CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022532Orig1s000

CHEMISTRY REVIEW(S)

Memorandum	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research
Date:	23-Sep-2010
To:	NDA 22-532 CMC Review #2
From:	Hitesh Shroff, Ph.D.
Through:	Moo-Jhong Rhee, Ph.D. Chief, Branch IV ONDQA Division II
CC:	Donna Christner, Ph.D.
Subject:	Package insert labeling

The sponsor submitted a revised PI following the CMC related recommendations via email on 23-Sep-2010. The description of Levomefolate calcium in Section 11 Description of the PI is modified as shown below.

Levomefolate calcium (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) is a synthetic calcium salt of L-5-methyltetrahydrofolate (L-5-methyl-THF), which is a metabolite of vitamin B_9 and has a molecular weight of 497.5 and a molecular formula of $C_{20}H_{23}CaN_7O_6$

Now the labels have adequate information as required. Therefore, from the CMC perspective, this NDA is recommended for approval.

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
09/23/2010

DONNA F CHRISTNER on behalf of MOO JHONG RHEE
09/23/2010
I concur

NDA 22-532

(b) (4) (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) 3 mg/0.02 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 22-532
For the Division of Reproductive and Urologic Drug Products (HFD-580)

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1. NDA 22-532

2. REVIEW #:2

3. REVIEW DATE: 20-Sept-2010

4. REVIEWER: Hitesh Shroff, Ph.D.

5. PREVIOUS DOCUMENTS:

	Document date
Original	24-Aug-2009
Amendment - Response to IR	17-Nov-2009
Amendment - Labeling Draft	16-Dec-2009
Amendment – Response to IR	22-Apr-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment – Labeling Draft	09-Jul-2010
Amendment – Labeling Draft	14-Jul-2010
Amendment – Response to IR	09-Aug-2010
Amendment - Response to IR	24-Aug-2010

1. NAME & ADDRESS OF APPLICANT

Name:	Bayer HealthCare Pharmaceuticals Inc.
Address:	PO Box 1000 Montville, NJ 07045-1000
Representative:	Kavita Johal Assistant Director Global Regulatory Affairs
Telephone:	(973) 487-2078

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)
      Methylfolate micronized, Levomefolate calcium micronized
   c) Chem. Type/Submission Priority (ONDQA only):
      - Chem. Type: 4,7
      - 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 0.02 mg/ Levomefolate calcium 0.451 mg

13. ROUTE OF ADMINISTRATION: Oral

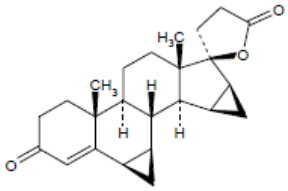
14. Rx/OTC DISPENSED: X Rx ___OTC

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:

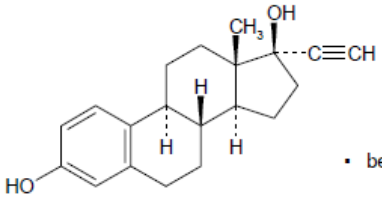
Drug Substance #1: Drospirenone



Drospirenone

Chemical Name:	6β, 7β,15β,16β-Dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone
Molecular Formula:	$C_{24}H_{30}O_3$
Molecular Weight:	366.5 g/mol

Drug Substance #2: Ethinyl Estradiol



- beta-Cyclodextrin-clathrate 1:2

Chemistry Review Data Sheet

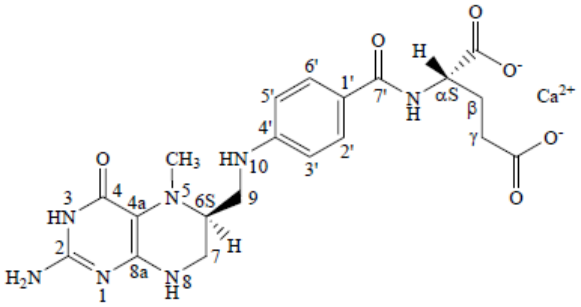
Ethinyl Estradiol

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

Molecular Formula: $C_{104}H_{164}O_{72}$

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: $C_{20}H_{23}CaN_7O_6$
Free acid: $C_{20}H_{25}N_7O_6$

