

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-252, Original 1

CHEMISTRY REVIEW(S)

Memorandum:

Date: May 6, 2010
To: NDA: 22-252
From: Tarun Mehta
Reviewer, Branch III / DPA II / ONDQA
Subject: An addendum to CMC Review # 1

In CMC Review #1, the following pending issues were noted:

1. Regarding cGMP compliance,
 - A “Withhold” recommendation was made from the Office of Compliance on the facilities.

2. Regarding pending labeling issues,
 - The established names for the drug product were not resolved due to the unique combination of the drug substance (more than one combination of drug substances) within one blister card.
 - The dosage strengths were not included in the primary panel of both immediate container and carton labels.
 - Missing “lot number” and “expiration date” in the carton label.
 - Inadequate font size of the established name on carton label which is less than 50% of the trade name.
 - “See enclosed information” on the carton label should be reworded as “See package insert for dosage information”.

Now the Office of Compliance has issued an overall “Acceptable” recommendation (see the Appendix – 1).

All the labeling issues are satisfactorily resolved, and the revised PI and labels for carton and blister were submitted (see the Appendix – 2).

Therefore, from the CMC perspective, this NDA is now recommended for approval.

Appendix – 1:

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 22252/000	Sponsor:	BAYER HLTHCARE
Org. Code:	580		1000
Priority:	14		MONTVILLE, NJ 070451000
Stamp Date:	06-JUL-2009	Brand Name:	Qlaira
PDUFA Date:	06-MAY-2010	Estab. Name:	
Action Goal:		Generic Name:	ESTRADIOL VALERATE/DIENOGEST TABS
District Goal:	07-MAR-2010	Product Number; Dosage Form; Ingredient; Strengths	
			001; TABLET; ESTRADIOL VALERATE; 3MG 001; TABLET; DIENOGEST; 2MG 001; TABLET; DIENOGEST; 3MG 001; TABLET; ESTRADIOL VALERATE; 2MG 001; TABLET; ESTRADIOL VALERATE; 2MG 001; TABLET; ESTRADIOL VALERATE; 1MG
FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	T. MEHTA	Review Chemist	301-796-1712
	D. CHRISTNER	Team Leader	301-796-1341

Overall Recommendation:	ACCEPTABLE	on 09-APR-2010	by E. JOHNSON	(HFD-320)	301-796-3334
	WITHHOLD	on 04-JAN-2010	by E. JOHNSON	(HFD-320)	301-796-3334

Appendix-2

Labeling & Package Insert:

Package Insert

(a) “Highlights” Section

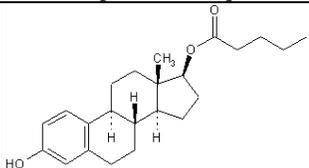
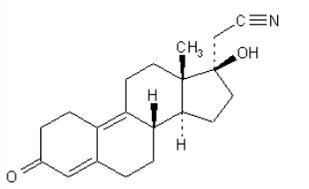
Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	Natazia™ (estradiol valerate and estradiol valerate/dienogest) tablets - Adequate
Dosage form, route of administration	Oral, Tablets - Adequate
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (201.57(a)(8))	
Each blister of 28 tablets	2 dark yellow tablets each containing 3 mg estradiol valerate 5 medium red tablets each containing 2 mg estradiol valerate and 2 mg dienogest 17 light yellow tablets each containing 2 mg estradiol valerate and 3 mg dienogest 2 dark red tablets each containing 1 mg estradiol valerate 2 white film-coated tablets - Adequate
Whether the drug product is scored	NA

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths:

Item	Information Provided in NDA
Available dosage forms	Tablets - Adequate
Strengths: in metric system	2 dark yellow tablets each containing 3 mg estradiol valerate 5 medium red tablets each containing 2 mg estradiol valerate and 2 mg dienogest 17 light yellow tablets each containing 2 mg estradiol valerate and 3 mg dienogest 2 dark red tablets each containing 1 mg estradiol valerate 2 white film-coated tablets - Adequate
Active moiety expression of strength with equivalence statement (if applicable)	See above
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	See strengths box above - Adequate

