CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-367

MEDICAL REVIEW(S)

NDA 21-367/S-000

Date Original Labeling Submitted:	**12/21/01**
Date Revised Labeling Submitted:	**1/20/03**
Date Labeling Review Finalized:	**3/18/03**

Medical Officer's Review

Sponsor:	**Galen Limited** **Rockaway 80 Corporate Center** **100 Enterprise Drive, Suite 280** **Rockaway, NJ 07866**
Drug Name:	
Generic:	**Estradiol Acetate**
Trade:	**Femring™**
Chemical:	**Estra-1,3,5(10)-triene-3, 17β-diol-3-acetate**
Pharmacologic category:	**Estrogen**
Dosage Form:	**Vaginal ring**
Strength:	**0.05 mg estradiol acetate per day** **0.10 mg estradiol acetate per day**
Indications:	**1) Treatment of moderate to severe vasomotor symptoms associated with the menopause.** **2) Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associate with the menopause.**
Related Submissions:	**IND** [redacted]

Background

NDA 21-367/S-000 was submitted on December 21, 2001. On October 18, 2002, Femring™ 0.05 mg estradiol/day and Femring™ 0.10 mg estradiol/day received an approvable action from the Agency for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause pending agreement on final labeling. Please see the Medical Officer's Review of NDA 21-367/S-000, dated October 18, 2002.

The sponsor was advised that the Agency would review the published findings of the National Heart, Lung, and Blood Institute's (NHLBI) Women's Health Initiative (WHI) study (see Journal of the American Medical Association, July 17, 2002, Volume 288, No. 3, pages 321-333), and revise the Agency's 1999 draft Guidance for Industry entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products – Prescribing Information for Healthcare Providers and Patient labeling" to include the safety information resulting from the WHI study.

On January 8, 2003, the Sponsor received revised Femring™ labeling incorporating the Agency's recommended changes. The Sponsor resubmitted revised draft labeling to the Agency on January 20, 2003, February 14, 2003, and March 5, 2003.

Chemistry, Manufacturing and Controls

Please see the Chemistry, Manufacturing and Controls Review.

Final Labeling

Please see the attached Femring™ label.

The proposed labeling, initially submitted on December 21, 2001, was modified in accordance with the Agency's 2003 draft labeling guidance entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Health Care Providers and Patient Labeling" (see **Federal Register**/ Volume 68/ Monday, February 3, 2003/Notices).

The **BOXED WARNING** was expanded to include information regarding **CARDIOVASCULAR AND OTHER RISKS**. Minor revisions have been made to the **DESCRIPTION** section to update the text and the **CLINICAL PHARMACOLOGY** section under the **Pharmacokinetics** subsections to update the text and Figure 1. In addition, the **Drug Interactions** subsection was updated.

The sponsor was requested to delete [redacted] and to add two new tables under ***Effects on vasomotor symptoms***. In addition, it was requested that [redacted] be deleted as well as proposed [redacted]

[redacted]

A ***Women's Health Initiative Studies*** subsection (text and a new Table 4) has been added.

Per the draft labeling guidance for noncontraceptive estrogen drug products, the following sections have been revised accordingly: **INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION**.

The **PATIENT INFORMATION** insert has been modified in compliance with the plain language initiative, recommendations from the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Division of Surveillance, Research & Communication Support (DSRCS), and the Agency's 2003 draft labeling guidance for noncontraceptive estrogen drug products.

On January 20, 2003, February 14, 2003, and March 5, 2003, the Sponsor resubmitted proposed draft labeling incorporating the recommended changes to labeling. Minor edits to the March 5, 2003 submission include the following:

1) The asterisk included in the Estradiol 0.05 mg/day and Estradiol 0.10 mg/day columns at [redacted] in Table 2 and Table 3 should be deleted or [redacted] should be deleted from Tables 2 and 3.
2) The phrase, CI=confidence interval, in the footnote of Table 2 and Table 3 should be revised to read, CI = confidence interval.
3) In the **WARNINGS** section, # 5. **Visual Abnormalities** subsection, the word diploia should be corrected to read, diplopia.

In a fax dated March 12, 2003, the Sponsor advised the Agency that [redacted] would be deleted from Table 2 and Table 3. The phrase CI = confidence interval, and the word diplopia were corrected.

Conclusions and Recommendations

From a clinical perspective, NDA 21-367/S-000 can be approved. The Sponsor should submit copies of final printed labeling revised as the enclosed labeling for NDA 21-367/S-000.

Theresa H. van der Vlugt, MD, M.P.H.
Medical Officer

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DRAFT

LABELING

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

/s/

Theresa Van Der Vlugt
3/20/03 02:38:32 PM
MEDICAL OFFICER

Shelley Slaughter
3/20/03 03:18:13 PM
MEDICAL OFFICER
I concur with Medical Officer Review and negotiated label.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-367/S-000

Date NDA Submitted:	**12/21/01**
Date NDA Received:	**12/21/01**
Review Completed:	**10/9/02**
Review Finalized:	**10/18/02**

Medical Officer's Review
(Original Review)

Sponsor:	**Galen Limited** **Rockaway 80 Corporate Center** **100 Enterprise Drive, Suite 280** **Rockaway, NJ 07866**
Drug Name:	
Generic:	**Estradiol Acetate**
Trade:	**Tradename**
Chemical:	**Estra-1,3,5(10)-triene-3, 17β-diol-3-acetate**
Pharmacologic category:	**Estrogen**
Dosage Form:	**Vaginal ring**
Strength:	**0.05 mg estradiol per day** **0.10 mg estradiol per day**
Proposed Indications:	**1) Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.** **2)**
Related Submission:	**IND**
Related Documents:	**NDA 21-367/S-000 Amendments dated 2/28/02, 4/4/02, 4/18/02, 4/22/02, 5/10/02, 6/19/02, 7/12/02, 7/19/02, 8/23/02, 9/12/02, 9/19/02, 10/1/02**