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	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
12138	II	Bayer Schering Pharma AG, Germany	Drospirenone	1	Adequate	15-Feb-2010	Reviewed to support NDA 22-532
14960	II	Bayer Schering Pharma AG, Germany	Ethinyl Estradiol	1	Adequate	31-Dec-2009	Reviewed to support NDA 22-532
(b) (4)	II	(b) (4)		1	Adequate	23-Nov-2009	Reviewed to support NDA 22-532

(b) (4)	III	(b) (4)	1	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: N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	20-May-2010	Hitesh Shroff
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical exclusion is granted (see review)	5-Oct-2009	Hitesh Shroff
Microbiology	N/A		

The Chemistry Review for NDA 22-532

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The previous Review #1 noted that this NDA has provided sufficient information to assure identity, strength, purity and quality of the drug products with all facilities in compliance with cGMP. However, issues on labels/labeling were pending.

Now, the labels and labeling have all the required information.

Therefore, from the CMC perspective, this NDA is now 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)

(b) (4) is a combination oral contraceptive including 24 pink tablets containing drospirenone (3.0 mg), ethinyl estradiol beta-cyclodextrin clathrate (0.02 mg) and levomefolate calcium (0.451 mg) and 4 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 YAZ.

Drug Substances

Drospirenone

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.

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 (b) (4) 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 combinantion oral contraceptive. Each package contains 24 pink tablets and 4 light orange tablets. The pink tablet contains drospirenone (3 mg), ethinyl estradiol beta-cyclodextrin (0.02 mg) and levomefolate calcium (0.451 mg). It is round, biconvex, (b) (4) in a regular hexagon is printed on one side and the other side is blank.

The 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 were manufactured (b) (4)

The tablets also contain other USP/NF ingredients such as magnesium stearate (b) (4) (b) (4), ferric oxide yellow and red (b) (4).

The release specification for tablets include identification and assay of each active ingredient (HPLC), degradation products (HPLC), dissolution, content uniformity and microbial purity.

The commercial tablets will be packaged in (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 expiry period of 24 months. Based on the submitted stability data, an expiration dating period of 24 months can be granted.

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. 24 tablets contain 3.0 mg drospirenone/0.02 mg ethinyl estradiol beta-cyclodextrin and 0.451 mg levomefolate and the remaining 4 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 container/closure system is adequate to protect the drug products. The application also provided sufficient stability information on the drug products to assure strength, purity, and quality of the drug products during the expiration dating period. All facilities are in compliance with cGMP. Now all the labels/labeling have the required information. Therefore, this NDA is now recommended for "Approval" from the CMC perspective.

III. Administrative

A. Reviewer's Signature

Hitesh Shroff/ September 20, 2010

B. Endorsement Block

Moo-Jhong Rhee, Branch Chief, Branch IV, Division 2
Donna Christner
Jeanie Roule
Pam Lucarelli

C. CC Block

4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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
09/20/2010

MOO JHONG RHEE
09/20/2010
Chief, Branch IV

NDA 22-532

(b) (4) (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) 3 mg/0.02 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 22-532
For the Division of Reproductive and Urologic Drug Products (HFD-580)

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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. 8

Ethinyl estradiol beta-cyclodextrin clathrate 8

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C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

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I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: 15

Body Of Data 15

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I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: 19

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Chemistry Review Data Sheet

1. NDA 22-532

2. REVIEW #:1

3. REVIEW DATE: 25-Apr-2010

4. REVIEWER: Hitesh Shroff, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	24-Aug-2009
Amendment - Response to IR	17-Nov-2009
Amendment - Labeling Draft	16-Dec-2009
Amendment – Response to IR	22-Apr-2010

1. NAME & ADDRESS OF APPLICANT

Name:	Bayer HealthCare Pharmaceuticals Inc.
Address:	PO Box 1000 Montville, NJ 07045-1000
Representative:	Kavita Johal Assistant Director Global Regulatory Affairs
Telephone:	(973) 487-2078

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)
      Methylfolate micronized, Levomefolate calcium micronized
   c) Chem. Type/Submission Priority (ONDQA 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 0.02 mg/ Levomefolate calcium 0.451 mg

13. ROUTE OF ADMINISTRATION: Oral

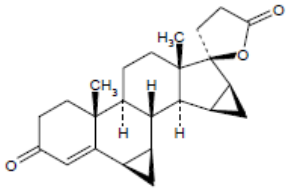
14. Rx/OTC DISPENSED: X Rx ___OTC

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:

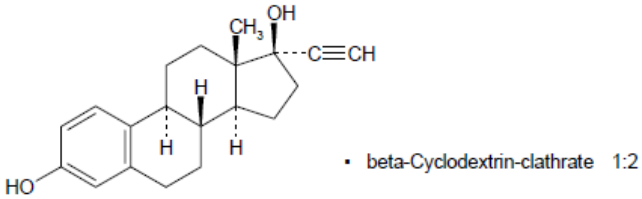
Drug Substance #1: Drospirenone



Drospirenone

Chemical Name: 6β, 7β,15β,16β-Dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone
Molecular Formula: $C_{24}H_{30}O_3$
Molecular Weight: 366.5 g/mol

Drug Substance #2: Ethinyl Estradiol

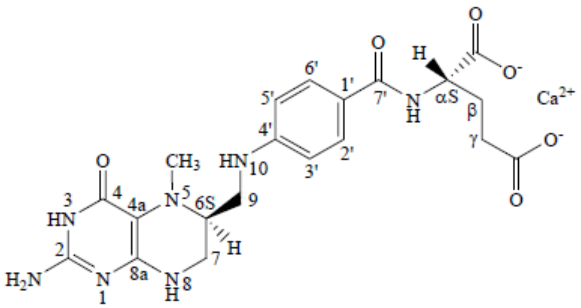


Ethinyl Estradiol

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

Molecular Formula: $C_{104}H_{164}O_{72}$
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: $C_{20}H_{23}CaN_7O_6$
(b) (4)

Molecular Weight: Calcium salt: 497.52 g/mol
(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
12138	II	Bayer Schering Pharma AG, Germany	Drospirenone	1	Adequate	15-Feb-2010	Reviewed to support NDA 22-532
14960	II	Bayer Schering Pharma AG, Germany	Ethinyl Estradiol	1	Adequate	31-Dec-2009	Reviewed to support NDA 22-532
(b) (4)	II	(b) (4)		1	Adequate	23-Nov-2009	Reviewed to support NDA 22-532

(b) (4)	III	(b) (4)	1	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: N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	20-May-2010	Hitesh Shroff
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical exclusion is granted (see review)	5-Oct-2009	Hitesh Shroff
Microbiology	N/A		

The Chemistry Review for NDA 22-532

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 24 pink tablets containing drospirenone (3.0 mg), ethinyl estradiol beta-cyclodextrin clathrate (0.02 mg) and levomefolate calcium (0.451 mg) and 4 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 YAZ.

Drug Substances

Drospirenone

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.

Ethinyl estradiol beta-cyclodextrin clathrate

The ethinyl estradiol beta-cyclodextrin clathrate is manufactured by Bayer Schering Pharma AG, Germany. Complete CMC information on drospirenone 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 # (b) (4) 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 combinantion oral contraceptive. Each package contains 24 pink tablets and 4 light orange tablets. The pink tablet contains drospirenone (3 mg), ethinyl estradiol beta-cyclodextrin (0.02 mg) and levomefolate calcium (0.451 mg). It is round, biconvex, (b) (4) in a regular hexagon is printed on one side and the other side is blank.

The 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 were manufactured (b) (4)

The tablets also contain other USP/NF ingredients such as magnesium stearate (b) (4) (b) (4), ferric oxide yellow and red (b) (4)

The release specification for tablets include identification and assay of each active ingredient (HPLC), degradation products (HPLC), dissolution, content uniformity and microbial purity.

The commercial tablets will be packaged (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 expiry period of 24 months. Based on the submitted stability data, an expiration dating period of 24 months can be granted.

