

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-367

**CHEMISTRY REVIEW(S)**



**NDA 21-367**

**Drug Product:  
Femring (Estradiol-3-Acetate Ring)**

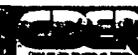
**Galen, Ltd**

**J. Salemme, Ph.D**

**Reproductive and Urologic Drug Products (HFD-580)**

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*NOTE: This Table of Contents is provided for Chemistry Review number 2. The identical executive Summary presented for chemistry review number 1 is provided for this review. The additional information reviewed for Chemistry Review number 2 concerns a change to a component of the container sachet for the drug product and a final label review.*

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**CHEMISTRY REVIEW**



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## Chemistry Review Data Sheet

1. **NDA** 21-367
2. **REVIEW** # 2
3. **REVIEW DATE:** 03-Mar-2003
4. **REVIEWER:** J. Salemm, Ph.D., HFD-820
5. **PREVIOUS DOCUMENTS** Reviewed in Chemistry Review 1

<u>Document</u>	<u>Document Date</u>
Original NDA	21-Dec-2001
Amendment	23-Sep-2002
Amendment	11-Oct-2002
Amendment	16-Oct-2002

6. **SUBMISSION(S) BEING REVIEWED** in Chemistry Review 2:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Stamp Date</u>
Amendment (labeling changes)	20-Jan-2003	21-Jan-2003
	14-Feb-2003	19-Feb-2003
Amendment (CMC)	04-Feb-2003	5-Feb-2003

7. **NAME & ADDRESS OF APPLICANT:**

Name: Galen Ltd.  
 Rockaway 80 Corporate Center  
 Address: 100 Enterprise Drive, Suite 280  
 Rockaway, NJ 07866  
 Representative: Alvin Howard



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

Telephone: (973) 442-3233

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Femring  
b) Non-Proprietary Name (USAN): Estradiol acetate vaginal ring  
c) Code Name/# (ONDC only): Insert ER/ 812  
d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 2
  - Submission Priority: S

**9. LEGAL BASIS FOR SUBMISSION:** N/A for NDAs

**10. PHARMACOLOGICAL CATEGORY:** Estrogen/Hormone Replacement

**11. DOSAGE FORM:** Insert (vaginal ring)

**12. STRENGTH/POTENCY:**

- Estradiol-3-acetate ring, approximately 0.05 mg/day per ring for three months
- Estradiol-3-acetate ring, approximately 0.10 mg/day ring for three months

**13. ROUTE OF ADMINISTRATION:** Vaginal

**14. Rx/OTC DISPENSED:**  Rx  OTC

**15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:**

SPOTS product – Form Completed  Not a SPOTS product

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



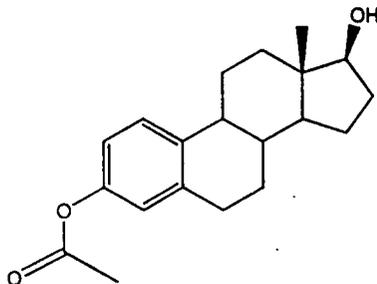
# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

Estra-1,3,5(10)-triene-3,17-beta-diol-3-acetate; 17-beta-estradiol-3-acetate

### STRUCTURE



Molecular Formula:  $C_{20}H_{26}O_3$

Molecular Mass: 314.41

### A. RELATED/SUPPORTING DOCUMENTS

#### A. Drug Master Files Reviewed in Chemistry Review Number 1

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
1	II	[ ]	[ ]	1	Adequate	7-Sept-2002	Reviewer: J. Salemme
1	II	[ ]	[ ]	1	Adequate	7-Oct-2002	Reviewer: J Salemme

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Status codes for DMF table:

Adequate, Inadequate, or N/A (N/A = There is enough information in the application; therefore, the DMF does not need to be reviewed)

Chemistry Review Data Sheet

**B. Other Documents**

DOCUMENT	DESCRIPTION	STATUS OF REVIEW
Device Master File	[ ]	Adequate; 10-Oct-2002
Chemistry Review No. 1 dated 16-Oct-2002		CMC adequate; approvable pending Agency decision regarding labeling for estrogen replacement therapy

