

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022574Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-574

**Safyral (drospirenone/ethinyl estradiol/levomefolate calcium
tablets and levomefolate calcium tablets)
3 mg/0.03 mg/0.451 mg and 0.451 mg**

Bayer HealthCare Pharmaceuticals Inc.

Hitesh Shroff, Ph.D.

Review Chemist

Branch IV

**Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment**

**CMC Review of NDA 22-574
For the Division of Reproductive and Urologic Drug
Products (HFD-580)**

Table of Contents

Table of Contents	2
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
<u>Drug Substances</u>	8
Drospirenone	8
Ethinyl estradiol beta-cyclodextrin clathrate.....	9
<u>Drug Products</u>	9
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block	10
I. Review of Common Technical Document –Quality (CTD-Q) Module 3.2	11
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	12
A. Labeling & Package Insert	12

Chemistry Review Data Sheet

1. NDA 22-574
2. REVIEW #: 2
3. REVIEW DATE: 15-DEC-2010
4. REVIEWER: Hitesh Shroff, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

<u>Submissions</u>	<u>Document Date</u>
Original	16-Nov-2009
Amendment – Draft Labeling	2-Jun-2010
Amendment – Container Closure	3-Jun-2010
Amendment – Draft Labeling	13-Jul-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment – Proprietary name	12-Aug-2010
Amendment- Draft Labeling	26-Oct-2010
Amendment – Labeling	15-Dec-2010

1. NAME & ADDRESS OF APPLICANT

Name: Bayer HealthCare Pharmaceuticals Inc.
Address: PO Box 1000
Montville, NJ 07045-1000
Representative: Robert J. Haydu
Associate Director
Global Regulatory Affairs
Telephone: (973) 487-2411

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Safyral
Non-Proprietary Name (USAN): Drospirenone/Ethinyl Estradiol/
Levomefolate Calcium
- b) Code Name/# (ONDQA only): ZK 30595 (Drospirenone)
ZK 227269 (Ethinyl Estradiol betadex
clathrate)
Methylfolate (b)(4) Levomefolate
calcium (b)(4)
- c) Chem. Type/Submission Priority (ONDQA only):

Chemistry Review Data Sheet

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Oral contraceptive

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: Drospirenone 3.0 mg/Ethinyl estradiol 0.03 mg/
Levomefolate calcium 0.451 mg

13. ROUTE OF ADMINISTRATION: Oral

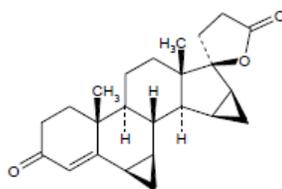
14. Rx/OTC DISPENSED: Rx OTC

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

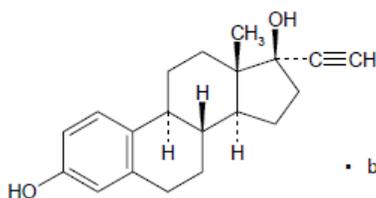


Drospirenone

Chemical Name: 6 β , 7 β , 15 β , 16 β -Dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone
Molecular Formula: C₂₄H₃₀O₃
Molecular Weight: 366.5 g/mol

Drug Substance #2: Ethinyl Estradiol

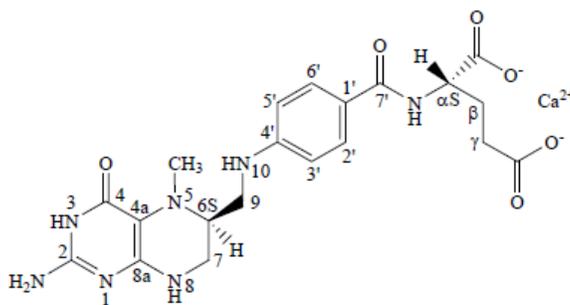
Chemistry Review Data Sheet



• beta-Cyclodextrin-clathrate 1:2

Ethinyl Estradiol

Chemical Name: 19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol,Bis(β -cyclodextrin-clathrate)
 Molecular Formula: C₁₀₄H₁₆₄O₇₂
 Molecular Weight: 2566.4 g/mol

Drug Substance #3: Levomefolate Calcium**Levomefolate Calcium**

Chemical Name: N-[4-[[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridiny]methyl]amino]benzoyl]-L-glutamic acid, calcium salt
 Molecular Formula: Calcium salt: C₂₀H₂₃CaN₇O₆
 Free acid: C₂₀H₂₅N₇O₆
 Molecular Weight: Calcium salt: 497.52 g/mol
 Free acid: 459.46 g/mol

17. RELATED/SUPPORTING DOCUMENTS:**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
12138	II	Bayer Schering Pharma AG, Germany	Drospirenone	2	Adequate	15-Feb-2010	Reviewed to support NDA 22-532
14960	II	Bayer Schering	Ethinyl Estradiol- β -cyclodextrin	2	Adequate	31-Dec-2009	Reviewed to support

Chemistry Review Data Sheet

		Pharma AG, Germany	clathrate				NDA 22-532
20040	II	MERCK EPROVA AG, Switzerland	Levomefolate calcium	2	Adequate	23-Nov-2009	Reviewed to support NDA 22-532
(b) (4)	III	(b) (4)	(b) (4)	2	Adequate	17-Apr-2010	Reviewed to support NDA 22-532

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
IND	72,287	Drospirenone 3mg/ethinylestradiol 0.030mg/L-methylfolate calcium 0.451mg
IND	60,738	drospirenone/ethinylestradiol for oral contraceptive
IND	65,370	drospirenone/ethinylestradiol for acne
IND	51,693	drospirenone 3mg/ethinylestradiol 0.03mg for oral contraceptive
IND	53,905	drospirenone/ethinylestradiol
NDA	21-098	Yasmin(drospirenone/ethinylestradiol) for oral contraceptive
NDA	21-676	drospirenone 3mg/ethinylestradiol 0.02mg
NDA	22-532	drospirenone 3mg/ethinylestradiol 0.02mg/methylfolate Ca 0.451mg

Chemistry Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	03-May-2010	E. Johnson
Pharm/Tox	N/A		
Biopharm	Acceptable	08-Dec-2010	Sandra Suarez-Sharp
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical exclusion is granted (see review)	8-Oct-2009	Hitesh Shroff
Microbiology	N/A		

The Chemistry Review for NDA 22-574

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The previous CMC Review #1 noted,

“This NDA has provided sufficient information to assure identity, strength, purity and quality of the drug products and an “Acceptable” site recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review.”

Now, the issues on labels/labeling have been corrected and deemed adequate. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

No recommendations at this time.

II. Summary of Chemistry Assessments

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

Safyral is a combination oral contraceptive including 21 orange tablets containing drospirenone (3.0 mg), ethinyl estradiol beta-cyclodextrin clathrate (0.03 mg) and levomefolate calcium (0.451 mg) and 7 light orange tablets containing levomefolate calcium (0.451 mg) as active ingredients. Drospirenone and ethinyl estradiol as beta-cyclodextrin clathrate are in the approved drug product YASMIN.