#11: Description

Item	Information Provided in NDA
Proprietary name and established name	Natazia™ (estradiol valerate and estradiol valerate/dienogest) tablets - Adequate
Dosage form and route of administration	Tablets, Oral - Adequate
Active moiety expression of strength with equivalence statement (if applicable)	2 dark yellow tablets each containing 3 mg estradiol valerate 5 medium red tablets each containing 2 mg estradiol valerate and 2 mg dienogest 17 light yellow tablets each containing 2 mg estradiol valerate and 3 mg dienogest 2 dark red tablets each containing 1 mg estradiol valerate 2 white film-coated tablets
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	lactose monohydrate, maize starch, maize starch pre-gelatinized, povidone 25, magnesium stearate, hypromellose, macrogol 6,000, talc, titanium dioxide, ferric oxide pigment, yellow, or ferric oxide pigment, red. - Adequate
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Contraceptive - Adequate
Chemical name, structural formula, molecular weight Estradiol valerate: Dienogest: - Adequate	 <p>The empirical formula: C₂₃ H₃₂ O₃ Chemical Name: Estra-1,3,5(10)-triene-3,17-diol(17β),17-pentanoate Adequate</p>  <p>The empirical formula: C₂₀ H₂₅ NO₂ The chemical name: (17α)-17-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile - Adequate</p>
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	none

Evaluation: Information is Adequate.

#16: How Supplied/Storage and Handling

Item	Information Provided in NDA
Strength of dosage form	Part of Identification section
Available units (e.g., bottles of 100 tablets)	Blister of 28 tablets
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<p>Natazia™ (estradiol valerate and estradiol valerate/dienogest) tablets are available in packages of three blister packs (NDC 50419-409-03).</p> <p>The active and inert tablets are rounded with biconvex faces, one side is embossed with a regular hexagon shape with the letters DD or DJ or DH or DN or DT.</p> <p>Each blister pack (28 film-coated tablets) contains in the following order:</p> <p>2 round biconvex dark yellow film-coated tablets with embossed “DD” in a regular hexagon on one side each containing 3 mg estradiol valerate</p> <p>5 round biconvex medium red film-coated tablets with embossed “DJ” in a regular hexagon on one side each containing 2 mg estradiol valerate and 2 mg dienogest</p> <p>17 round biconvex light yellow film-coated tablets with embossed “DH” in a regular hexagon on one side each containing 2 mg estradiol valerate and 3 mg dienogest</p> <p>2 round biconvex dark red film-coated tablets with embossed “DN” in a regular hexagon on one side each containing 1 mg estradiol valerate</p> <p>2 white round biconvex white film-coated tablets with embossed “DT” in a regular hexagon on one side</p>
Special handling (e.g., protect from light)	Keep out of reach of children
Storage conditions	<p>Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature].</p> <p>- Adequate</p>
Manufacturer/distributor name (21 CFR 201.1(h)(5))	<p>Manufactured for: Bayer HealthCare Pharmaceuticals Inc. Wayne, NJ 07470 Manufactured in Germany © 2009, Bayer HealthCare Pharmaceuticals Inc., All Rights Reserved. 3288396 Bayer HealthCare Pharmaceuticals Inc. Provided at the end of PI</p>

Evaluation: Information is Adequate.

7 pp Withheld in Full immed. after this page as (b)(4) Draft Labeling.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22252	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	Natazia
NDA-22252	ORIG-2	BAYER HEALTHCARE PHARMACEUTICA LS INC	Natazia

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

/s/

TARUN D MEHTA
05/06/2010

MOO JHONG RHEE
05/06/2010
Chief, Branch III

NDA 22-252

Trademark (estradiol valerate/dienogest) Tablets

Bayer Healthcare Pharmaceuticals

Tarun Mehta

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III**

**CMC REVIEW OF NDA 22-252
For the Division of Reproductive and Urology products (HFD-580)**

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Executive Summary Section

CMC Review Data Sheet

1. NDA 22-252
2. REVIEW #: 1
3. REVIEW DATE: 23-March-2010
4. REVIEWER: Tarun Mehta
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	July 06, 2009
Amendment 0006	October 15, 2009
Amendment 0009	November 13, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Bayer HealthCare Pharmaceuticals, Inc.
Address: PO Box 1000
Montville, NJ 07045-1000
Representative: Sharon W. Brown, Director, Global Regulatory Affairs
Telephone: (973) 487-2162