APPEARS THIS WAY
ON ORIGINAL

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The Executive Summary of the Primary Clinical Review

1. RECOMMENDATION

1.1. Recommendations on Approvability

From a clinical perspective, the reviewer recommends approval of the 0.05 mg/day Tradename (estradiol acetate vaginal ring) and the 0.10 mg/day Tradename. The data presented in the new drug application provides sufficient evidence from one US controlled clinical trial and one UK controlled clinical trial to support the safety and efficacy of Tradename in two dosage strengths, 0.05 mg estradiol/day intravaginal ring (IVR) and 0.10 mg estradiol/day IVR, for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

1.2. Recommendations on Postmarketing Studies and/or Risk Management Steps Where Appropriate

No postmarketing studies and/or risk management steps are recommended.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of the Clinical Program

Tradename is a soft, flexible, silicone polymer intravaginal ring with a central core containing estradiol-3-acetate (also referred to as estradiol acetate or estradiol) The drug substance estradiol acetate is synthesized

Tradename 0.05 mg/day has a central core that contains 12.4 mg of estradiol acetate, which releases at a rate equivalent to 0.05 mg estradiol/day over a three month period. Tradename 0.10 mg estradiol/day has a central core that contains 24.8 mg of estradiol acetate, which releases at a rate equivalent to 0.10 mg estradiol/day over a three month period. Estradiol acetate is rapidly hydrolyzed to estradiol. Estradiol is an estrogen class hormone.

The proposed indications for Tradename being sought by Galen Limited are:

- The treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

[ ]

Some of the more commonly reported symptoms of postmenopausal vulvar and vaginal atrophy are vaginal dryness, vaginal and/or vulvar irritation/itching, painful urination, vaginal pain with sexual activity, and vaginal bleeding associated with sexual activity. Symptomatic postmenopausal women may experience some or all of these symptoms or other symptoms. Because vaginal atrophy is neither a complex (i.e., the sum or a combination of symptoms) or a syndrome (a symptom complex), the Division of Reproductive and Urologic Drug Products (DRUDP) recommends that this indication read:

- The treatment of vulvar and vaginal atrophy associated with the menopause.

NDA 21-367 was submitted on December 21, 2001. Two Phase III studies were submitted for review. Primary Phase III Study IVR 1002, conducted in the US, was a 13-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study (35 US centers) of 333 healthy postmenopausal women meeting the inclusion and exclusion criteria. Subjects 29 to 85 years of age (mean age 51.7 ± 7.2 years) who had undergone spontaneous amenorrhea at least 12 months prior to randomization or were surgically menopausal (hysterectomy with or without bilateral oophorectomy greater than 6

weeks prior to randomization) experiencing at least 7 moderate-to-severe hot flushes/day (or an average of 56 per week) received treatment with intravaginal rings delivering estradiol acetate equivalent to 0.05 mg or 0.10 mg estradiol/day or placebo for 13 weeks.

Supportive Phase III Study HRT 8, conducted in the UK, was a prospective, randomized, double-blind, double-dummy, multicenter, comparator controlled, parallel group study in which 159 healthy postmenopausal women were treated with either 0.05 mg estradiol/day IVR or 1 mg oral estradiol/day for 24 weeks. After the first 12 weeks, the dosage could be increased to 0.10 mg estradiol/day IVR or 2 mg oral estradiol/day for the second 12 weeks for those women whose symptoms were not adequately controlled at the lower dosage strengths. An open label extension for a further 24 weeks followed with active IVRs only.

Study HRT 8 is considered supportive because it did not comply with the Division's recommended inclusion criteria for clinical trials of estrogen-alone drug products for the treatment of vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA). In Study HRT 8, subjects were included with at least 20 hot flushes/night sweats per week and not the Division recommended 7 to 8 moderate-to-severe hot flushes per day or 50 to 60 moderate-to-severe hot flushes per week. Therefore, Study HRT 8 is considered supportive and was reviewed only for safety outcomes and not for efficacy outcomes.

2.2. Efficacy

From the data presented in Phase III Study IVR 1002, the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR are effective in relieving moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

Three hundred and thirty-three healthy postmenopausal women were randomized to one of three treatment groups in Study IVR 1002:

- 108 subjects to the placebo IVR treatment group,
- 113 subjects to the 0.05 mg estradiol/day IVR treatment group, and
- 112 subjects to the 0.10 mg estradiol/day IVR treatment group.

The investigators at study centers inserted the assigned IVR vaginally following randomization. IVRs were to be worn until end-of-study at week 13. At the end-of-study (or early withdrawal), retained intravaginal rings were then removed by the study investigator. Study subjects were provided with one "spare" ring to be used in the event that the original intravaginal ring was expelled and could not be re-inserted by the subject.

Overall, for Study IVR 1002, there were no major differences in the demographics and baseline characteristics among the three treatment groups. Subjects were predominately white (77.2%, 257 of 333 subjects, 12.3 % were black [41 of 333 subjects], 9% were Hispanic [30 of 333 subjects], and 1.5% were "other" [5 of 333 subjects]) with an average age of 51.7 ± 7.2 years. The majority of subjects were nonsmokers (81.1%, 270 of 333 subjects) and nondrinkers (87.7%, 292 of 333 subjects).