Drug Substances

Drospirenone

Drospirenone is manufactured by Bayer Schering Pharma AG, Germany. Complete CMC information on ethinyl estradiol- β -cyclodextrin clathrate is provided in the DMF # 12138 from Bayer Schering Pharma AG, Germany. The most recent review was dated 15-FEB-2010 and found **adequate**. The applicant provided LoA to reference the DMF for the CMC information.

Executive Summary Section

Ethinyl estradiol beta-cyclodextrin clathrate

The ethinyl estradiol beta-cyclodextrin clathrate is manufactured by Bayer Schering Pharma AG, Germany. Complete CMC information on ethinyl estradiol beta-cyclodextrin clathrate is provided in the DMF # 14960 from Bayer Schering Pharma AG, Germany. The most recent review was dated 31-DEC-2009 and found **adequate**. The applicant provided LoA to reference the DMF for the CMC information.

Levomefolate calcium

Levomefolate calcium is manufactured by Merck Eprova AG, Switzerland. Complete CMC information on levomefolate calcium is provided in the DMF # 20040 from Merck Eprova AG, Switzerland. The most recent review was dated 23-NOV-2009 and found **adequate**. The applicant provided LoA to reference the DMF for the CMC information.

Drug Products

Safyral is a combination oral contraceptive. Each package contains 21 orange tablets and 7 light orange tablets. The orange tablet contains drospirenone (3 mg), ethinyl estradiol beta-cyclodextrin (0.03 mg) and levomefolate calcium (0.451 mg). It is round, biconvex, "Y⁺" in a regular hexagon is printed on one side and the other side is blank. The light orange tablet contains levomefolate calcium (0.451 mg). It is round, biconvex, "M⁺" in a regular hexagon is printed on one side and the other side is blank. The tablets also contain other USP/NF ingredients such as magnesium stearate as a (b) (4), titanium oxide, ferric oxide yellow and ferric oxide red as color pigments.

The tablets are manufactured as immediate release formulation with a (b) (4) (b) (4) and film-coating. Each manufacturing process is controlled by optimized operating ranges during the development and well justified by developmental studies.

The release specification for tablets includes identification and assay of each active ingredient (HPLC), degradation products (HPLC), dissolution, content uniformity and microbial purity. The proposed acceptance criteria for the tests are acceptable based on their developmental studies, and the analytical methods for the tests are adequately validated.

The commercial tablets will be packaged in (b) (4) foil blisters (b) (4) sealed to (b) (4) aluminum foil or alternatively in (b) (4) blisters sealed to (b) (4) foil (b) (4) aluminum foil wrapped in a (b) (4). The container closure systems are adequate to protect the drug products from air, oxygen and moisture during the long term storage at 25 °C. The applicant requested an expiration dating period of 24 months

Executive Summary Section

and based on the submitted stability data for three registration batches, the proposed expiration dating period is granted. Environmental assessment was done and found no significant impact is expected.

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

Safyral is prescribed to women who elect to an oral contraceptive with drospirenone and ethinyl estradiol with added benefit of levomefolate calcium. It is supplied in a blister package containing 28 tablets. 21 tablets contain 3.0 mg drospirenone/0.03 mg ethinyl estradiol beta-cyclodextrin and 0.451 mg levomefolate and the remaining 7 tablets contain 0.451 mg levomefolate calcium as active ingredients. One tablet per day must be taken orally for 28 consecutive days.

C. Basis for Approvability Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substances and drug products. The NDA also has sufficient stability information on the drug products to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have acceptable site recommendations. All labels have the required information. Therefore, from the CMC perspective, this NDA is recommended for approval.

III. Administrative**A. Reviewer's Signature**

Hitesh Shroff/ December 15, 2010

B. Endorsement Block

Moo-Jhong Rhee, Branch Chief, Branch IV, Division 2
Donna Christner
Pam Ducarelli

C. CC Block

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/s/

HITESH N SHROFF
12/15/2010

MOO JHONG RHEE
12/15/2010
Chief, Branch IV

NDA 22-574

(b) (4) (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) 3 mg/0.03 mg/0.451 mg and 0.451 mg

Bayer HealthCare Pharmaceuticals Inc.

Hitesh Shroff, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

**CMC Review of NDA 22-574
For the Division of Reproductive and Urologic Drug
Products (HFD-580)**

Table of Contents

Table of Contents	2
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s).....	9
<u>Drug Substances</u>	9
Drospirenone	9
Drospirenone is manufactured by Bayer Schering Pharma AG, Germany. Complete CMC information on drospirenone is provided in the DMF # 12138 from Bayer Schering Pharma AG, Germany. The most recent review was dated 15-FEB-2010 and found adequate. The applicant provided LoA to reference the DMF for the CMC information.	9
Ethinyl estradiol beta-cyclodextrin clathrate.....	9
<u>Drug Products</u>	10
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	11
A. Reviewer’s Signature.....	11
B. Endorsement Block.....	11
C. CC Block	11
Chemistry Assessment	12
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:	12
Body Of Data	12
Chemistry Assessment	16
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:	16
Body Of Data	16

Chemistry Review Data Sheet

Chemistry Assessment	20
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:	20
Body Of Data	20
DRUG PRODUCT [levomefolate calcium 0.451 mg, Tablet].....	26
P DRUG PRODUCT.....	68
[drospirenone/ethinyl estradiol/levomefolate calcium, tablet]	68
[drospirenone/ethinyl estradiol/levomefolate calcium, tablet]	68
[drospirenone/ethinyl estradiol/levomefolate calcium, tablet]	70
[drospirenone/ethinyl estradiol/levomefolate calcium, tablet]	81
[drospirenone/ethinyl estradiol/levomefolate calcium, tablet]	88
P.4.1 Specifications	88
[drospirenone/ethinyl estradiol/levomefolate calcium, tablet]	90
R REGIONAL INFORMATION	126
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	127
A. Labeling & Package Insert	127
B. Environmental Assessment Or Claim Of Categorical Exclusion Adequate.....	134
III. List Of Deficiencies To Be Communicated.....	134

Chemistry Review Data Sheet

1. NDA 22-574
2. REVIEW #: 1
3. REVIEW DATE: 19-AUG-2010
4. REVIEWER: Hitesh Shroff, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	16-Nov-2009
Amendment – Draft Labeling	2-Jun-2010
Amendment – Container Closure	3-Jun-2010
Amendment – Draft Labeling	13-Jul-2010

1. NAME & ADDRESS OF APPLICANT

Name: Bayer HealthCare Pharmaceuticals Inc.
Address: PO Box 1000
Montville, NJ 07045-1000
Representative: Robert J. Haydu
Associate Director
Global Regulatory Affairs
Telephone: (973) 487-2411