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Trademark
- b) Non-Proprietary Name: Estradiol Valerate /Dienogest
- c) Code Name/# (ONDQA only): None
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 1,4
 - Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Hormonal Contraceptive

Executive Summary Section

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: Estradiol Valerate (EV) /Dienogest (DNG)
2 dark yellow tablets each containing 3 mg EV
5 medium red tablets each containing 2 mg EV and 2 mg DNG
17 light yellow tablets each containing 2 mg EV and 3 mg DNG
2 dark red tablets each containing 1 mg EV
2 white placebo tablets

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

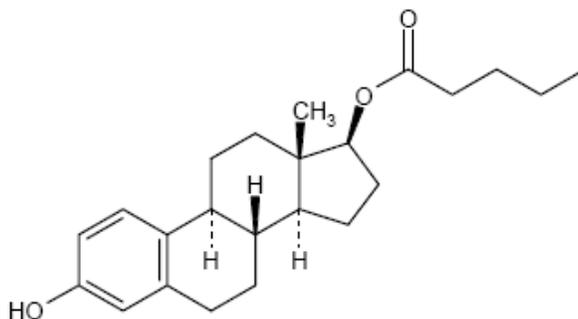
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

STRUCTURE (Estradiol Valerate):

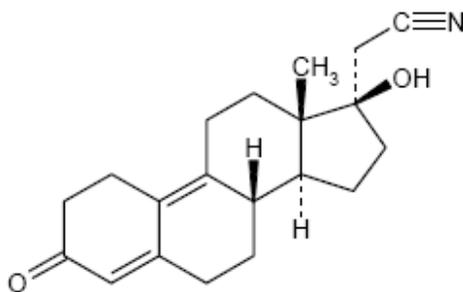


Molecular Formula: C₂₃H₃₂O₃

Molecular Weight: 356.51

STRUCTURE (Dienogest):

Executive Summary Section



Molecular Formula: $C_{20}H_{25}NO_2$
 Molecular Weight: 311.43

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
3379	II	Bayer Schering Pharma AG.	Estradiol valerate	1	Adequate	Tarun Mehta 15-Mar-2010	No update since last review
14014	II	Bayer Schering Pharma AG.	Dienogest	1	Adequate	Tarun Mehta 15-Mar-2010	No update since last review
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	Reviewed on 12-Mar-2001 by M. Heimann	No update since last review
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	Tarun Mehta 15-Mar-2010	No update since last review
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	Reviewed on 29-Jul-2004 by D. Christner.	No update since last review
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	Tarun Mehta 15-Mar-2010	No update since last review

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

Executive Summary Section

- 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:

INDs: 64809, (b) (4)

18. STATUS:**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Withhold	3/15/10	E. Johnson (HFD-320)
EA	Categorical exclusion (see review)	3/15/10	Tarun Mehta

Executive Summary Section

The CMC Review for NDA 22-252

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 product. However, labeling issues are still pending and a site recommendation from the Office of Compliance is overall “Withhold” as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

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

Not applicable

II. Summary of CMC Assessments

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

(1) Drug Substances

Trademark tablet formulations contains two drug substances: estradiol valerate micro (EV), and dienogest micro (DNG). Estradiol valerate is marketed by the sponsor in USA, however the drug substance dienogest considered to be a new molecule entity for US market. The drug substance estradiol valerate is a compendial (USP) material, dienogest is non compendial materials. The drug substances are practically insoluble in water. Adequate chemistry, manufacturing and controls information for both the drug substances is provided in the DMF. The quality of the drug substance is controlled by the compendial (USP) monographs and/or in-house specification. Based on the stability data, adequate re-test period of (b) (4) for both the drug substances are established by the manufacturers.

