2004
Amendment	1-Jul-2004
Amendment (2004-08-06A)	06-Aug-2004
Amendment (2004-11-04B)	04-Nov-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	23-Jun-2005
Amendment	12-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-β-cyclodextrin clathrate
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

11. DOSAGE FORM: Tablet

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

13. ROUTE OF ADMINISTRATION: Oral

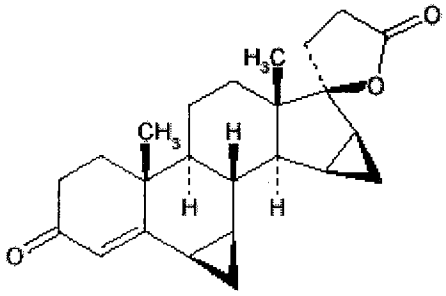
14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

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_____ Draft Labeling

_____ Deliberative Process

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	Schering AG	Drospirenone	3	Adequate	11-May-2004	NDA 21-098/ SCS010 by S.Tran
	II	Schering AG	Ethinylestradiol-β-cyclodextrin clathrate	3	Adequate	26-Jul-2004	NDA 21-676 by D. Christner
	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 21-676 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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	11-Jun-2005	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Will be submitted		
DMETS/DDMAC	Submitted		
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. 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 ——— The drug product is also manufactured by Schering AG.

Drug Substances

Drosperinone

Complete information on drospirenone is contained in Schering AG's DMF # — 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 original NDA submission. Drospirenone is a ———

— 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.

Ethinyl estradiol (as the β-cyclodextrin clathrate)

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

Basic information is provided in the original NDA submission. Ethinyl estradiol-B-cyclodextrin clathrate is

Acceptance criteria include

y. 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.

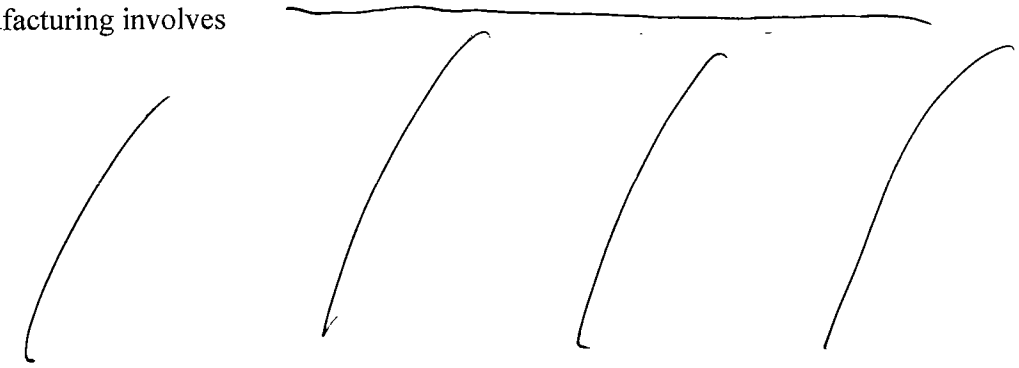
Drug Product

Yaz is indicated for use as an oral contraceptive. 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 —ıg, colored light pink and — th "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 — ng, colored white and — 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 β-cyclodextrin 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 — , at accelerated stability conditions, the assay for the

ethinyl estradiol tablets dropped from — to —, with an increase in total degradation products from — to —, while the ethinyl estradiol-β-cyclodextrin clathrate tablets showed a change in assay from — to — with total degradation products increasing from — to — The sponsor has submitted — month stability data during the first cycle review of NDA 21-676 and requested an expiry of — months. In the second review cycle, the sponsor submitted 48 months of stability data. 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), 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 during the first cycle review of NDA 21-676.

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 — expiry date.

C. Basis for Approvability or Not-Approval Recommendation

Recommendations are based on the initial evaluation of the data for NDA 21-676.

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

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_____ Deliberative Process

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/s/

Donna Christner
9/30/2005 01:00:58 PM
CHEMIST

OC indication/complete response

Moo-Jhong Rhee
9/30/2005 04:50:04 PM
CHEMIST
I concur

NDA 21-676

Yaz

Berlex Labs

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-676

2. REVIEW #: 1

3. REVIEW DATE: 15-Nov-2004

4. REVIEWER: Donna F. Christner

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-Oct-2003
Amendment	25-Nov-2003
Amendment	29-Jan-2004
Amendment	16-Apr-2004
Amendment	26-Apr-2004
Amendment	28-Apr-2004
Amendment	06-May-2004
Amendment	09-Jun-2004
Amendment	11-Jun-2004
Amendment	1-Jul-2004
Amendment (2004-08-06A)	06-Aug-2004
Amendment (2004-11-04B)	04-Nov-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Berlex Laboratories, 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 (pending)
b) Non-Proprietary Name (USAN): Drospirenone
Ethinyl estradiol-β-cyclodextrin clathrate
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