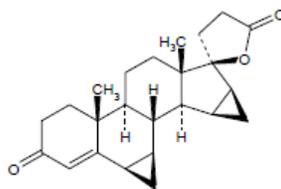
8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
Non-Proprietary Name (USAN): Drospirenone/Ethinyl Estradiol/
Levomefolate Calcium
- b) Code Name/# (ONDQA only): ZK 30595 (Drospirenone)
ZK 227269 (Ethinyl Estradiol betadex
clathrate)
Methylfolate (b) (4), Levomefolate
calcium (b) (4)
- c) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

Chemistry Review Data Sheet

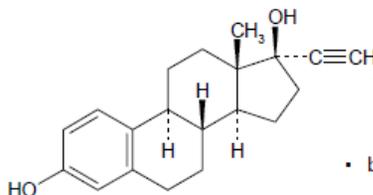
10. PHARMACOL. CATEGORY: Oral contraceptive
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: Drospirenone 3.0 mg/Ethinyl estradiol 0.03 mg/
Levomefolate calcium 0.451 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Drug Substance #1: Drospirenone**Drospirenone**

Chemical Name: 6 β , 7 β , 15 β , 16 β -Dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone

Molecular Formula: C₂₄H₃₀O₃

Molecular Weight: 366.5 g/mol

Drug Substance #2: Ethinyl Estradiol

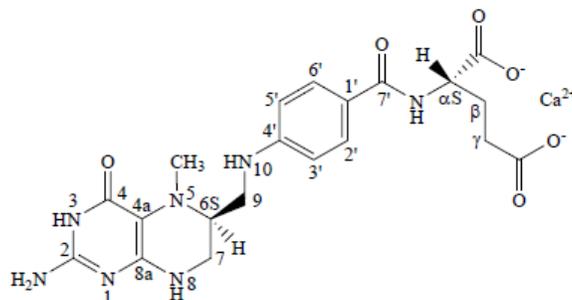
• beta-Cyclodextrin-clathrate 1:2

Ethinyl Estradiol

Chemical Name: 19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol, Bis(β -

Chemistry Review Data Sheet

cyclodextrin-clathrate)
 Molecular Formula: C₁₀₄H₁₆₄O₇₂
 Molecular Weight: 2566.4 g/mol

Drug Substance #3: Levomefolate Calcium**Levomefolate Calcium**

Chemical Name: N-[4-[[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridinyl)methyl]amino]benzoyl]-L-glutamic acid, calcium salt
 Molecular Formula: Calcium salt: C₂₀H₂₃CaN₇O₆
 Free acid: C₂₀H₂₅N₇O₆
 Molecular Weight: Calcium salt: 497.52 g/mol
 Free acid: 459.46 g/mol

17. RELATED/SUPPORTING DOCUMENTS:**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
12138	II	Bayer Schering Pharma AG, Germany	Drospirenone	2	Adequate	15-Feb-2010	Reviewed to support NDA 22-532
14960	II	Bayer Schering Pharma AG, Germany	Ethinyl Estradiol-β-cyclodextrin clathrate	2	Adequate	31-Dec-2009	Reviewed to support NDA 22-532
20040	II	MERCK EPROVA AG, Switzerland	Levomefolate calcium	2	Adequate	23-Nov-2009	Reviewed to support NDA 22-532

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	(b) (4)	2	Adequate	17-Apr-2010	Reviewed to support NDA 22-532
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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
IND	72,287	Drospirenone 3mg/ethinylestradiol 0.030mg/L-methylfolate calcium 0.451mg
IND	60,738	drospirenone/ethinylestradiol for oral contraceptive
IND	65,370	drospirenone/ethinylestradiol for acne
IND	51,693	drospirenone 3mg/ethinylestradiol 0.03mg for oral contraceptive
IND	53,905	drospirenone/ethinylestradiol
NDA	21-098	Yasmin(drospirenone/ethinylestradiol) for oral contraceptive
NDA	21-676	drospirenone 3mg/ethinylestradiol 0.02mg
NDA	22-532	drospirenone 3mg/ethinylestradiol 0.02mg/methylfolate Ca 0.451mg

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	03-May-2010	E. Johnson
Pharm/Tox	N/A		
Biopharm	Acceptable	05-Jul-2010	Sandra Suarez-Sharp

Chemistry Review Data Sheet

LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical exclusion is granted (see review)	8-Oct-2009	Hitesh Shroff
Microbiology	N/A		

The Chemistry Review for NDA 22-574

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity and quality of the drug products. An "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling issues are resolved.

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

No recommendations at this time.

II. Summary of Chemistry Assessments

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

(b) (4) is a combination oral contraceptive including 21 orange tablets containing drospirenone (3.0 mg), ethinyl estradiol beta-cyclodextrin clathrate (0.03 mg) and levomefolate calcium (0.451 mg) and 7 light orange tablets containing levomefolate calcium (0.451 mg) as active ingredients. Drospirenone and ethinyl estradiol as beta-cyclodextrin clathrate are in the approved drug product YASMIN.

Drug Substances

Drospirenone

Drospirenone is manufactured by Bayer Schering Pharma AG, Germany. Complete CMC information on ethinyl estradiol- β -cyclodextrin clathrate is provided in the DMF # 12138 from Bayer Schering Pharma AG, Germany. The most recent review was dated 15-FEB-2010 and found **adequate**. The applicant provided LoA to reference the DMF for the CMC information.

Ethinyl estradiol beta-cyclodextrin clathrate

The ethinyl estradiol beta-cyclodextrin clathrate is manufactured by Bayer Schering Pharma AG, Germany. Complete CMC information on ethinyl estradiol beta-cyclodextrin clathrate is provided in the DMF # 14960 from Bayer Schering Pharma

Executive Summary Section

AG, Germany. The most recent review was dated 31-DEC-2009 and found **adequate**. The applicant provided LoA to reference the DMF for the CMC information.

Levomefolate calcium

Levomefolate calcium is manufactured by Merck Eprova AG, Switzerland. Complete CMC information on levomefolate calcium is provided in the DMF # 20040 from Merck Eprova AG, Switzerland. The most recent review was dated 23-NOV-2009 and found **adequate**. The applicant provided LoA to reference the DMF for the CMC information.

Drug Products

(b) (4) is a combination oral contraceptive. Each package contains 21 orange tablets and 7 light orange tablets. The orange tablet contains drospirenone (3 mg), ethinyl estradiol beta-cyclodextrin (0.03 mg) and levomefolate calcium (0.451 mg). It is round, biconvex, "Y⁺" in a regular hexagon is printed on one side and the other side is blank. The light orange tablet contains levomefolate calcium (0.451 mg). It is round, biconvex, "M⁺" in a regular hexagon is printed on one side and the other side is blank. The tablets also contain other USP/NF ingredients such as magnesium stearate as a (b) (4), titanium oxide, ferric oxide yellow and ferric oxide red as color pigments.

The tablets are manufactured as immediate release formulation with a (b) (4) (b) (4) and film-coating. Each manufacturing process is controlled by optimized operating ranges during the development and well justified by developmental studies.