Three hundred and twenty-five subjects comprised the intent-to-treat (ITT) population (treated subjects who had a baseline measurement of moderate-to-severe vasomotor symptoms (MSVS) and had at least one MSVS evaluation following insertion of the intravaginal ring. Of the 8 subjects not included in the ITT population, six discontinued on the first day of treatment (2 subjects discontinued due to inability to retain the intravaginal ring, 2 due to intolerance to the ring, and 2 subjects experienced adverse events). The remaining 2 subjects were lost to follow-up prior to having a post-insertion evaluation.

Effects on Vasomotor Symptoms

Results of comparison among treatment groups of MSVS at baseline showed that the placebo IVR treatment group had a higher mean number of MSVS at baseline (83.1) compared to the 0.05 mg

estradiol/day IVR treatment group (MSVS = 73.7) and the 0.10 mg estradiol/day IVR treatment group (MSVS = 74.7). This finding was due, in part, to one subject in the placebo IVR treatment group who reported 630 MSVS during the 2-week screening period. The Agency's Statistical Reviewer recalculated the mean number of MSVS at baseline for the placebo treatment group eliminating the one subject reporting 630 MSVS at screening. This recalculated data was used in this review of efficacy for the treatment of MSVS associated with the menopause indication.

A statistically significant difference in the mean number of hot flushes versus placebo was demonstrated for both IVR dosage strengths (p-values <0.0001 at weeks 4, 8, and 12). Statistically significant differences in the mean severity of hot flushes versus placebo was also demonstrated: p-value <0.0001at weeks 4, 8, and 12 for the 0.10 mg estradiol/day IVR; p-value =0.0001 at week 4, p-value =0.0009 at week 8, and p-value =0.0002 at week 12 for the 0.05 mg estradiol/day IVR.

In Study IVR 1002, both proposed IVR dosage strengths demonstrated a clinically significant difference of 2 or more MSVS per day (or 14 per week). The 0.10 mg estradiol/day IVR demonstrated a slightly stronger initial reduction in MSVS than the 0.05 mg estradiol/day IVR, from a baseline of 10.7/day down to 1.6/day and 10.5/day down to 3.1/day, respectively, at week 4. The study results reported for weeks 8 and 12 were similar for both dosage strengths.

Given that the 12-weeks efficacy results in the intent-to-treat (ITT) population with the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR are almost indistinguishable for the relief of the frequency and severity of moderate-to-severe vasomotor symptoms, and that the 0.10 mg estradiol/day IVR contains twice as much estradiol acetate as the 0.05 mg estradiol/day IVR, approval of both doses would not be justified on the basis of these results.

However, the Agency's Statistical Reviewer analyzed the relief of MSVS for both IVR dosage strengths by age groups (< 50, 50 to 59, > 59 years of age). These results show that the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR performed similarly in the 50 to 59 years of age subgroup. Both dosage strengths showed statistically significant differences in the relief of MSVS (frequency and severity) at week 4 that was maintained through week 12 ($p<0.05$ at weeks 4, 8, and 12). This was not the case, however, in the < 50 years of age subgroup.

The results in the < 50 years of age subgroup clearly demonstrates more consistent effectiveness in the relief of MSVS in the 0.10 mg estradiol/day IVR as compared to the 0.05 mg estradiol/day IVR. The 0.10 mg estradiol/day IVR relieved both the frequency and severity of hot flushes at weeks 4, 8, and 12 ($p<0.05$ at all time points). The 0.05 mg estradiol/day IVR showed a delayed treatment effect in the number of hot flushes until week 8 that was not sustained through week 12. In addition, the 0.05 mg estradiol/day IVR did not relieve the severity of hot flushes at any time point in the < 50 years of age subgroup analysis (p-values > 0.05 at weeks 4, 8, and 12). The > 59 years of age subgroup had too few subjects to permit an observational assessment of treatment effect.

This reviewer recommends the approval of the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause. The 0.05 mg estradiol/day IVR is demonstrated to be the lowest effective dose, and this dose should be the starting dose recommended in labeling. However, the availability of the 0.10 mg estradiol/day IVR will provide the healthcare provider with options to better manage moderate-to-severe vasomotor symptoms unresponsive to the 0.05 mg estradiol/day IVR dosage strength, especially in the newly menopausal woman.

Effects on Vulvar and Vaginal Atrophy

Vaginal cytology specimens for Maturation Index were collected at baseline and final evaluation (end-of-study or early withdrawal) in Study IVR 1002. The Maturation Index represents the proportion of vaginal superficial cells relative to the number of parabasal and intermediate cells in a vaginal cytology smear. Vaginal Maturation Index results obtained from evaluable vaginal cytology smears in Study IVR 1002 demonstrated an estrogenic effect on vaginal tissue for the 0.05 mg estradiol/day IVR and

the 0.10 mg estradiol/day IVR. The data from Study IVR 1002 showed a statistically significant mean percent increase in superficial cells and a corresponding mean percent reduction in parabasal cells for the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR. Superficial cells increased by a mean of 16.0% and 18.9% for the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR as compared to 1.11% for placebo. Parabasal cells decreased by a mean of 25.3% and 20.7%, respectively, as compared to 8.3% for placebo. In addition, both IVR dosage strengths showed similar mean decreases in vaginal pH (0.73 for the 0.05 mg estradiol/day IVR and 0.60 for the 0.10 mg estradiol/day IVR) as compared to a mean decrease of 0.25 in the placebo IVR treatment group.