**18. STATUS**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION or Comment	DATE	REVIEWER
Biometrics	None		
EES			
• Drug Product – Ivex Pharmaceuticals	Acceptable	7-Oct-02	S. Adams
• _____	Acceptable	14-Feb-02	
• _____	Acceptable	19-Aug-02	
Pharm/Tox	For safety of _____	10-Oct-02	L. Reid
Biopharm	For dissolution specifications	October 02	S. Al-Habet
LNC			
Methods Validation	Pending		
OPDRA (Drug Safety)	Femring tradename acceptable	11-Oct-2002	S. Dallas
EA	Exemption claimed	16-Oct-02	
Microbiology	N/A		

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Executive Summary Section

The Chemistry Review for NDA 21-367

The Executive Summary

**I. Recommendations**

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls point of view this NDA may be approved.

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

None recommended.

**II. Summary of Chemistry Assessments**

A. Description of the Drug Product and Drug Substance

**Drug Product**

The drug product is a \_\_\_\_\_ silicone ring containing the drug substance estradiol-3-acetate in a core within the ring. The drug product is to be placed in the vagina and used for three months for the treatment of menopausal symptoms.

The drug product is considered to be a type referred to as a reservoir system. In these systems, the drug substance is contained within the drug product and slowly migrates through the drug product before and during use. During use, the drug substance is released from the ring at a predictable and continuous rate. For this drug product, the rate of release of the drug substance from the ring is controlled by \_\_\_\_\_ . The amount released, i.e. the release rate, on the first day of use or in solution will always be greater than any later days. This day 1 effect is called a burst effect, and is caused by the fact the drug substance \_\_\_\_\_

\_\_\_\_\_ After the initial burst, the release rate steadily decreases such that by day 4 the release rate is the expected rate, that of 0.050 mg/day ring or 0.10 mg/day ring.

For this product a predictable amount of drug substance is delivered over the 90 days of use, as measured in in-vitro dissolution studies of the release rate over 90 days. The average release rate of 0.050 mg/day per ring and 0.10 mg/day per ring is achieved up until about 26 days of the 90 day period. After this time, the rate steadily decreases until at 90 days the release rate is typically around 0.040 mg/day/ring for the 0.050 mg/day/ring size and around 70 mg/day/ring for the 0.10 mg/day/ring size. Additionally, over storage the drug substance \_\_\_\_\_ such that

the Day 1 burst steadily increases. After 24 months of storage, the Day 1 burst effect can be as much as 4 times the amount seen at Day 1 for newly manufactured rings.

A regulatory dissolution test is proposed in which the release rate determined on \_\_\_\_\_ and the release rate determined during \_\_\_\_\_ dissolution testing period are the chosen time intervals for testing. The regulatory specifications do not include testing for the entire period of use; however, the testing times chosen will provide a release rate that is representative of the expected release rate. Ideally, the release rate should be the stated label rate, but due to the nature of reservoir systems, a constant rate through the use life of the product is not possible to attain. The age of rings used in clinical trials has been evaluated by the Medical Officer reviewer to determine the approximate amount of burst exposure patients have received. The oldest rings tested clinically, as part of a study on a small number of patients, were 36 months of age. This information was used to support the limit on the maximum amount of burst that could take place during the shelf-life of the product.

Each ring consists of a core containing drug substance within a silicone ring. Each core is made of \_\_\_\_\_ estradiol acetate \_\_\_\_\_. For the 0.050 mg/day ring the core is 8 mm in length and contains 12.4 mg of estradiol acetate and for the 0.100 mg/day ring the core is 16 mm in length and contains 24.8 mg of estradiol acetate. The core is surrounded by a silicone polymer ring \_\_\_\_\_. The silicone polymer \_\_\_\_\_

\_\_\_\_\_ Toxicological studies and a study of the amount of leachables present after rings remained in pH 4.5 phosphate buffer solution for three months were reviewed by the Pharm-Tox reviewer and found to be satisfactory.

Each ring is tested by the following attributes that control the quality of the product: appearance, stress testing, weight, tensile strength, total drug assay, content uniformity, dissolution (in-vitro release rate determination), related substances, and microbial contamination.