The release specification for tablets includes identification and assay of each active ingredient (HPLC), degradation products (HPLC), dissolution, content uniformity and microbial purity. The proposed acceptance criteria for the tests are acceptable based on their developmental studies, and the analytical methods for the tests are adequately validated.

The commercial tablets will be packaged in (b) (4) foil blisters ((b) (4) (b) (4)) (b) (4) foil sealed to (b) (4) aluminum foil or alternatively in (b) (4) blisters sealed to (b) (4) foil aluminum foil wrapped in a (b) (4). The container closure systems are adequate to protect the drug products from air, oxygen and moisture during the long term storage at 25 °C. The applicant requested an expiration dating period of 24 months and based on the submitted stability data for three registration batches, the proposed expiration dating period is granted. Environmental assessment was done and found no significant impact is expected.

Executive Summary Section

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

(b) (4) is prescribed to women who elect to an oral contraceptive with drospirenone and ethinyl estradiol with added benefit of levomefolate calcium. It is supplied in a blister package containing 28 tablets. 21 tablets contain 3.0 mg drospirenone/0.03 mg ethinyl estradiol beta-cyclodextrin and 0.451 mg levomefolate and the remaining 7 tablets contain 0.451 mg levomefolate calcium as active ingredients. One tablet per day must be taken orally for 28 consecutive days.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substances and drug products. The NDA also has sufficient stability information on the drug products to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have acceptable site recommendations. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is NOT recommended for approval until the labeling issues are resolved.

III. Administrative**A. Reviewer's Signature**

Hitesh Shroff/ August 01, 2010

B. Endorsement Block

Moo-Jhong Rhee, Branch Chief, Branch IV, Division 2
Donna Christner
Pam Ducarelli

C. CC Block

130 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22574	ORIG-1	BAYER CORP PHARMACEUTICA L DIV	YASMIN PLUS (DEOSPIRENONE ETHINYL ESTRAD

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

/s/

HITESH N SHROFF
08/23/2010

MOO JHONG RHEE
08/23/2010
Chief, Branch IV

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Reproductive and Urologic Products
NDA: 22-574
Applicant: Bayer Corporation
Stamp Date: 16-Nov-2009
PDUFA Date: 16-Sep2010
Trademark: Yasmin Plus
Established Name: Drospirenone/ethinyl estradiol/levomefolate calcium
Dosage Form: Tablet
Route of Administration: Oral
Indication: Improvement in folate status in women who elect to use an oral contraceptive

PAL: Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	X	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

The drug product is an oral contraceptive which consists of two different tablets for use in a 28 day regimen. The first tablet contains drospirenone/ethinyl estradiol (as the β -cyclodextrin clathrate)/Levomefolate calcium (3.0mg/0.03 mg/0.451 mg) which is taken for 21 days followed by 7 days of a tablet containing 0.451 mg levomefolate calcium. The combination tablet is an orange, round, biconvex shaped tablet with a "Y+" in a regular hexagon on one side, whereas the levomefolate tablet is presented as a light orange, round, biconvex shaped tablet with an "M+" in a regular hexagon on one side. Tablets are packaged in a (b) (4) foil blister or (b) (4) blisters in a (b) (4).

(b) (4) Because levomefolate calcium has never been approved in the US, it is currently designated as a New Molecular Entity (NME) (b) (4).

B. Critical issues for review

The justification for the levomefolate calcium overage and the supporting data should be carefully reviewed to see if it is adequate.

For drospirenone and ethinyl estradiol, the impurity acceptance criteria are different that what was approved in the original YASMIN application. However, the acceptance criteria for these active ingredients could have been changed in Post Approval supplements. The reviewer should check the regulatory history of NDAs 21-676 and 21-098 (cross-referenced on the 356h form) to see if the wider acceptance criteria have been approved in the past.

For levomefolate calcium, the PharmTox reviewer should be consulted to determine if there are no toxicological concerns for the limits of (b) (4) for (b) (4) and (b) (4) for (b) (4). The limits should also be carefully reviewed to determine if the data support the limits.

As per policy, it appears that the acceptance criteria for (b) (4) in the drug product are met. However, this should be confirmed during the NDA review.

All tests and acceptance criteria will require review. The justification for skip testing for microbial limits and impurities will require careful evaluation.

The sponsor states that statistical analysis of the data and 24 months of supporting data on one batch of levomefolate calcium tablets support the 24 month expiration dating period. However, since levomefolate appears to be highly susceptible to degradation, the reviewer should carefully evaluate whether the data show a significant change (as defined in QIE) to determine whether statistical analysis and expiration dating period extension are appropriate. Since there are two different container closure systems, it will need to be evaluated whether there are significant differences between the stability characteristics and if different expiration dating periods are appropriate depending on the closure system used.

Taking into account the propensity for degradation of the levomefolate calcium, it would be valuable to know the age of the clinical trial supplies to further help in the evaluation of expiration dating period and to set an appropriate specification for degradation products. The sponsor will be asked for the age of the supplies used in the clinical trials.

C. Comments for 74-Day Letter

Taking into account the propensity for degradation of the levomefolate calcium, provide the age of the clinical trial supplies to further help in the evaluation of expiration dating period and to set an appropriate acceptance criteria for degradation products.

D. Recommendation:

This NDA is fileable from a CMC perspective. It has several issues which need to be critically evaluated during the review. There is one comment which should be included in the 74-day letter. Hitesh Shroff, Ph.D., has been assigned as the primary CMC reviewer.

Donna F. Christner, Ph.D.

NDA Number: 22-574 Type: 1,4

Established/Proper Name:
drospirenone/ethinyl
estradiol/levomefolate

Applicant: Bayer
Corporation

Letter Date: 16-Nov-2009

Stamp Date: 16-Nov-2009

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.		X	N/A

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical Exclusion as per 21 CFR 25.31(b)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMFs 12138, 14960, 20040 for full information.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMFs 12138, 14960, 20040 for full information.
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMFs 12138, 14960, 20040 for full information.
15.	Does the section contain controls for the DS?	X		Cross-reference to DMFs 12138, 14960, 20040 for full information.
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMFs 12138, 14960, 20040 for full information.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	N/A

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Cross-reference to DMFs 12138, 14960, 20040 for full information.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
14960	II	Bayer Schering Pharma AG	Ethinylestradiol-B-cyclodextrin clathrate	19-Oct-2009	ADEQUATE on 26-Jul-2004 by D. Christner. Amendments submitted since last review. May require review.
12138	II	Bayer Schering Pharma AG	Drospirenone	21-Oct-2009	ADEQUATE on 15-Feb-2006 by J. Salemme. Amendments submitted since last review. May require review.
20040	II	Merck Eprova AG	L-Methylfolate, calcium	17-Mar-2009	ADEQUATE on 23-Nov-2009 by H. Shroff.
(b) (4)	III	(b) (4)	(b) (4)	24-Jun-2009	May require review
			(b) (4)	24-Jun-2009	May require review
			(b) (4)	24-Jun-2009	May require review
					See ONDC Policies on Bottles and Blisters*

*Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001
 Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		SPL label with DLDE tables is contained in Section 1.14.1.3 Draft Labeling Text
33.	Have the immediate container and carton labels been provided?	X		Black-and-white labels with "TRADENAME" are available for review of placement. As per cover letter, the sponsor will update the Draft Carton/Container Labels with the proposed tradename, design and color after FDA feedback on YAZ Folate tradename.