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. 24 tablets contain 3.0 mg drospirenone/0.02 mg ethinyl estradiol beta-cyclodextrin and 0.451 mg levomefolate and the remaining 4 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/ April 25, 2010

B. Endorsement Block

Moo-Jhong Rhee, Branch Chief, Branch IV, Division 2
Donna Christner
Jeanie Roule

C. CC Block

132 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	YAZ Folate

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/s/

HITESH N SHROFF
06/02/2010

MOO JHONG RHEE
06/02/2010
Chief, Branch IV

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Reproductive and Urologic Products
NDA:	22-532
Applicant:	Bayer Healthcare Pharmaceuticals, Inc.
Stamp Date:	24-Aug-2009
PDUFA Date:	24-Jun-2010
Trademark:	(b) (4)
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	☐
Comments for 74-Day Letter	X	☐

Summary and Critical Issues:

A. Summary

The drug product is a combined oral contraceptive containing levomefolate calcium in a 28 day regimen. The blister contains 24 tablets containing drospirenone, ethinyl estradiol and levomefolate calcium followed by 4 tablets containing levomefolate calcium. The sponsor states that fortification of the OC provides an effective means of providing folate supplementation to women of reproductive potential.

The combination tablet contains 3.0 mg drospirenone, 0.02 mg ethinyl estradiol (as the β-cyclodextrin clathrate) and 0.451 mg levomefolate calcium. Each tablet is pink, round, and biconvex, marked with a "Z+" in a regular hexagon on one side. The Levomefolate calcium tablet contains 0.451 mg of active and is a light orange, round, biconvex shaped tablet marked with an "M+" in a regular hexagon on one side.

The commercial product will be packaged in (b) (4) foil blisters or PVC blisters in a (b) (4) pouch. The sponsor is requesting a 24 month expiration dating period for the commercial product.

B. Critical issues for review

All three drug substance DMFs will require review. There may be adequate information in the NDA so that the coating DMFs will not require review.

The justification for the [redacted] (b) (4) *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 YAZ 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 it there are no toxicological concerns for the limits of [redacted] (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 Residual Solvents 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 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.

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 critical issues which need to be critically evaluated during the review. There is one comment to be sent to the sponsor in the 74 day letter. A single reviewer, Hitesh Shroff, Ph.D. has been assigned.

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Donna F. Christner, Ph.D.

NDA/BLA Number: 22-532 **Applicant: Bayer Healthcare** **Stamp Date: 24-Aug-2009**

Drug Name: (b) (4) **NDA/BLA Type: 1, 5**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		Confirmed by Jeannie David, ONDQA PM
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		Categorical exclusion as per 21 CFR 25.31(b). Calculation provided
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		DMFs 12138, 14960, (b) (4)
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		Amendment 1 provides for updated labeling
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	X		N/A

IS THE CMC SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Donna F. Christner, Ph.D. 25-Sep-2009

Pharmaceutical Assessment Lead Date

Moo-Jhong Rhee, Ph.D.

Branch Chief Date

DMF	Holder	Description	LOA	Status
12138	Bayer Healthcare	Drospirenone	Yes	ADEQUATE on 15-Feb-2006 by J. Salemme. Amendments submitted since last review. **May require review.**
14960	Bayer Healthcare	Ethinylestradiol-β-cyclodextrin clathrate	Yes	ADEQUATE on 26-Jul-2004 by D. Christner. Amendments submitted since last review. **May require review.**
		(b) (4)	Yes	**Will require review.**
			Yes	**May require review.**
			Yes	**May require review.**
			Yes	**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

REVIEW NOTES

The drug product is a combined oral contraceptive composed of two different tablets. It is based on the approved drug product YAZ, with the addition of a folate to provide folic acid supplementation. The first tablet which is taken for 24 days contains drospirenone, ethinyl estradiol and levomefolate calcium. The second tablet which is taken for 4 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.

Clinical trials were performed under IND 72,287.

There have been a number of meetings prior to submission of the NDA. The following CMC-related issues were discussed:

Correspondences dated 26-Aug-2005 and 29-Aug-2005: In order to adequately address CMC questions for a preIND meeting scheduled for 8-Sep-2005, FDA (26-Aug-2005) asked for clarification on the formulations to be used in the proposed BE studies and if the to-be-marketed formulation and clinical trial formulations would be the same. The sponsor submitted the requested information (29-Aug-2005) and confirmed that the clinical and commercial formulations would be the same.