Each ring is placed into a sachet composed of medical paper on one side and a polymer laminate on the other, \_\_\_\_\_. The sachet protects the ring from grime but is not used to provide a sterile or tightly sealed environment.

A 24 month expiry has been granted for the 0.050 mg/day strength and the 0.100 mg/day strength based on an evaluation of stability data from pilot-scale batches.

**Drug Substance**

The drug substance is estradiol-3-acetate, manufactured \_\_\_\_\_ . Although estradiol acetate is not an NME, it is a new ester of estradiol. Estradiol, also manufactured \_\_\_\_\_ is described in \_\_\_\_\_ . The E3A manufactured for the primary NDA batches was manufactured \_\_\_\_\_ . Additionally, the sponsor has proposed that \_\_\_\_\_



Executive Summary Section

\_\_\_\_\_ manufacturers produced the estradiol-3-acetate used in all preclinical and clinical trials. The spectral data for show that all \_\_\_\_\_ give the same spectral data. Additionally, the impurity profiles have been reviewed and found to be comparable.

The quality of the drug substance is controlled by tests for identity, appearance, specific rotation, melting point; related substances; residual solvent, \_\_\_\_\_ water; assay; and particle size. A retest period of 12 months is granted for drug substance stored at ambient conditions.

Pre-approval inspections were conducted for \_\_\_\_\_ and, for the drug product at Ivex Pharmaceuticals in Northern Ireland. The Office of Compliance has recommended the sites for approval.

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

The drug product is intended to be inserted into the vagina and left in place for three months. During this time the drug is released continuously at a targeted rate of 0.050 mg/day per ring and 0.100 mg/day ring. An expiry of 24 months is granted for rings stored at 25°C/60%RH

C. Basis for Approvability or Not-Approval Recommendation

The information provided is adequate to support the NDA; therefore, the NDA may be approved.

III. Administrative

A. Reviewer's Signature

Chemist Name/Date:  
J. Salemme, Ph.D., 3-March-2003

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Executive Summary Section

B. Endorsement Block

Chemistry Team Leader Name/Date  
David T. Lin, Ph.D.

C. Project Manager Name/Date  
Karen Anderson

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/s/  
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Jean Salemmé  
3/19/03 02:48:21 PM  
CHEMIST

Allan Fenselau  
3/19/03 03:00:35 PM  
CHEMIST  
AF Acting TL for David Lin, Chemistry Team Leader, HFD-580

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**NDA 21-367**

**Drug Product: Estradiol-3-Acetate Ring  
Tradename: Not Yet Approved**

**Galen, Ltd**

**by**

**Chemistry Reviewer: J. Salemme, Ph.D  
Division of New Drug Chemistry II – HFD-820**

**For  
Clinical Review Division, HFD-580  
Reproductive and Urologic Drug Products**

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CHEMISTRY REVIEW



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# Chemistry Review Data Sheet

- 1. **NDA**      21-367
- 2. **REVIEW #** 1
- 3. **REVIEW DATE:** 16-October-2002
- 4. **REVIEWER:** J. Salemme, Ph.D., HFD-820
- 5. **PREVIOUS DOCUMENTS:** None

**6. SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	21-Dec-2001
Amendment	23-Sep-2002
Amendment	11-October-2002
Amendment	16-October-2002

**7. NAME & ADDRESS OF APPLICANT:**

Name: Galen Ltd.  
 Rockaway 80 Corporate Center  
 Address: 100 Enterprise Drive, Suite 280  
 Rockaway, NJ 07866  
 Representative: Alvin Howard  
 Telephone: (973) 442-3233

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Tradename not yet selected
- b) Non-Proprietary Name (USAN): Estradiol acetate vaginal ring
- c) Code Name/# (ONDC only): Insert ER /8.12
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 2

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A for NDAs

10. PHARMACOLOGICAL CATEGORY: Estrogen/Hormone Replacement

11. DOSAGE FORM: Insert [vaginal ring]

12. STRENGTH/POTENCY:

- Estradiol-3-acetate ring, approximately 0.05 mg/day per ring for three months
- Estradiol-3-acetate ring, approximately 0.10 mg/day ring for three months