This reviewer recommends the approval of the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR for the treatment of vulvar and vaginal atrophy associated with the menopause.

2.3. Safety

In the Integrated Summary of Safety (ISS), the safety data from the primary Phase III Study IVR 1002 and the blinded portion of supportive Phase III Study HRT 8 (first 24 weeks) have been integrated and is presented. The safety data from 6 Phase I studies and one Phase II study, while presented in the ISS, are not integrated. Unblinded results for Study HRT 10 were provided in the 4-Month Safety Update dated April 18, 2002.

The safety data presented in the submission shows that the overall safety profile of the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR is acceptable. No deaths occurred during the conduct of 9 completed Phase I, II, and III studies and one completed but blinded study at the time of the NDA submission (Study HRT 10). Overall, a total of 22 subjects reported serious adverse events (SAEs) in 10 completed studies with use of the placebo IVR, 0.05 mg or 0.10 mg estradiol/day IVR (3.4%, 22 of 642 subjects assigned to placebo IVR or estradiol acetate IVRs). Among the 22 subjects with SAEs, there was one case of cholelithiasis with cholecystectomy (Subjects 75, 0.05 mg estradiol/day IVR, 92 treatment days, causality reported as possible), one case of rectal cancer (Subject 431, 0.10 mg estradiol/day IVR, 91 treatment days, causality reported as unlikely), one case of complex endometrial hyperplasia (Subject 8144, 24 weeks blinded oral 1 mg estradiol tablet and approximately 12 weeks open-label 0.05 mg estradiol/day IVR, causality reported as possible), and one case of breast cancer (Subject 10163, 0.05 mg estradiol/day, treatment days unavailable, causality reported as possible). Six subjects with SAEs discontinued due to their SAE (0.9%, 6 of 642 subjects). The reported number of SAEs with use of the placebo or estrogen-containing IVRs in the ISS does not suggest a safety risk.

In Phase III Studies IVR 1002 and HRT 8, a total of 197 subjects were exposed to the 0.05 mg estradiol/day IVR, 112 subjects were exposed to the 0.10 mg estradiol/day IVR (in the initial 12 weeks of study participation), and 108 subjects were exposed to the placebo IVR. In the second 12 weeks of Study HRT 8, eighteen subjects were exposed to the 0.10 mg estradiol/day IVR after completing 12 weeks of exposure to the 0.05 mg estradiol/day IVR. Overall, the mean duration of exposure ranged from 11weeks (SD 4.233) for placebo, 15 weeks (SD 6.146) for the 0.05 mg estradiol/day IVR and 12 weeks (SD 2.925) for the 0.10 mg estradiol/day IVR.

Headaches (19.5%, 85 of 435 subjects), breast tenderness (8.0%, 35 of 435 subjects), and vaginal discharge (7.3%, 33 of 435 subjects) were some of the more common treatment-emergent adverse events reported in the two integrated safety studies (Studies IVR 1002 and HRT 8). These are the common adverse events reported with estrogen-alone use, however, and are not unexpected.

In the ISS, the reported incidence of treatment-emergent adverse events, under reproductive system and breast disorders, for the two estrogen-containing IVRs combined is generally higher than that reported for the placebo IVR, with a few exceptions. The placebo IVR treatment group showed a higher incidence of:

- vaginal discharge than shown for the combined estrogen-containing IVR treatment groups (8.3 % for placebo IVR, 9 of 108 subjects; 7.0% for the combined estrogen IVR treatment groups, 23 of 327 subjects);
- genital disorders than shown for the combined estrogen-containing IVR treatment groups (8.3% for placebo IVR, 9 of 108 subjects; 1.8% for the combined estrogen IVRs, 6 of 327 subjects);
- vulvovaginitis than shown for the combined estrogen-containing IVR treatment groups (6.5% for placebo IVR, 7 of 108 subjects; 2.1% for the combined estrogen IVRs, 7 of 327 subjects);
- vaginal irritation than shown for the combined estrogen-containing IVR treatment groups (3.7% for placebo IVR, 4 of 108 subjects; 1.5% for the combined estrogen IVRs, 5 of 327 subjects).

These findings are not unexpected, however, and likely show the effect of the placebo IVR in an estrogen-deprived atrophic vagina.

The safety assessments conducted in Study IVR 1002 and Study HRT 8 were appropriate and adequate. In Study IVR 1002, one hundred and sixty-eight subjects (168) with a uterus, who had taken study medication for at least 4 weeks, were provided post-treatment progestin for 14 days (151 took medroxyprogesterone acetate, 6 took norethindrone, and 1 took another progestin). In Study HRT 8, 88 subjects with a uterus were provided with 1 mg norethisterone (Micronor-HRT®) daily for the last 12 days of each 28-day cycle (days 17 to 28) for the study duration. One subject was diagnosed with complex endometrial hyperplasia in Study HRT 8 (Subject 8144, 24 weeks blinded oral 1 mg estradiol and approximately 12 weeks open-label 0.05 mg estradiol/day IVR, subject discontinued study medication, pathology diagnosis of two polyps was benign).