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.		X	N/A
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		See Section C above

{See appended electronic signature page}

Donna F. Christner, Ph.D.
 Pharmaceutical Assessment Lead
 Division of Pre-Marketing Assessment # 2
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Branch Chief
 Division of Pre-Marketing Assessment # 2
 Office of New Drug Quality Assessment

Date

REVIEW NOTES

The drug product is a combined oral contraceptive composed of two different tablets. It is based on the approved drug product YASMIN, with the addition of a folate to provide folic acid supplementation. The first tablet which is taken for 21 days contains drospirenone, ethinyl estradiol and levomefolate calcium. The second tablet which is taken for 7 days contains levomefolate calcium. Levomefolate calcium is used in some dietary supplements in the US, but it has never been approved as a drug. Therefore, it is designated as an NME. (b) (4)

(b) (4)

It should also be noted, that although the sponsor states that this drug product is the same as YASMIN with the addition of a folate, the drug substance ethinyl estradiol is in a different form. In YASMIN, ethinyl estradiol occurs as the molecule alone, which in the current NDA, the ethinyl estradiol is in the form of the β -cyclodextrin clathrate. From looking at the Clinical study Report A27410, it appears that this difference has been addressed in the BE study, which looked at a comparison of the currently marketed YASMIN (EE), YASMIN PLUS (EE as the clathrate), and Metafolin alone.

Clinical trials were performed under IND 72,287.

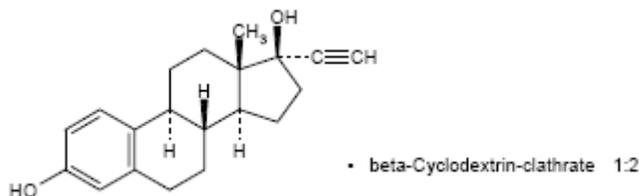
DRUG SUBSTANCES

There are three drug substances in the combination tablet. The majority of the information is provided in the referenced DMFs. The following general information has been provided in the NDA. The manufacturing sites are listed in a common table in the NDA, and this table follows after the overview of the three drug substances.

ETHINYL ESTRADIOL (AS THE β -CYCLODEXTRIN CLATHRATE)

The majority of the information is provided in DMF 14960.

Structural formula



Chemical name	19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol,Bis(β -cyclodextrin-clathrate)
Other names	Ethinylestradiol (INN) Betadex (INN) Internal names: Ethinylestradiol- β -cyclodextrin clathrate Ethinylestradiol- β -cyclodextrin complex Ethinylestradiol- β -cyclodextrin clathrate, micro Ethinylestradiol- β -cyclodextrin complex micro Ethinylestradiol-betadex clathrate Ethinylestradiol-betadex complex Ethinylestradiol-betadex clathrate, micro Ethinylestradiol-betadex complex, micro
Internal code	ZK 227269
CAS name	19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17. α)-, compd. with beta.-Cyclodextrin (1:2) (9CI)
CAS number	256463-26-0
Empirical formula	C ₁₀₄ H ₁₆₄ O ₇₂
Relative molecular weight	2566.4 g/mol
Stereochemistry	Ethinyl estradiol has five chiral centers, corresponding to the normal stereochemistry of naturally occurring steroids described in literature. β -cyclodextrin (Betadex NF) is a cyclic structure of seven glycopyranose units. The glucose units have a covalent 1,4 α -bond, so that there are no stereoisomers of β -cyclodextrin. Under the moderate complex formation conditions there is no regio- or stereoisomerization of ethinyl estradiol or β -cyclodextrin in the EE- β -cyclodextrin clathrate.

Table 4-1: Specification and test methods for Ethinylestradiol betadex clathrate micronized

Test	Acceptance criteria	Analytical method
Appearance:	white to off-white powder	visual test
Identity (IR Spectrum)	matches reference spectrum	IR Spectroscopy
	(b) (4)	Same as for assay Same as for assay Headspace GC Headspace GC Gradient HPLC on C18, 3 µm (or equivalent), UV detection at 220 nm
		Karl-Fischer-Titration Gradient HPLC on C18, 3 µm (or equivalent) UV detection at 220 nm
		Gradient HPLC on RP-NH ₂ , e.g. Spherisorb-NH ₂ , 5 µm (or equivalent), RI detection
Particle size		Light microscopy
	(b) (4)	
		laser diffraction spectroscopy
		(b) (4)

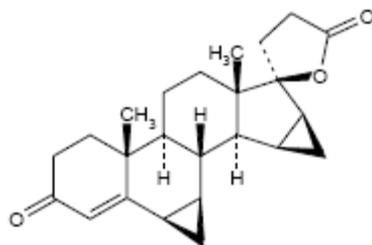
Batch analysis is provided on three lots of drug substance.

Comment: Information is adequate to allow review. The DMF is currently under review by Hitesh Shroff, Ph.D., for NDA 22-532.

DROSPIRENONE

Full information is provided in DMF 12138.

Structural formula



Chemical name	6 β , 7 β , 15 β , 16 β -Dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone
Other names	Drospirenone (INN) Dihydrospirenone DRSP
Internal codes	Drospirenone micronized ZK 30595
CAS name	6R-(6 α , 7 α , 8 β , 9 α , 10 β , 13 β , 14 α , 15 α , 16 α , 17 β)-1,3',4',6,7,8,9,10,11,12,13,14,15,16,20,21-Hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa[6,7:15,16]cyclopenta[a]phenanthrene-17,2'(5'H)-furan]-3,5'(2H)-dione
CAS number	67392-87-4
Empirical formula	C ₂₄ H ₃₀ O ₃
Relative molecular weight	366.5 g/mol
Chirality	Drospirenone has 10 asymmetric centers (C-6, C-7, C-8, C-9, C-10, C-13, C-14, C-15, C-16, C-17) As a representative of the class of pregnenes the typical configuration at the following five carbons is fixed to be 8 β -H, 9 α -H, 10 β -CH ₃ , 13 β -CH ₃ , 14 α -H. The asymmetric centers at C-6, C-7, C-15, C-16 and C-17 are introduced by highly stereoselective reactions to fix the following configurations: 6 β , 7 β , 15 β , 16 β , 17 α .