(2) Drug Product

The drug product is an oral contraceptive supplied in (b) (4) film/aluminum foil blister each contains 28 film-coated tablets. Each blister includes five different strengths of EV and DNG alone or in combination. The tablets are differ in color and strength combination: first 2 dark yellow tablets each containing 3 mg EV, followed by 5 medium red tablets each containing 2 mg EV and 2 mg DNG, 17

Executive Summary Section

light yellow tablets each containing 2 mg EV and 3 mg DNG, 2 dark red tablets each containing 1 mg EV and last 2 white placebo tablets. The drug product is an immediate-release, round biconvex colored film-coated tablet with embossed in a regular hexagon on one side. The composition, manufacturing process, batch scale and manufacturing site of the clinical batches and stability batches are identical to those of proposed commercial product. All the excipients used in the drug product are compendial (USP/NF) grade. All excipients used in the formulations are listed in the FDA inactive ingredient list and have been used in the pharmaceutical products at or below the proposed concentration. The drug product was developed based on the sponsor's currently marketed oral contraceptive. The identity, strength, purity and quality of the final drug product are assured by the specification: appearance, ID, content uniformity, assay of APIs and degradation products, dissolution and microbial contamination testing. Based on available stability data, the expiration dating period of 48 months is granted for the proposed drug product.

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

The drug product is indicated for the prevention of pregnancy in women of reproductive age and for the treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception. To achieve maximum contraceptive effectiveness, oral contraceptives (COCs) must be taken exactly as directed. Take one tablet by mouth the same time every day. Tablets must be taken in the order directed on the blister pack. Tablets should not be skipped or intake delayed by more than 12 hours.

C. Basis for Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

The labeling issues are not resolved, and the site recommendation from the Office of Compliance is overall "Withhold" as of the date of this review.

Executive Summary Section

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

(See appended electronic signature page)

Tarun Mehta, M.Sc.

B. Endorsement Block:

(See appended electronic signature page)

Rhee Moo Jhong, Ph.D. Branch Chief, Branch III, ONDQA

C. CC Block: entered electronically in DFS

117 pp withheld in full immed. after this page as (b)(4) CCI/TS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22252	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	Qlaira

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/s/

TARUN D MEHTA
03/23/2010

MOO JHONG RHEE
03/23/2010
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Reproductive and Urologic Products
NDA: 22-252
Applicant: Bayer Healthcare Pharmaceuticals
Stamp Date: 06-Jul-2009
PDUFA Date: 06-May-2010
Trademark: Qlaira
Established Name: Estradiol valerate and dienogest
Dosage Form: Tablet
Route of Administration: Oral
Indication: Prevention of pregnancy and treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an OC for contraception

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 containing Estradiol valerate (EV) and Dienogest (DNG) in fixed combinations or EV alone in a sequential application regimen, consisting of 4 phases with active tablets and one placebo phase. Each blister package contains 28 film-coated tablets in the following order:

2 dark yellow tablets each containing 3 mg EV
5 medium red tablets each containing 2 mg EV and 2 mg DNG
17 light yellow tablets each containing 2 mg EV and 3 mg DNG
2 dark red tablets each containing 1 mg EV
2 white placebo tablets

The drug product is packaged in a blister package composed of (b) (4) aluminum blister composed of a lidding foil and a forming film. The primary packaging is packaged in a non-functional secondary packaging carton which also contains a (b) (4) wallet.

B. Critical issues for review

The two drug substance DMFs will require review.

The application contains five 3.2.P sections and will require careful review.

C. Comments for 74-Day Letter

It is noted that in Module 2, the specifications repeat the assay for estradiol valerate. The specification sheets in Module 3 are correct, however. Please provide corrected specification sheets in Module 2.

Because the packaged drug product contains 5 different tablet formulations that are distinguished by color (medium versus dark red and light versus dark yellow), please submit at least two samples of packaged drug product. These should include one batch of recently-manufactured drug product and another batch of aged drug product samples for comparison to determine if the colors fade upon storage.

Please submit a copy of the blister pack. Color mock-ups for the carton and immediate container labels, including any logos, should be provided in order to allow full review of these labels. Please ensure that when the SPL label is submitted that it contains a DLDE table for review.