Hemostasis parameters were collected in two Phase I studies (Studies IVR 1005 and 1006) as a consequence of the observed rapid, high serum estradiol concentrations demonstrated in Phase I Study IVR 1001 (C_{max} rose to 1664.7 pg/ml in 0.7 hours post-insertion with IVRs at least 36 months from the manufactured date), and concerns regarding the activation of coagulation in an older postmenopausal population. Selected anticoagulant proteins, procoagulant proteins, and markers of ongoing coagulation/fibrinolysis were collected at all specified time points in Studies IVR 1005 and 1006 (thrombin-antithrombin complex, prothrombin fragment 1+2, von Willebrand factor antigen, Factor VIII coagulant activity, protein S antigen, and activated protein C sensitivity ratio). Estradiol plasma and/or blood concentrations were also collected.

The analysis showed isolated, transient, but statistically significant, changes in the concentrations of some factors, namely, von Willebrand factor antigen (increased at 24 and 72 hours but not at 1 hour), Factor VIII coagulant activity (increased at 24 and 72 hours but not at 1 hour), and activated protein C sensitivity ratio (15 and 45 minutes only) (based on mean levels of each hemostatic parameter and a paired t-test statistical comparison performed at each time point with the baseline value). In Amendment 13 to the NDA, dated October 1, 2002, the Sponsor provided scatter plots for each hemostatic parameter against estradiol concentration to demonstrate any observable dependence of these hemostatic parameters on effects of estradiol. The analysis showed no evidence of an association between any of these parameters and the simultaneous estradiol concentration, or any late effects of the peak short-term estradiol concentrations.

No clinically evident thromboses were reported in Study IVR 1002 and Study HRT 8. In addition, no serious adverse events were reported in the first 5 days following IVR insertion in these two Phase III studies. Headaches (6.8%, 30 of 435 subjects), vaginal discharge (3.6%, 16 of 435 subjects), and nausea (2.7%, 12 of 435 subjects) were the adverse events reported most frequently during the first five days after IVR insertion. These adverse events are commonly reported with estrogen-alone drug products both within the first 5 days of use and beyond.

2.4. Dosing, Regimen, and Administration

Estradiol, given alone, is approved for use in a variety of delivery systems that include one vaginal ring (Estring®), one vaginal tablet (Vagifem®), one vaginal cream (Estrace® Cream), one tablet

(Estrace®), and several transdermal patch systems (Estraderm®, Vivelle®, Climara®, Alora®, and Esclim®).

The estradiol intravaginal ring drug product Estring®, the estradiol vaginal tablet drug product Vagifem®, and the estradiol vaginal cream drug product Estrace® Cream are only approved for the treatment of vulvar and vaginal atrophy associated with the menopause. To date, no product delivering intravaginal estradiol is approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause. Estring® releases estradiol over 90 days (approximately 7.5 micrograms/day). Each Vagifem® vaginal tablet delivers 25 micrograms of estradiol. Estrace® Cream delivers 0.10 mg estradiol per gram of cream.

The literature supports the use of low dosage strengths of estrogens to relieve vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. Oral estradiol tablets, Estrace® 1mg and 2 mg, are approved for VMS and VVA given in a cyclic regimen (e.g., 3 weeks on and 1 week off). For estradiol transdermal patch systems, approved dosage strengths for the treatment of VMS and VVA range from 0.025 mg to 0.10 mg.

The 0.05 mg estradiol/day IVR dosage strength and the 0.10 mg estradiol/day IVR dosage strength pose no dose-toxicity when used over a three month period.

2.5. Drug-Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. This information will be provided in labeling.

2.6. Special Populations

Tradename is only indicated for use in postmenopausal women. The 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR were not studied in women with liver disease or with renal impairment in this submission. Tradename is contraindicated in pregnancy.

No subgroup analysis by age group was provided in this submission. However, the Agency's Statistical Reviewer analyzed the relief of moderate-to-severe vasomotor symptoms (MSVS) for both IVR dosage strengths by age groups (< 50, 50 to 59, ≥ 60 years of age). As previously noted, these results showed that the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR performed similarly in the 50 to 59 years of age subgroup. Both dosage strengths showed statistically significant differences in the relief of MSVS (frequency and severity) at week 4 that was maintained through week 12 ($p<0.05$ at weeks 4, 8, and 12). However, this was not the case in the < 50 years of age subgroup.

In the < 50 years of age subgroup the 0.10 mg estradiol/day IVR relieved both the frequency and severity of hot flushes at weeks 4, 8, and 12 ($p<0.05$ at all time points) while the 0.05 mg estradiol/day IVR showed a delayed treatment effect that was not sustained. The 0.05 mg estradiol/day IVR did not relieve the number of MSVS compared to placebo until week 8 ($p=0.01$) and this relief was not maintained through week 12. In addition, the 0.05 mg estradiol/day IVR did not relieve the severity of hot flushes at any time in the age subgroup analyses (p-values > 0.05 at weeks 4, 8, and 12). The > 59 years of age subgroup had too few subjects to permit an observational assessment of treatment effect.

The majority of subjects in the ISS population (n = 492) were white (84%, 414 of 492 subjects), 16% were non-white (78 of 492 subjects). Among subjects in Study IVR 1002 and HRT 8, 77% and 99% were white. Therefore, it is not possible to adequately compare adverse events by race groups. Nonetheless, in the overall ISS population, the adverse event most often reported in both race groups was headache.