Table 4-1: Specification and test methods for drospirenone micronized

Test	Acceptance criteria	Analytical method	
[Redacted]	(b) (4)	visual test	
		IR Spectroscopy	
		Thermometry, USP, class I Polarimetry	
		visual	
		Headspace GC Headspace GC Color reaction	
		Gravimetry Gradient HPLC on Spherisorb-ODS II, 5 µm (or equivalent), UV detection at 245 nm	
		Karl-Fischer-Titration Gradient HPLC on Spherisorb-ODS II, 5 µm (or equivalent), UV detection at 245 nm	
		Light microscopy	
	Particle size	(b) (4)	
	[Redacted]		spec. external surface according to Blaine

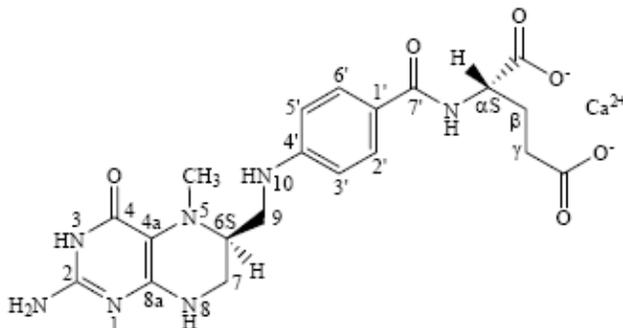
Batch analysis is provided on three lots of drug substance.

Comment: Information is adequate to allow review. The DMF is currently under review by Hitesh Shroff, Ph.D., for NDA 22-532.

LEVOMEFOLATE CALCIUM

Full information is provided in DMF 20040. The sponsor states that the INN/USAN “Levomefolate calcium” was recently granted (in 2008) and therefore is not included in the DMF.

Structural formula



Chemical name	N-[4-[[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridinyl)methyl]amino]benzoyl]-L-glutamic acid, calcium salt
Other names	(6S)-5-Methyltetrahydrofolic acid, calcium salt N-[4-[[[(2-amino-5,6,7,8-tetrahydro-4-hydroxy-5-methyl-(6S)-pteridinyl)methyl]amino]benzoyl]-L-glutamic acid, calcium salt (6S)-5-methyl-5,6,7,8-tetrahydropteroyl-L-glutamic acid, calcium salt L-5-methyltetrahydrofolic acid, calcium salt L-Mefolate, calcium L-Calcium mefolinate
Internal code/name	Methylfolate ^{(b) (4)} Levomefolate calcium ^{(b) (4)}
CAS name	N-{4-[[[(6S)-2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-pteridinyl)methyl]amino]benzoyl}-L-glutamic acid, calcium salt
CAS number	129025-21-4: Calcium salt with not specified ratio of (6S)-5-Methyltetrahydrofolic acid / Ca ²⁺ 151533-22-1: Calcium salt with specified 1:1 ratio of (6S)-5-Methyltetrahydrofolic acid / Ca ²⁺

Chirality (isomerism)

L-Methylfolate, calcium is the natural diastereoisomer (6S, αS). The molecule has two chiral centres: the C-atom in position 6 of the tetrahydropteroyl moiety and the α-C atom in the glutamic acid moiety (see Module 3, Volume 1, Section 3.2.S.1.2). The chiral centre at the C-atom in position 6 of the tetrahydropteroyl moiety is formed during the synthesis process by reduction of the starting material folic acid. The (αS)-configuration of the α-C atom in the glutamic acid moiety originates from folic acid and remains unchanged during the whole synthesis process.

Table 4-1: Specification and test methods for levomefolate calcium (b) (4)

Test	Acceptance criteria	Analytical method
Appearance	White to yellow or beige powder	visual inspection
	(b) (4)	Curr. USP <197K>; IR spectroscopy HPLC
		Curr. Ph. Eur. (2.3.1.) Curr. USP <921> Method Ic Curr. Ph. Eur. (2.2.20) Curr. USP <231 II> Curr. Ph. Eur. (2.5.11) GLC
		Inductively coupled Plasma Inductively coupled Plasma HPLC
		HPLC

Test	Acceptance criteria	Analytical method
	(b) (4)	HPLC
		HPLC
		Stereoselective HPLC
		Curr. USP <61>, <62>, <1111> Curr. USP <61>, <62>, <1111> Curr. USP <61>, <62>, <1111> Laser diffraction

Batch analysis is provided on three lots of drug substance.

Comment: Information is adequate to allow review. The DMF was recently reviewed by Hitesh Shroff, Ph.D., for NDA 22-532.

MANUFACTURERS

The following sites have responsibilities for the manufacture and control of the drug substances.

Drug Substance							
Name and Address	Contact Person at Site	Telephone Number	Fax Number	E-mail Address	Registration Number	Stage of Manufacturing	Ready for Inspection
Bayer Schering Pharma AG Ernst-Schering Str. 14 D-59179 Bergkamen, Germany	Dr. Franz-Josef Renneke	011 49 2307 65-2222	011 49 2307 65-69809	Franz-josef.renneke@bayerhealthcare.com	3003678526	Facility for synthesis, purification, testing, release and stability testing of drug substances (Drospirenone and Ethinylestradiol)	Yes
Bayer Schering Pharma AG Max-Dohm-Straße 8 D-10589 Berlin, Germany	Dr. Hans-Joachim Raubach	011 49 30 4681 6826	011 49 30 4689 6826	Hans-joachim.raubach@bayer-ag.de	3002808063	Facility for (b) (4) micronization, and particle size testing of drug substances (Drospirenone and Ethinylestradiol)	Yes
MERCK EPROVA AG Im Laternenacker 5 CH-8200 Schaffhausen Switzerland	René Christinat	011 41 52 630 72 72 (switchboard) / 011 41 52 630 72 60 (direct)	+51 52 630 72 55	mfo@eprova.com	3002806918	Facility for synthesis, purification and stability testing of drug substance levomefolate calcium	Yes

Comment: The EES was submitted on 15-Dec-2009 by Jeannie David.

DRUG PRODUCT

The drug product is an oral contraceptive which consists of two different tablets for use in a 28 day regimen. The first tablet contains drospirenone/ethinyl estradiol (as the β -cyclodextrin clathrate)/Levomefolate calcium (3.0mg/0.03 mg/0.451 mg) which is taken for 21 days followed by 7 days of a tablet containing 0.451 mg levomefolate calcium. The combination tablet is an orange, round, biconvex shaped tablet with a “Y+” in a regular hexagon on one side, whereas the levomefolate tablet is presented as a light orange, round, biconvex shaped tablet with an “M+” in a regular hexagon on one side. Tablets are packaged in a (b) (4) foil blister or (b) (4) blisters in a (b) (4). The composition of both tablets is shown below:

Table 1-1: Composition of Drospirenone + Ethinylestradiol + Levomefolate calcium coated tablet 3.0 mg + 0.03 mg + 0.451 mg