13. ROUTE OF ADMINISTRATION: Vaginal

14. Rx/OTC DISPENSED:  Rx  OTC

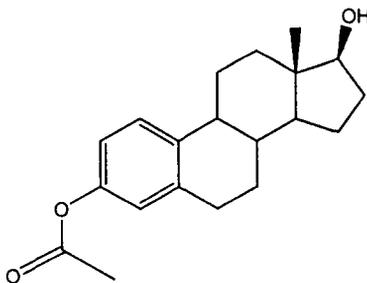
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

SPOTS product – Form Completed  Not a SPOTS product

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

Estra-1,3,5(10)-triene-3,17-beta-diol-3-acetate; 17-beta-estradiol-3-acetate

STRUCTURE



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Chemistry Review Data Sheet

Molecular Formula: C<sub>20</sub>H<sub>26</sub>O

Molecular Mass: 314.41

**17. RELATED/SUPPORTING DOCUMENTS**

A. Drug Master Files

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	II	[ ]	[ ]	1	Adequate	7-Sept-2002	Reviewed by J. Salemme
—	II	[ ]	[ ]	1	Adequate	7-Oct-2002	Reviewed by J. Salemme

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Status codes for DMF table:

Adequate, Inadequate, or N/A (N/A = There is enough information in the application; therefore, the DMF does not need to be reviewed)

B. Other Documents

DOCUMENT	DESCRIPTION	STATUS OF REVIEW
Device Master File —	[ ]	Adequate; Reviewed by J. Salemme October 10, 2002

**18. STATUS**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION or Comment	DATE	REVIEWER
Biometrics	None		
EES			S. Adams

Chemistry Review Data Sheet

• Drug Product – Ivex Pharmaceuticals	Acceptable	7-Oct-2002	
• _____	Acceptable	14-Feb-2002	
• _____	Acceptable	19-Aug-2002	
Pharm/Tox	For safety of _____	10-Oct-2002	L. Reid
Biopharm	For dissolution acceptance criteria	October 2002	S. Al-Habet
LNC			
Methods Validation	Will be requested after approval		
OPDRA	Tradename not approved	29-Aug-2002	C. Holquist
EA	Exemption claimed	16-Oct-2002	J. Salemme
Microbiology	N/A		

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Executive Summary Section

The Chemistry Review for NDA 21-367

The Executive Summary

**I. Recommendations**

- A. Recommendation and Conclusion on Approvability  
From a Chemistry, Manufacturing and Controls point of view this NDA may be approved.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable  
None recommended.

**II. Summary of Chemistry Assessments**

A. Description of the Drug Product and Drug Substance

**Drug Product**

The drug product is a — silicone ring containing the drug substance estradiol-3-acetate in a core within the ring. The drug product is to be placed in the vagina and used for three months for the treatment of menopausal symptoms.

The drug product is considered to be a type referred to as a reservoir system. In these systems, the drug substance is contained within the drug product and slowly migrates through the drug product before and during use. During use, the drug substance is released from the ring at a predictable and continuous rate. For this drug product, the rate of release of the drug substance from the ring is controlled by \_\_\_\_\_ . The amount released, i.e. the release rate, on the first day of use or in solution will always be greater than any later days. This day 1 effect is called a burst effect, and is caused by the fact the drug substance \_\_\_\_\_

\_\_\_\_\_ . After the initial burst, the release rate steadily decreases such that by day 4 the release rate is the expected rate, that of 0.050 mg/day ring or 0.10 mg/day ring.

For this product a predictable amount of drug substance is delivered over the 90 days of use, as measured in in-vitro dissolution studies of the release rate over 90 days. The average release rate of 0.050 mg/day per ring and 0.10 mg/day per ring is achieved up until about 26 days of the 90 day period. After this time, the rate steadily decreases until at 90 days the release rate is typically around 0.040 mg/day/ring for the 0.050 mg/day/ring size and around 70 mg/day/ring for the 0.10 mg/day/ring size. Additionally, over storage the drug substance \_\_\_\_\_ such that



Executive Summary Section

the Day 1 burst steadily increases. After 24 months of storage, the Day 1 burst effect can be as much as 4 times the amount seen at Day 1 for newly manufactured rings.