PreIND meeting held 08-Sep-2008: Three CMC issues were raised at the meeting. The following responses were conveyed:

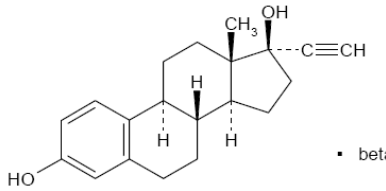
- Information on each drug substance could be provided in a DMF
- L-methylfolate is considered a drug substance and should therefore meet assay acceptance criteria of 90-110%
- Agreement could not be given that (b) (4)

PreNDA meeting scheduled for 06-Apr-2009 (cancelled at sponsor's request after receipt of preliminary comments): A CMC comment was made that 12 months of stability data at submission in both container closure systems was acceptable, and that additional stability data could be submitted by month 6 for a Standard review or month 3 of a Priority review.

DRUG SUBSTANCES

Ethinyl estradiol β-cyclodextrin clatharate

The majority of the information is provided in DMF 14960. The following information has been provided in the application.



- beta-Cyclodextrin-clathrate 1:2

Empirical formula	$C_{104}H_{164}O_{72}$
Relative molecular weight	2566.4 g/mol
Stereochemisty	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.

Manufacturing information is provided in tabular form for all drug substances. The table is provided after the drug substance sections.

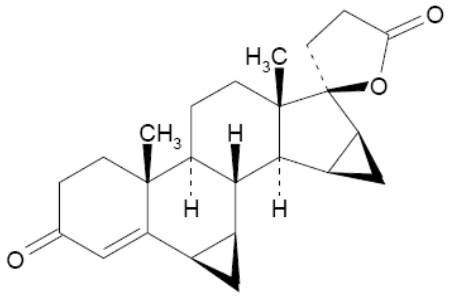
(b) (4)

The sponsor has provided batch release information on three batches of drug substance.

Comment: *Information is adequate to allow review. Since the DMF has not been reviewed in 5 years and there have been updates submitted, the DMF will require review.*

Drospirenone

The majority of the information is provided in DMF 12138. The following information has been provided in the application.



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 typic configuration at the following five carbons is fixed to be 8β-H, 9α-H, 10β-CH_3, 13β-CH_3, 14α-H. The asyymetric centers at C-6, C-7, C-15, C-16 and C-17 are introduced by highly stereoselective reactions to fix the following configurations: 6β, 7β, 15β, 16β, 17α.

Manufacturing information is provided in tabular form for all drug substances. The table is provided after the drug substance sections.

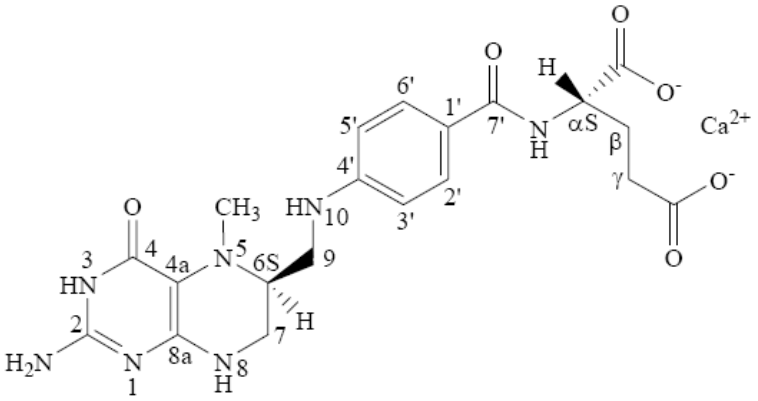
(b) (4)

The sponsor has provided batch release information on three batches of drug substance.

Comment: *Information is adequate to allow review. Since the DMF has not been reviewed in 3 years and there have been updates submitted, the DMF will require review.*

Levomefolate calcium

The majority of the information is provided in DMF (b) (4) The USAN/INN name was recently designated. The following information has been provided in the application.



Empirical formula	Calcium salt:	$C_{20}H_{23}CaN_7O_6$
	(b) (4)	
Relative molecular weight	Calcium salt:	497.52 g/mol
	(b) (4)	

Manufacturing information is provided in tabular form for all drug substances. The table is provided after the drug substance sections.

(b) (4)

The sponsor has provided batch release information on three batches of drug substance.