Composition	Reference to standard	Function	Amount [mg]
Drug substance			
Drospirenone micronized	specification	drug substance	3.000
Ethinylestradiol betadex clathrate micronized ^a	specification	drug substance	0.030
Levomefolate calcium (b) (4)	specification	drug substance	0.451
Excipients		(b) (4)	(b) (4)
Lactose monohydrate	Ph. Eur., USP/NF, Ph. Jap.	(b) (4)	(b) (4)
Cellulose microcrystalline	Ph. Eur., USP/NF		
Croscarmellose sodium	Ph. Eur., USP/NF, Ph. Jap.		
Hydroxypropylcellulose (b) (4)	Ph. Eur., USP/NF		
Magnesium stearate	Ph. Eur., USP/NF, Ph. Jap.		
(b) (4)			
(b) (4)	specification	(b) (4)	(b) (4)
or alternatively			
Hypromellose (b) (4)	Ph. Eur., USP/NF, Ph. Jap.		
(b) (4)	Ph. Eur., USP/NF		
Talc	Ph. Eur., USP/NF, Ph. Jap.		
Titanium dioxide	Ph. Eur., USP/NF, Ph. Jap. Directive 95/45/EC		
Ferric oxide yellow	USP/NF, JPE Directive 95/45/EC		
Ferric oxide red	USP/NF, JPE Directive 95/45/EC		
(b) (4)			
(b) (4)			

a calculated as ethinylestradiol

b (b) (4)

(Remark: The excipients hypromellose (b) (4), talc, titanium dioxide, ferric oxide red, and ferric oxide yellow are (b) (4).)

Table 1-1: Composition of Levomefolate calcium coated tablet 0.451 mg

Composition	Reference to standard	Function	Amount [mg]
Drug substances			
Levomefolate calcium (b) (4)	specification	drug substance	(b) (4)
Excipients			
Lactose monohydrate	Ph. Eur., USP/NF, Ph. Jap.	(b) (4)	(b) (4)
Cellulose microcrystalline	Ph. Eur., USP/NF		
Croscarmellose sodium	Ph. Eur., USP/NF, Ph. Jap.		
Hydroxypropylcellulose (b) (4)	Ph. Eur., USP/NF		
Magnesium stearate	Ph. Eur., USP/NF, Ph. Jap.		
Weight (uncoated tablet)			
(b) (4)	specification	(b) (4)	(b) (4)
Hypromellose (b) (4)	Ph. Eur., USP/NF, Ph. Jap.	(b) (4)	(b) (4)
(b) (4)	Ph. Eur., USP/NF		
Talc	Ph. Eur., USP/NF, Ph. Jap.		
Titanium dioxide	Ph. Eur., USP/NF, Ph. Jap.		
Ferric oxide red	Directive 95/45/EC USP/NF, JPE		
Ferric oxide yellow	Directive 95/45/EC USP/NF, JPE		
(b) (4)	Directive 95/45/EC		
a	(b) (4)	(b) (4)	(b) (4)

(Remark: The excipients hypromellose (b) (4), talc, titanium dioxide, ferric oxide red, and ferric oxide yellow are (b) (4).)

In both tablets, (b) (4) LOAs for the coating are provided.

All excipients are compendial and are controlled by compendial methods. Lactose complies with the EMEA guidance and, as per ONDQA policy, is exempt from concerns of TSE/BSE.

Comment: Adequate information is provided to allow review.

Extensive work was performed during the Pharmaceutical Development to develop a formulation that would provide sufficient stabilization of the levomefolate calcium. The sponsor states that levomefolate calcium can be assessed as moderately stable. It exhibits sensitivity to oxygen and heat, and increased degradation occurs in the presence of water.

The sponsor also states that the formulation is manufactured with a (b) (4) overage of (b) (4) to account for losses during manufacturing. Data is provided to support the use of the overage.

Comment: The justification for the (b) (4) overage and the supporting data should be carefully reviewed to see if it is adequate.

MANUFACTURING

The following facilities have been identified in the application:

Drug Product							
Name and Address	Contact Person at Site	Telephone Number	Fax Number	E-mail Address	Registration Number	Stage of Manufacturing	Ready for Inspection
Schering GmbH and Co. Produktions KG Weimar Plant Döbereinerstrasse 20 99427 Weimar, Germany	Dr. Alfred Merz	011 49 3643 433-1300	011 49 3643 433-261300	Alfred.merz@bayerhealthcare.com	3002808091	Manufacturing and bulk packaging QC Release testing of bulk tablets	Yes
Schering GmbH and Co. Produktions KG Weimar Plant Riessnerstrasse 12b 99427 Weimar, Germany	Dr. Gabriele Schubert	011 49 3643 433-1315	011 49 3643 433-261315	Gabriele.schubert@scheringpg.de	3002808091	Stability testing QC Stability testing of final packaged/labelled product*	Yes
Bayer Schering Pharma AG Wedding Plant Müllerstr. 170 - 178 D-13353 Berlin, Germany	Dr. Hans-Joachim Raubach	011 49 30 4681 6826	011 49 30 4689 6826	Hans-joachim.raubach@bayer-ag.de	3002808086	Final Packaging of product Final Labeling of product Release of marketed product	Yes
Bayer Healthcare LLC Animal Health 12809 Shawnee Mission Parkway Shawnee, KS 66216, USA	Jim Watson, Director of Quality	913-268-2711	913-268-2160	jim.watson.b@bayer.com	1910953	Secondary Packaging	Yes
(b) (4)							
(b) (4)							
Name and Address	Contact Person at Site	Telephone Number	Fax Number	E-mail Address	Registration Number	Stage of Manufacturing	Ready for Inspection
Bayer HealthCare Pharmaceuticals 6 West Belt Wayne, NJ 07470, USA	Dr. Horst Heimbach	973-305-5143	973-305-3533	horst.heimbach@bayer.com	2243252	Administrative (paper) Release for distribution	Yes

Comment: The EES was submitted on 15-Dec-2009 by Jeannie David.

The sponsor has provided an overview of their risk assessment for manufacturing, using the failure mode effect analysis (FEMA) method. They have assigned a risk priority number (RPN) for attributes that effect drug product quality and have developed a process challenge program. In addition, they have developed a Design Space based on the results of the challenge program and the validation of the process design space.

Table 2-4: Design space

(b) (4)							
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Source: [P.2.3.01-02](#) Pharmaceutical Development – Manufacturing Process / Drospirenone + Ethinylestradiol + Levomefolate calcium coated tablet 3.0 mg + 0.03 mg + 0.451 mg

The tablets are manufactured according to the following flow chart:



(b) (4)

The following in process controls are used for both tablets:

Table 3-3: Process controls

Test	Acceptance criteria	Procedure
		relative humidity measuring instrument
		Ph. Eur.
		thickness measuring instrument Ph. Eur. Ph. Eur. Ph. Eur.
		Ph. Eur. Ph. Eur.

Table 3-4: Process controls during packaging process

Process controls


Comment: Information is adequate to allow review.