D. Recommendation:

This NDA is fileable from a CMC perspective. A single reviewer, Tarun Mehta, has been assigned. There are two comments to be conveyed to the sponsor.

Donna F. Christner, Ph.D.

NDA Number: 22-252

**Applicant: Bayer Healthcare
Pharmaceuticals**

Stamp Date: 06-Jul-2009

Drug Name: Qlaira

NDA Type: 1, 4

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		Sponsor has updated information on 14-Jun-2009 as per ONDQA PM request
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)
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		DMF 3379 DMF 14014
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		Blister labels not provided and will be requested. SPL not provided.
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.

10-Aug-2009

Pharmaceutical Assessment Lead

Date

Moo-Jhong Rhee, Ph.D.

Branch Chief

Date

DMF	Holder	Description	LOA	Status
3379	Bayer Schering Pharma AG	Estradiol valerate	Yes	ADEQUATE on 16-Oct-2001 by J. Boal. Updates submitted. Will require review.
14014	Bayer Schering Pharma AG	Dienogest	Yes	Will require review.
(b) (4)			Yes	ADEQUATE on 12-Mar-2001 by M. Heimann as part of review (b) (4) See ONDC Policies on Bottles and Blisters*
			Yes	Reviewed in 04-Nov-1997 (b) (4)
			Yes	No Review found.
			Yes	ADEQUATE on 29-Jul-2004 by D. Christner. See ONDC Policies (b) (4)
				No review found (b) (4)

**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*

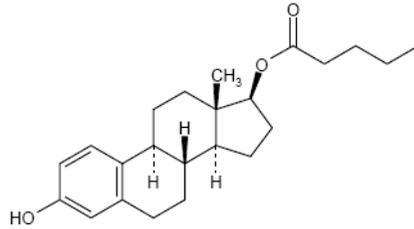
DRUG SUBSTANCE

Two drug substances are used in this combination drug product:

Estradiol valerate (EV)

The majority of the information is provided in the referenced DMF 3379. EV has been previously approved in the US in an injectable formulation. The sponsor has provided the following information in the NDA.

- **Structural formula**



- **Molecular formula**

C₂₃ H₃₂ O₃

- **Relative molecular mass**

356.51

- **International Nonproprietary Name (INN)**

Estradiol valerate

- **Compendial name**

Estradiol valerate (USP)
Oestradiol valerate (BAN)

- **Chemical name(s)**

Estra-1,3,5(10)-triene-3,17 β -diol-17-valerate (WHO)
Estradiol 17-valerate
Estradiol 17 β -valerate
Estra-1,3,5(10)-triene-3,17-diol (17 β), 17-pentanoate
1,3,5(10)-Estratriene-3,17 β -diol-17-valerate

- **Other name(s)**

Estradiol valerate, pure
Estradiol valerate, micro 20
Estradiol valerate, pure (S96)
Estradiol valerate, micro 20 (S96)

- **Laboratory code**

ZK 5104

- **CAS registry number**

979-32-8

Estradiol valerate is controlled by the following specifications:



(b) (4)

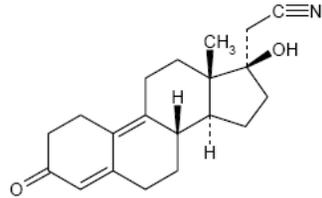
COAs provided for 2 lots of EV used in pivotal clinical trials.

Comment: The provided information is adequate to allow review. The DMF will require review.

Dienogest (DNG)

The majority of the information is provided in the referenced DMF 14014. The sponsor has provided the following information in the NDA. Dienogest is an NME since it has not been approved or marketed in the US.

- **Structural formula**



- **Molecular formula**

C₂₀ H₂₅ NO₂

- **Relative molecular mass**

311.43

- **Chirality**

Dienogest is the levorotatory enantiomer of 17 α -cyanomethyl-17 β -hydroxy-estra-4,9-dien-3-one.