Primary Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication (s), Dose, Regimen, Age Groups

Tradename (estradiol acetate intravaginal ring), henceforth in this review, referred to as 0.05 mg estradiol/day intravaginal ring (IVR) or 0.10 mg estradiol/day IVR, is a soft, flexible silicone ring with a central core containing estradiol-3-acetate (also referred to as estradiol acetate or estradiol). The proposed indications for Tradename are:

- The treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

[ ]

Some of the more commonly reported symptoms of postmenopausal vulvar and vaginal atrophy are vaginal dryness, vaginal and/or vulvar irritation/itching, painful urination, vaginal pain with sexual activity, and vaginal bleeding associated with sexual activity. Symptomatic postmenopausal women may experience some or all of these symptoms or other symptoms. Because vaginal atrophy is neither a complex (i.e., the sum or a combination of symptoms) or a syndrome (a symptom complex), the Division of Reproductive and Urologic Drug Products (DRUDP) recommends that this indication read:

- The treatment of vulvar and vaginal atrophy associated with the menopause.

1.2. State of Armamentarium for Indication(s)

The Division of Reproductive and Urologic Drug Products (DRUDP) recommends that products intended to treat moderate-to-severe vasomotor symptoms (VMS) should show both a clinically and a statistically significant reduction in the frequency and severity of hot flushes in the treated groups compared to the control groups. This reduction in the frequency and severity of hot flushes should occur within 4 weeks of initiation of treatment and should be maintained throughout 12 weeks of treatment. Subjective measures (i.e., patient daily diaries) are used as primary efficacy endpoints.

For products intended to treat vulvar and vaginal atrophy (VVA), prestudy and end-of-study (12 week treatment duration) vaginal cytology smears are collected to determine the percentages of parabasal, intermediate and superficial cells (Maturation Index). In 1999, the Division incorporated the assessment of vaginal pH (along with other physician assessment of signs) and the patient self-assessment of symptoms at baseline and at end-of-study. The physician assessment of signs includes the following categories: vaginal pH, color of the vaginal epithelium, and vaginal mucosal integrity (friability and petechiae). The subject's self-assessment of vaginal symptoms includes the following categories: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity. Currently, three primary efficacy variables are considered for a treatment of vulvar and vaginal atrophy indication:

- The change in the Maturation Index between baseline and week 12 (statistically significant increase in superficial vaginal cells and decrease of parabasal vaginal cells).
- The change in vaginal pH between baseline and week 12 (statistically significant lowering of vaginal pH).
- The change in the subject self-assessment of symptoms between baseline and week 12. The primary efficacy analysis should show statistically significant improvement in the moderate-to-severe symptom identified by the subject as the most bothersome.

1.3. Important Milestones in Product Development

Galen Limited met with DRUDP on April 29, 1998 (pre-IND), May 26, 1999 and November 7, 2000 (pre-NDA). As a result of the initial meetings with the Sponsor, subsequent protocol changes were made to allow for a subset of subjects at 6 study sites to have colposcopy, assessments for chlamydia and mount for the presence of bacterial vaginosis, and a potassium hydroxide (KOH) prep for candidiasis performed at baseline and end-of-study. In addition, at week 4 a vaginal examination, colposcopy, and measurement of vaginal pH was completed. A vaginal activity questionnaire was completed at baseline, week 4 and end-of-study.

1.4. Other Relevant Information

A 0.05 mg estradiol/day IVR is approved in the United Kingdom. Menoring® 50 received approval on April 3, 2001 for the relief of hot flushes, sweating at night, dryness or soreness of the vagina or pain during sexual intercourse in women who have had a hysterectomy. Menoring® 50 is labeled for use in women without a uterus.

1.5. Important Issues with Pharmacologically Related Agents

Estring® (2 mg estradiol vaginal ring) is the only intravaginal ring approved for use in postmenopausal women in the US. Estring® is approved for the treatment of urogenital symptoms associated with postmenopausal atrophy of the vagina (such as dryness, burning, pruritis and dyspareunia) and/or the lower urinary tract (urinary urgency and dysuria).

In addition, there is one conjugated estrogens vaginal cream (Premarin® Vaginal Cream), one estradiol vaginal cream (Estrace®), and one estradiol vaginal tablet (Vagifem®) approved for use in the US for the treatment of vulvar and vaginal atrophy.

2. SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY

2.1. Chemistry, Manufacturing and Controls

The drug substance estradiol acetate is synthesized The chemical structure of a sample of estradiol acetate was confirmed using methods.

The Tradename™ intravaginal ring can be described as a reservoir system designed to release drug in a controlled and continuous manner for 3 months. Estradiol acetate is contained in a central core propylorthosilicate and stannous octoate . The outer diameter of the IVR is 56 mm, the cross-section diameter is 7.6 mm, and the inner core diameter is 2 mm. Ivex Pharmaceuticals in the UK (a Division of Galen Limited) is the manufacture of the drug product.

Stability testing of the finished product was performed on three batches of the Tradename™ 0.05 mg estradiol/day and three batches of the Tradename™ 0.10 mg estradiol/day.

The day 1 release rate of estradiol acetate increases with storage time. This increase with storage time is known as a burst effect and is characteristic of reservoir type systems, including vaginal rings. Per the Sponsor, the day one release rate increases until equilibrium is reached between the amount of estradiol acetate in the core and in the at approximately 18 to 24 months.

Please see the Chemistry, Manufacturing and Controls Review for a more complete discussion.

2.2. Animal Pharmacology and Toxicology

The non-clinical development program focused on demonstrating that the rate of hydrolysis of estradiol acetate was very rapid resulting in no significant exposure to estradiol acetate. One *in vitro* study in human serum and whole blood cells (Study IVR/SP/011) showed that estradiol acetate was rapidly hydrolyzed to estradiol with a hydrolysis half-life of 28 seconds. In Phase 1 Study IVR 1005, estradiol-3-acetate was not detectable in any of the whole blood samples following insertion of the 0.10 mg estradiol/day IVR for a period of up to 72 hours.