SPECIFICATIONS

The quality of the combination tablets are controlled by the following specifications:

Table 5-1: Release and shelf life specification of Drospirenone + Ethinylestradiol + Levomefolate calcium coated tablet

Test	Acceptance Criterion	
	Release	Shelf Life (only where different)
Formulation	coated tablet	
Form	round, biconvex	
Color	orange	
Markings tablet top side	"Y+" in a regular hexagon	
		(b) (4)

Test	Acceptance Criterion	
	Release	Shelf Life (only where different)
Stage testing according to Ph. Eur., USP, Ph. Jap.		
		(b) (4)

Table 5-1: Release and shelf life specification of Levomefolate calcium coated tablet

Test	Acceptance Criterion	
	Release	Shelf Life (only where different)
Formulation	coated tablet	
Form	round, biconvex	
Color	light orange	
Markings tablet top side	"M+" in a regular hexagon	
Markings tablet bottom side	without	
Identity levomefolate calcium (HPLC)	must comply	
(b) (4)		

Methods and validation are provided.

The sponsor has provided a characterization of potential impurities. They stated that the impurities in the tablet are either by-products of the drug substance synthesis or degradation products that evolve during storage of the tablets. Individual impurities are listed in the specifications.

For levomefolate calcium, two specified impurities have been identified.

(b) (4)

The sponsor states that both are described in the literature as degradation products, formed through (b) (4) degradation of levomefolate calcium. They also state that there are no toxicological concerns for the limits of (b) (4).

Comment: For drospirenone and ethinyl estradiol, the impurity acceptance criteria are different that what was approved in the original YASMIN application. However, the acceptance criteria for these actives could have been changed in Post Approval supplements. The reviewer should check the regulatory history of NDAs 21-676 and 21-098 (cross-referenced on the 356h form) to see if the wider acceptance criteria have been approved in the past.

For levomefolate calcium, the PharmTox reviewer should be consulted to determine if there are no toxicological concerns for the limits of (b) (4). The limits should also be carefully reviewed to determine if the data support the limits.

For residual solvents, the sponsor provides an assessment of the residual solvents used in manufacture of the drug substances and the excipients. They state that no solvents are used in the manufacture of the tablets and that the residual solvent limits for all excipients and drug substances are at or below the limits according to option 1 in the ICH Q3C guidance, except for (b) (4). The sponsor has calculated the limits according to Option 2 in the guidance and state that the requirements are met and that the medicinal product complies with the ICH Q3C guidelines.

Comment: As per policy, it appears that the acceptance criteria for (b) (4) in the drug product are met. However, this should be confirmed during the NDA review.

The sponsor has provided justification for all tests. They have also provided a justification for skip testing for microbial limits and impurities.

Comment: All tests and acceptance criteria will require review. The justification for skip testing for microbial limits and impurities will require careful evaluation.

The sponsor has provided batch release data on three batches of each tablet.

Comment: Information is adequate to allow review.

CONTAINER CLOSURE

The sponsor states that two different container closure systems are used to provide sufficient stability for the levomefolate calcium which is known for its instability and sensitivity to water, (b) (4)

(b) (4)

(b) (4)

Comment: Information is adequate to allow review.

STABILITY

The sponsor requests an expiration dating period of 24 months based on the following stability package. They state that the degradation of the levomefolate calcium will limit the shelf life of the drug product. In addition to the stability data outlined below, the sponsor also has 24 months of stability data on one production scale batch of the levomefolate calcium tablets packaged in the proposed container closure system.

Stability data for the combination tablets:

Table 8-2 : Batches used for stability studies

Studies	Packaging	No of batches	Batches investigated
Long-term studies	(b) (4) blister	3	WEC527, WEC528, WEC529
	Blister in (b) (4)	3	WEC527, WEC528, WEC529
Studies under accelerated conditions	(b) (4) blister	3	WEC527, WEC528, WEC529
	Blister in (b) (4)	3	WEC527, WEC528, WEC529
Thermal/Humidity Stress testing	(b) (4) blister	1	WEC527
	(b) (4) blister	1	WEC527
Photostability study	(b) (4)	1	WEC527
Bulk stability	Bulk in (b) (4)	3	WEC527, WEC528, WEC529

Table 8-3: Overview of long-term, accelerated studies and bulk stability

Batch no.	Date of manufacture	Batch size	Batch no. API	Packaging type	Start of stability	Storage condition [°C/% RH]	Data to date [months]
WEC527	2007-10						(b) (4)
WEC528	2007-10						
WEC529	2007-10						

EEBC: ethinylestradiol betadex clathrate
 DRSP: drospirenone
 LMCA: levomefolate calcium

Stability data for the levomefolate tablets:

Table 8-2: Batches used for stability studies

Studies	Packaging	No of batches	Batches investigated
Long-term studies	(b) (4) blister	3	WEC53S, WEC53T, WEC53U
	Blister in (b) (4)	3	WEC53S, WEC53T, WEC53U
Studies under accelerated conditions	(b) (4) blister	3	WEC53S, WEC53T, WEC53U
	Blister in (b) (4)	3	WEC53S, WEC53T, WEC53U
Thermal/Humidity Stress testing	(b) (4) Blister	1	WEC53S
	(b) (4) Blister	1	WEC53S
Photostability study	(b) (4)	1	WEC53S
Bulk stability	Bulk in (b) (4)	3	WEC53S, WEC53T, WEC53U

Table 8-3: Overview of long-term, accelerated stability studies and bulk stability

Batch no.	Date of manufacture	Batch size	Batch no. API	Packaging type	Start of stability	Storage condition [°C/% RH]	Data to date [months]
WEC53S	2007-09	(b) (4)					(b) (4)
WEC53T	2007-09						(b) (4)
WEC53U	2007-09						(b) (4)

Comment: The sponsor states that statistical analysis of the data and 24 months of supporting data on one batch of levomefolate calcium tablets support the 24 month expiration dating period. However, since levomefolate appears to be highly susceptible to degradation, the reviewer should carefully evaluate whether the data show a significant change (as defined in Q1E) to determine whether statistical analysis and expiration dating period extension are appropriate. Since there are two different container closure systems, it will need to be evaluated whether there are significant differences between the stability characteristics and if different expiration dating periods are appropriate depending on the closure system used.

Taking into account the propensity for degradation of the levomefolate calcium, it would be valuable to know the age of the clinical trial supplies to further help in the evaluation of

expiration dating period and to set an appropriate specification for degradation products. The sponsor will be asked for the age of the supplies used in the clinical trials.

A standard stability commitment is provided in the application.

Comment: *Information is adequate to allow review.*

LABELING

Black-and-white labels with “TRADENAME” are available for review of placement. As stated in the cover letter, the sponsor will update the Draft Carton/Container Labels with the proposed tradename, design and color after the receive FDA feedback on the YAZ FOLATE tradename. A DLDE table is provided in the SPL table and will require review.

Comment: *Information is adequate to allow review.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22574	ORIG-1	BAYER CORP PHARMACEUTICA L DIV	YASMIN PLUS (DEOSPIRENONE ETHINYL ESTRAD

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

/s/

DONNA F CHRISTNER
12/31/2009

MOO JHONG RHEE
12/31/2009
Chief, Branch III