- **International Nonproprietary Name (INN)**

Dienogest

- **Compendial name**

Not applicable

- **Chemical name(s)**

19-Norpregna-4,9-diene-21-nitrile, 17-hydroxy-3-oxo-17 α -Cyanomethyl-17 β -hydroxy-estra-4,9-dien-3-one (CAS)

17 α -Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile (IUPAC)

17 β -Hydroxy-3-oxo-19-nor-17 α -pregna-4,9-diene-21-nitrile

(17 α)-17-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile

- **CAS registry number**

65928-58-7

- **National approved name(s)**

Dienogest (USAN)

Dienogest is controlled by the following specifications:



(b) (4)

COAs provided for 2 lots of EV used in pivotal clinical trials.

***Comment:** The provided information is adequate to allow review. The DMF will require review.*

Manufacturers:

The following sites are responsible for the manufacture of the two drug substances. This information was provided upon request of the ONDQA PM, Jeannie David on 17-Jul-2009.

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 substance	Yes
Bayer Schering Pharma AG Max-Dohrn-Strasse 8 D-10589 Berlin, Germany	Dr. Hans-Joachim Raubach	011 49 30 4681 6826	011 49 30 4689 16826	Hans-joachim.raubach@bayer-ag.de	3002808063	Facility for (b) (4) and particle size testing of drug substances	Yes

Comment: The EES was submitted on 07-Aug-2009.

DRUG PRODUCT

The drug product is an oral contraceptive containing EV and DNG in fixed combinations or EV alone in a sequential application regimen, consisting of 4 phases with active tablets and one placebo phase. Each blister package contains 28 film-coated tablets in the following order:

- 2 dark yellow tablets each containing 3 mg EV
- 5 medium red tablets each containing 2 mg EV and 2 mg DNG
- 17 light yellow tablets each containing 2 mg EV and 3 mg DNG
- 2 dark red tablets each containing 1 mg EV
- 2 white placebo tablets

The sponsor has provided the following overview of the film-coated tablets and the composition information for each formulation.

Table 1: Overview on EV/DNG film-coated tablets (internal code SH T00658ID)

Internal code	EV [mg]	DNG [mg]	Color	No. of tablets in the blister	Position in the blister
SH T00658EA	3	-	dark yellow	2	1-2
SH T00658GA	2	2	medium red	5	3-7
SH T00658M	2	3	light yellow	17	8-24
SH T00658HA	1	-	dark red	2	25-26
SH T00658P	Placebo		white	2	27-28

Table 2: Composition of the film-coated tablets SH T00658EA, SH T00658GA, SH T00658M, SH T00658HA and SH T00658P

		SH T00658EA	SH T00658GA	SH T00658M	SH T00658HA	SH T00658P
(b) (4)	Estradiol valerate, (b) (4)	3.000 mg	2.000 mg	2.000 mg	1.000 mg	-
	Dienogest (b) (4)	-	2.000 mg	3.000 mg	-	-
	Lactose monohydrate	(b) (4)				
	Maize starch					
	Maize starch, pregelatinized					
	Povidone 25					
	Magnesium stearate					
(b) (4)	Hypromellose, (b) (4)					
	Macrogol 6000					
	Titanium dioxide					
	Ferric oxide pigment yellow					
	Ferric oxide pigment red					
	Talc					
Total weight		83.000 mg	83.000 mg	83.00000 mg	83.0000 mg	82.0000 mg

Comments: Excipients are compendial and are controlled by adherence to compendial specifications.

The application contains five 3.2.P sections, one for each different dosage strength. The sponsor has provided the following reviewer's guide to the application:

In the following, a reviewer's guide is given to explain the content of information in the QOS of each formulation.

2.3.P.1. Description and composition of the drug product:

Separate description for each formulation.

2.3.P.2. Pharmaceutical Development:

This section is identical for SH T00658EA, SH T00658GA and SH T00658HA.

Separate descriptions for SH T00658M and SH T00658P, respectively.

2.3.P.3. Manufacture:

This section is identical for SH T00658EA, SH T00658GA, SH T00658M and SH T00658HA.

Separate description for the placebo formulation SH T00658P.

2.3.P.4. Control of Excipients:

This section is identical for all formulations.

2.3.P.5. Control of Drug Product:

Separate description for each formulation except the information regarding validation. The information on validation is identical for the corresponding formulations

SH T00658EA/SH T00658HA (containing only EV) and SH T00658GA/SH T00658M (containing a combination of EV and DNG).