A regulatory dissolution test is proposed in which the release rate determined on \_\_\_\_\_ and the release rate determined during \_\_\_\_\_ dissolution testing period are the chosen time intervals for testing. The regulatory specifications do not include testing for the entire period of use; however, the testing times chosen will provide a release rate that is representative of the expected release rate. Ideally, the release rate should be the stated label rate, but due to the nature of reservoir systems, a constant rate through the use life of the product is not possible to attain. The age of rings used in clinical trials has been evaluated by the Medical Officer reviewer to determine the approximate amount of burst exposure patients have received. The oldest rings tested clinically, as part of a study on a small number of patients, were 36 months of age. This information was used to support the limit on the maximum amount of burst that could take place during the shelf-life of the product.

Each ring consists of a core containing drug substance within a silicone ring. Each core is made of \_\_\_\_\_, estradiol acetate, \_\_\_\_\_. For the 0.050 mg/day ring the core is 8 mm in length and contains 12.4 mg of estradiol acetate and for the 0.100 mg/day ring the core is 16 mm in length and contains 24.8 mg of estradiol acetate. The core is surrounded by a silicone polymer ring \_\_\_\_\_. The silicone polymer \_\_\_\_\_

\_\_\_\_\_. Toxicological studies and a study of the amount of leachables present after rings remained in pH 4.5 phosphate buffer solution for three months were reviewed by the Pharm-Tox reviewer and found to be satisfactory.

Each ring is tested by the following attributes that control the quality of the product: appearance, stress testing, weight, tensile strength, total drug assay, content uniformity, dissolution (in-vitro release rate determination), related substances, and microbial contamination.

A 24 month expiry has been granted for the 0.050 mg/day strength and the 0.100 mg/day strength based on an evaluation of stability data from pilot-scale, or exhibition scale, batches.

**Drug Substance**

The drug substance is estradiol-3-acetate, manufactured \_\_\_\_\_

\_\_\_\_\_. Although estradiol acetate is not an NME, it is a new ester of estradiol. Estradiol, also manufactured \_\_\_\_\_ is described in \_\_\_\_\_

\_\_\_\_\_. The E3A manufactured for the primary NDA batches was manufactured \_\_\_\_\_

\_\_\_\_\_. Additionally, the sponsor has proposed that \_\_\_\_\_

**CHEMISTRY REVIEW**

Executive Summary Section

\_\_\_\_\_ manufacturers produced the estradiol-3-acetate used in all preclinical and clinical trials. The spectral data for show that all \_\_\_\_\_ give the same spectral data. Additionally, the impurity profiles have been reviewed and found to be comparable.

The quality of the drug substance is controlled by tests for identity, appearance, specific rotation, melting point; related substances; residual solvent, \_\_\_\_\_; \_\_\_\_\_; water; assay; and particle size. A retest period of 12 months is granted for drug substance stored at ambient conditions.

Pre-approval inspections were conducted for \_\_\_\_\_ and, for the drug product at Ivex Pharmaceuticals in Northern Ireland. The Office of Compliance has recommended the sites for approval.

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

The drug product is intended to be inserted into the vagina and left in place for three months. During this time the drug is released continuously at a targeted rate of 0.050 mg/day per ring and 0.100 mg/day ring. An expiry of 24 months is granted for rings stored at 25°C/60%RH

**C. Basis for Approvability or Not-Approval Recommendation**

The information provided is adequate to support the NDA; therefore, the NDA may be approved.

Deficiencies noted during the initial review were conveyed to the sponsor through a Information Request Letter dated 6-Sept-2002. The responses to the deficiencies were addressed in this review and found to be acceptable.

**III. Administrative**

**A. Reviewer's Signature**

ChemistName/Date:  
J. Salemme, Ph.D.

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Executive Summary Section

**B. Endorsement Block**

Chemistry Team Leader Name/Date  
David T. Lin, Ph.D.

Project Manager Name/Date  
Dornette Spell-Lesane

**C. CC Block**

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/s/  
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Jean Salemmé  
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CHEMIST

David T. Lin  
10/16/02 04:20:01 PM  
CHEMIST  
I concur.

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