In an Ames study, estradiol acetate is non-genotoxic. The — cured silicone elastomer ring was shown to release low levels of leachable substances ——————— which present no toxicological risk.

Please see the Pharmacology/Toxicology Review for a more complete discussion.

2.3. Microbiology

No microbiology review was conducted for this vaginal drug product.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

Four main pharmacokinetic studies were conducted to characterize the pharmacokinetic profile of the estradiol acetate vaginal ring. Study HRT 6A and Study IVR 1001 were designed to determine serum estradiol concentrations and C_{max} and t_{max}, respectively. A third study, multi-dose Study IVR 1006, determined the pharmacokinetic profile of the 0.05 mg estradiol /day IVR following administration of dose 1 for 13 weeks and dose 2 for 4 weeks. A fourth pharmacokinetic study, Study IVR 1005 utilizing the 0.10 mg estradiol/day IVR, was conducted to investigate the conversion of estradiol acetate to estradiol *in vivo*. Additional serum estradiol data was also obtained from the primary Phase III clinical trial, Study IVR 1002 (0.05 mg and 0.10 mg estradiol/day IVRs).

The first study, Study HRT 6A, was designed to determine serum estradiol concentrations from two dosage strength IVRs (0.05 and — mg estradiol/day IVRs) over a 2-week period and 0.10 mg estradiol/day IVR over a 12-week period. Serum estradiol concentrations were determined by an ——————— method with ——————— (also used in Studies IVR 1001). However, the C_{max} and t_{max} values from this study were not considered representative. Over 12 week of use of the 0.10 mg estradiol/day IVR, the estradiol C_{avg} was 76 pg/ml (the apparent *in vivo* estradiol delivery rate was 0.097 mg/day). Therefore, Study IVR 1001 was specifically designed to characterize the C_{max} and t_{max} of the 0.10 mg estradiol/day IVR. In three day Study IVR 1001, the C_{max} rose to 1665 pg/ml in 0.7 hours. Study IVR 1001 utilized intravaginal rings being retested to extend the expiration data. Therefore, subjects were exposed to IVRs manufactured at least 36 months before the start of Study IVR 1001.

In Study IVR 1006 (26 subjects), following administration of the 0.05 mg estradiol/day IVR, day 1 serum estradiol concentration increased rapidly to a C_{max} of 1129 pg/ml in 0.9 hours then decreases to relatively constant serum concentrations for the remaining 13 weeks. Serum estradiol concentrations were determined by ——————————— method. The average serum estradiol concentration (C_{avg}) was 40.6 pg/ml (the apparent *in vivo* estradiol delivery rate was 0.052 mg/day), the C_{max} was 1129 pg/ml, and the t_{max} was 0.9 hours. A second 0.05 mg estradiol/day IVR was then inserted in Study IVR 1006 and worn for 4 weeks. The estradiol C_{max} value following dose 2 was 31.3% lower than that following dose 1 (C_{max} of 772 pg/ml, t_{max} of 1.1 hours). The estradiol C_{avg} was 52.6 pg/ml following dose 2. The intravaginal rings utilized in Study IVR 1006 were not more than 24 months from the manufactured date.

In vitro experiments had revealed that estradiol acetate was very rapidly hydrolyzed in serum; the half-life for hydrolysis was 28 seconds (Study IVR/SP/011). In Study IVR 1005 (14 subjects), *in vivo* estradiol acetate concentrations were characterized following administration of 0.10 mg estradiol/day IVR for 72 hours. Blood estradiol and estradiol acetate concentrations were determined by [redacted] with [redacted] method. Serum estradiol concentrations were determined by an [redacted] method with [redacted] method. Estradiol acetate was not found in any of the blood samples (LOQ was [redacted]. Even when serum estradiol concentrations were as high as [redacted] pg/ml and [redacted] pg/ml in two subjects at 30 minutes post-insertion, estradiol acetate was not detected. In Study IVR 1005, the mean estradiol PK parameters showed a C_{max} of 1502 pg/ml and a t_{max} of 0.98 hours. The pg/ml mean serum estradiol levels (SD) by time points are as follows:

Pre-dose
20.4 (7.6)

Post-insertion

0.5 min	15 min	40 min	45 min	1 hr	1.5 hr	24 hrs	72 hrs
183 (177)	896 (674)	1211 (631)	1264 (581)	1280 (456)	1268 (296)	245 (54)	105 (25)

Like Study IVR 1001, Study IVR 1005 utilized intravaginal rings being retested to extend the expiration data. Therefore, subjects were exposed to IVRs manufactured at least 36 months before the start of the study.

Additional serum estradiol data were obtained from the primary, Phase III 13-week efficacy and safety clinical trial, Study IVR 1002. Blood samples were taken 5 times (screening, baseline, and weeks 4, 8, and 13) for determination of serum estradiol and estrone concentrations. In Study IVR 1002, the average serum estradiol concentrations for the 0.05 mg estradiol/day IVR and 0.10 mg estradiol /day IVR were 41.6 and 64.4 pg/ml, respectively.

Reviewer's Comments

From the data obtained from Study IVR 1005, the *in vivo* hydrolysis of estradiol-3-acetate to estradiol was rapid in both human serum and whole blood. A systemic exposure to estradiol acetate was not detectable.