Comment: *Information is adequate to allow review. Since the DMF has not been reviewed, it will require review.*

MANUFACTURING

The sponsor has provided the following information in tabular form for all three drug substance manufacturers:

Drug Substance

Name and Address	Contact Person at Site	Telephone Number	Fax Number	E-mail Address	Registration Number	Stage of Manufacturing	Ready for Inspection
							(b) (4)

Comment: *The sites were inputted into EES by Jeannie David on 29-Sep-2009.*

DRUG PRODUCT

The drug product is a combined oral contraceptive containing levomefolate calcium in a 28 day regimen. The blister contains 24 tablets containing drospirenone, ethinyl estradiol and levomefolate calcium followed by 4 tablets containing levomefolate calcium. The sponsor states that fortification of the OC provides an effective means of providing folate supplementation to women of reproductive potential.

The combination tablet contains 3.0 mg drospirenone, 0.02 mg ethinyl estradiol (as the β-cyclodextrin clathrate) and 0.451 mg levomefolate calcium. Each tablet is pink, round, and biconvex, marked with a "Z+" in a regular hexagon on one side. The Levomefolate calcium tablet contains 0.451 mg of active and is a light orange, round, biconvex shaped tablet marked with an "M+" in a regular hexagon on one side.

The commercial product will be packaged (b) (4)

The combination tablets have the following composition:

Table 1-1: Composition of Drospirenone + Ethinylestradiol + Levomefolate calcium coated tablet 3.0 mg + 0.02 mg + 0.451 mg

Composition	Reference to standard	Function	Amount [mg]
Drug substances			
Drospirenone micronized	specification	drug substance	3.000
Ethinylestradiol betadex clathrate micronized [a]	specification	drug substance	0.020
Levomefolate calcium micronized	specification	drug substance	0.451
Excipients	(b) (4)		
Lactose monohydrate			
Cellulose microcrystalline			
Croscarmellose sodium			
Hydroxypropylcellulose (b) (4)			
Magnesium stearate			
Weight (uncoated tablet)			
(b) (4)	(b) (4)		
Talc			
Titanium dioxide			
Ferric oxide red			
Weight (film-coating)			
Weight (coated tablet)			**82.0000**

[a] calculated as ethinylestradiol

(b) (4)

The levomefolate calcium tablets have the following composition:

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

Composition	Reference to standard	Function	Amount [mg]
Drug substances			
Levomefolate calcium micronized	specification	drug substance	0.451
Excipients	(b) (4)		
Lactose monohydrate			
Cellulose microcrystalline			
Croscarmellose sodium (b) (4)			
Hydroxypropylcellulose			
Magnesium stearate			
Weight (uncoated tablet)			
(b) (4)	(b) (4)		
Talc			
Titanium dioxide			
Ferric oxide red			
Ferric oxide yellow			
Weight (film-coating)			
Weight (coated tablet)			**82.0000**

(b) (4)

In both tablets, the coating (b) (4)

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. (b) (4)

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
							(b) (4)

Comment: *The sites were inputted into EES by Jeannie David on 29-Sep-2009.*

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

	Design space	Target
		(b) (4)

The tablets are manufactured according to the following flow chart:

Figure 3-1: Flowchart – Manufacture of Drospirenone + Ethinylestradiol + Levomefolate calcium coated tablet

(b) (4)

Figure 3-1: Flowchart – Manufacture of Levomefolate calcium coated tablet

(b) (4)

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(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)

Comment: *For drospirenone and ethinyl estradiol, the impurity acceptance criteria are different that what was approved in the original YAZ 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 it there are no toxicological concerns (b) (4) *. The limits should also be carefully reviewed to determine if the data support the limits.*

(b) (4)

Comment: *As per policy, it appears that the acceptance criteria for Residual Solvents 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 SYSTEM

The drug product is packaged wither in a (b) (4) blister composed of a combination of (b) (4) and aluminum blister, or in a conventional blister sealed inside an aluminum pouch. The sponsor states that either container closure system is adequate to protect the levomefolate calcium which is known for its instability and sensitivity to water vapor and oxygen. The sponsor has provided the following information:

(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 combination tablets:

(b) (4)

Stability data for the levomefolate calcium tablets:

(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

The sponsor submitted their proposed tradename and updated container/carton labels and PI in Amendment 1, dated 25-Sep-2009. Container/carton labels are in the proposed colors and fonts and are adequate to allow review. A DLDE table is provided in the SPL table and will require review.

Comment: *Information is adequate to allow review.*

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
10/16/2009

MOO JHONG RHEE
10/19/2009
Chief, Branch III