Separate description for the placebo formulation SH T00658P.

2.3.P.6. Reference Standards or Materials:

This section is identical for the corresponding formulations SH T00658EA/SH T00658HA (containing only EV) and SH T00658GA/SH T00658M. A separate description is given for SH T00658P.

2.3.P.7. Container Closure System:

The description of the container closure system is identical for all formulations.

2.3.P.8. Stability:

Separate description for each formulation. The conclusion for the blister is identical in each formulation.

MANUFACTURER

The sponsor has provided the following overview of their formulations in the Pharmaceutical Development Section:



A flow chart and narrative are provided for the manufacturing process for each drug product tablet.

The following sites are responsible for manufacture of the drug product tablets:

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 Release and stability testing	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@scheringnrg.de	3002808091	Release and stability testing	Yes
Bayer Schering Pharma AG Wedding Plant Müllerstr. 170 - 178 D-13353 Berlin, Germany	Dr. Hans-Joachim Raubach	011 49 30 4681 2162	011 49 30 4689 6826	Hans-joachim.raubach@bayer-ag.de	3002808086	Release and stability testing Packaging and release of marketed product	Yes
Bayer HealthCare Pharmaceuticals 6 West Belt Wayne, NJ 07470, USA	Dr. Horst Heimbach	973-305-5143	973-305-3533	horst.heimbach@bayer.com	2243252	Release for distribution	Yes

Comment: The EES was submitted on 07-Aug-2009.

SPECIFICATIONS:

The quality of the drug product tablets are controlled by the following specifications. Acceptance criteria for Appearance and Assay are set depending on their API composition:

Specification	Method	Acceptance Criteria	
		Release	Shelf-life



(b) (4)

2 pp withheld in full immed. after this page as (b)(4) CCI/TS.

The placebo is controlled with the following specifications: [REDACTED] (b) (4)

Comment: Information is adequate to allow review.

It is noted that in Module 2, the specifications repeat the assay for estradiol valerate. The specification sheets in Module 3 are correct, however. The sponsor should provide corrected specification sheets in Module 2.

CONTAINER CLOSURE SYSTEM

The drug product is packaged in a blister package composed of [REDACTED] (b) (4) aluminum blister composed of a lidding foil and a forming film. The primary packaging is packaged in a non-functional secondary packaging carton which also contains a [REDACTED] (b) (4) wallet. Information is provided in the application as well as in referenced DMFs.

Comment: Information is adequate to allow review.

STABILITY

The sponsor requests an expiry of 48 months based on the following Stability data package:



Photostability studies were also performed on all tablets.

Since all batches were manufactured at commercial scale, the sponsor commits to place one batch of drug product on stability annually. They also make the following stability commitment:

Bayer HealthCare Pharmaceuticals agrees to:

- Submit stability study results from any ongoing primary stability studies and from marketed product stability lots in the NDA annual report
- Recall any batch found to fall outside specifications during the shelf life unless, following discussions with the District Office, it is agreed that continued distribution of the affected batch is justified. The change or deterioration in the product will be reported to the Agency as required under 21 CFR 314.81 (b)(1)(ii).

***Comment:** Because the packaged drug product contains 5 different tablet formulations that are distinguished by color (medium verses dark red and light verses dark yellow), recently-manufactured and aged drug product samples should be submitted for comparison to determine if the colors fade upon storage.*

Information is adequate to allow review for determination of expiration dating period.

LABELING

Copies of the carton container label are provided. This is a white box with black lettering. The labels contain a placeholder for the tradename. The sponsor should provide updated container labels if they plan to use any colors or graphics. In addition, a copy of the blister label is not provided and should be submitted to allow full review. A copy of the Physician Insert is provided, but the SPL copy is not submitted, so there is no Drug Listing Data Elements table.

Comment: Please submit a copy of the blister pack. Color mock-ups for the carton and immediate container labels, including any logos, should be provided in order to allow full review of these labels. Please ensure that when the SPL label is submitted that it contains a DLDE table for 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
08/17/2009

MOO JHONG RHEE
08/17/2009
Chief, Branch III