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: Drospirenone 3.0 mg/Ethinyl estradiol 0.020 mg

13. ROUTE OF ADMINISTRATION: Oral

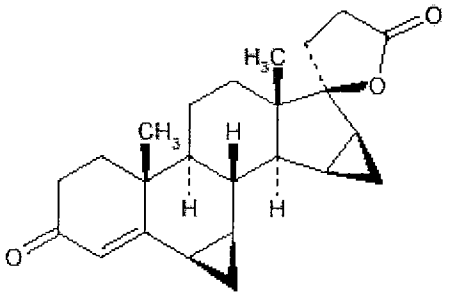
14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

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.

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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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	II	Schering AG	Ethinylestradiol-β-cyclodextrin clathrate	1	Adequate	26-Jul-2004	
	II	Schering AG	Ethinyl estradiol	3	Adequate	09-Dec-2002	NDA — by A. Mitra
	III			1	Adequate	28-May-2004	
	III			1	Adequate	02-Jun-2004	
	III			4	N/A		
	III			4	N/A		
	III			7		12-Mar-2001	
	IV			1	Adequate	28-May-2004	

[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

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	25-Oct-2004	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Will be submitted		
DMETS/DDMAC	Yaz not recommended	10-Mar-2004	Scott Dallas, R.Ph.
EA	Categorical exclusion is granted	28-May-2004	Donna F. Christner, Ph.D.
Microbiology	N/A		

The Chemistry Review for NDA 21-676

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 an oral contraceptive that contains two drug substances: drospirenone and ethinyl estradiol-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. Ethinyl estradiol has been included in numerous drug products, but this is the first use of the clathrate. Because it is ONDC policy that the cyclodextrin is considered an excipient and not part of the drug substance, it is not considered a New Molecular Entity. Each drug substance is discussed below, followed by detailed information on the drug product.

The sponsor is Berlex Labs, but both drug substances are manufactured by Schering AG and information is contained in DMFs The drug product is also manufactured by Schering AG.

Drug Substances

Drosperinone

Complete information on drospirenone is contained in Schering AG's DMF 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 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] is provided in the referenced DMF.

Ethinyl estradiol β-cyclodextrin clathrate

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

Basic information is provided in the NDA. Ethinyl estradiol-B-cyclodextrin clathrate [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] is provided in the referenced DMF.

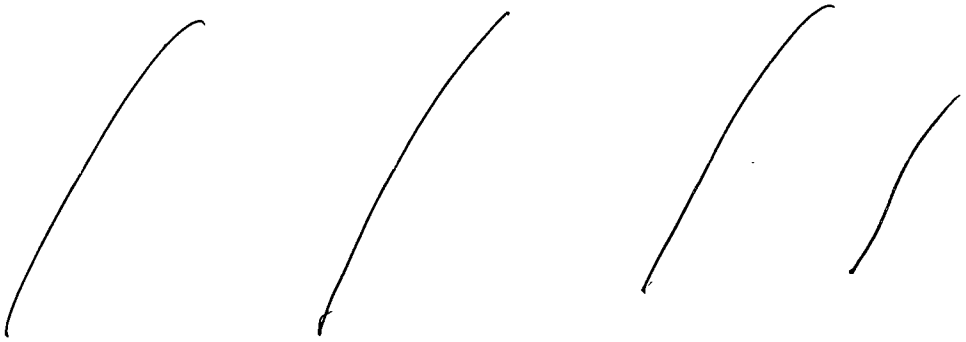
Drug Product

Yaz is an oral contraceptive 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 [redacted] 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 [redacted] 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] at accelerated stability

conditions, the assay for the ethinyl estradiol tablets dropped from — to — with an increase in total degradation products from — to — while the ethinyl estradiol-β-cyclodextrin clathrate tablets showed a change in assay from — to — with total degradation products increasing from — to —

Manufacturing involves —



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. The sponsor originally set the Dissolution acceptance criteria for both APIs at Q= — at 30 minutes. **A recommendation was made to tighten the specification to Q= — at 30 minutes** to better reflect the manufacturing capabilities for the product. The sponsor accepted the recommendation.

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.

In the original submission, the sponsor submitted — of stability data and requested a — expiry. During the review cycle, — stability data were submitted and an expiry of — equested. Based on the submitted data, **an expiry of — can be granted.** Tablets are to be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

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 complexed API.

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

The sponsor responded adequately to all deficiencies identified in the application.

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

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

DChristner/Date: Same date as draft review
MRhee/Date
CWilliamson/Date

C. CC Block

38 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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/s/

Donna Christner
11/15/04 10:49:57 AM
CHEMIST

Moo-Jhong Rhee
11/15/04 02:27:54 PM
CHEMIST
I concur