However, Studies IVR 1001, 1005, and 1006 all demonstrated a rapid spike in serum estradiol levels immediately after insertion of the IVR, followed by a decline in serum estradiol levels over 12 to 24 hours. [redacted] pg/ml is pre-menopause range) with achievement and maintenance of steady state for the remaining 12 weeks. This rapid surge in the rate of estradiol release from the IVR appears to be related to the "age" of the IVR. The IVRs utilized in Studies IVR 1001 and 1005 with C_{max} values of 1665 pg/ml and 1502 pg/ml within the first hour of IVR insertion, respectively, resulted from IVRs at least 36 months from the manufactured date.

The clinical consequence of the rapid and early estradiol spike caused concern, and the Sponsor obtained selected anticoagulant proteins, procoagulant proteins and markers of ongoing coagulation/fibrinolysis at all time points in Studies 1005 and 1006. Please see the INTEGRATED REVIEW OF SAFETY section of this review for results.

3.2. Pharmacodynamics

No pharmacodynamic data is presented from primary Study IVR 1002.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Source of Clinical Data

Galen Holding PLC in Rockaway, New Jersey, a subsidiary of Galen Limited is the Sponsor of NDA 21-367. NDA 21-367/S-000 was submitted on December 21, 2001.

This submission includes primary Phase III Study IVR 1002 conducted in the US to compare the effects of two intravaginal rings containing estradiol acetate (0.05 mg estradiol/day and 0.10 mg estradiol/day) with a placebo intravaginal ring on moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause after 13 weeks of treatment in 333 healthy postmenopausal women.

One supportive Phase III clinical trial, 24-week Study HRT 8 (blinded), conducted in the UK, was also submitted. Study HRT 8 does not comply with the Division's recommendations for the inclusion criteria for clinical trials of estrogen-alone drug products for the treatment of VMS and VVA, and will be used as supportive for safety only. Study HRT 8 is not considered a primary efficacy clinical trial.

4.2. Overview of Clinical Trials

See Table 1 for a summary of studies in the clinical development program.

Table 1: NDA 21-367/S-000 Clinical Development Program

Study No. (Report No.)	Status of Study Study Design	Treatment Group And Dose (mg)	Subjects Enrolled/ Completed
HRT 6A (RR 00601)	Completed, single-dose, open label, 3-treatment, dose-escalating	0.05 mg/day E3A-IVR x 14 day — mg/day E3A-IVR x 14 day 0.10 mg/day E3A-IVR x 84 day	12/11
IVR 1001 (RR00701)	Completed, single-dose, open label, 1-treatment	0.10 mg/day E3A-IVR x 3 day	12/12
IVR 1005 (RR00801)	Completed, single-dose, open-label, 1-treatment	0.10 mg/day E3A-IVR x 3 day	14/14
IVR 1006 (RR 00901)	Completed, double-dose, open-label, 1 treatment	0.05 mg/day E3A-IVR x 13 weeks 0.05 mg/day E3A-IVR x 28 day	26/25
HRT 8 (RR 01401)	Completed, multi-center, double-blind, comparator controlled, parallel group study followed by open label phase	Blinded phase 0.05 mg/day E3A-IVR x 12 weeks 1 mg oral estradiol/day x 12 weeks followed by 0.10 mg/day E3A-IVR x 12 weeks 2 mg oral estradiol/day x 12 weeks or 0.05 mg/day E3A-IVR x 12 weeks 1 mg oral estradiol/day x 12 weeks Open label phase 0.05 mg/day E3A-IVR x 24 weeks 0.10 mg/day E3A-IVR x 24 weeks (each IVR inserted for 12 weeks)	159/111
IVR 1002 (RR 01101)	Completed, multicenter, double-blind, randomized, placebo-controlled, parallel group	0.05 mg/day E3A-IVR x 13 weeks 0.10 mg/day E3A-IVR x 13 weeks Placebo IVR x 13 weeks	333/279
HRT 10	Ongoing (April 1998), multi-center, randomized, parallel group, single-blinded versus Estring®	0.05 mg/day E3A-IVR x 12 weeks 0.10 mg/day E3A-IVR x 12 weeks Estring® (0.008 mg/day estradiol intravaginal ring) 1 IVR every 12 weeks x 8 (96 weeks total)	170

Source: Adapted from NDA 21-367/S-000, Volume 94, pages 19975 – 19979.

Study IVR 1002 was a Phase 3, 13-week, randomized, double-blind, placebo-controlled, parallel group multicenter study (35 US centers) of 333 healthy postmenopausal women meeting the inclusion and exclusion criteria. Subjects 29 to 85 years of age (mean age 51.7 ± 7.2 years) who had undergone spontaneous amenorrhea at least 12 months prior to randomization or were surgically menopausal (bilateral oophorectomy, with or without hysterectomy, greater than 6 weeks prior to randomization) experiencing at least 7 moderate-to-severe hot flushes (or an average of 56/week) received treatment with intravaginal rings delivering estradiol acetate equivalent to 0.05 or 0.10 mg estradiol/day or placebo for 13 weeks.

4.3. Postmarketing Experience

Tradename™ intravaginal ring is not approved for use in the U.S.

4.3. Literature Review

References are provided in the submission that pertains, generally, to the overall risks and benefits of estradiol administration. Additional references are provided that pertains, specifically, to the pharmacokinetics and pharmacodynamic effects of vaginal estradiol administration and transdermal system estradiol administration. No additional FDA literature review was conducted.

5. CLINICAL REVIEW METHODS

5.1. Describe How Review was Conducted

NDA 21-367/S-000 was submitted in paper format on December 21, 2001. Requested SAS transport files and draft labeling have been submitted electronically to the Electronic Document Room (EDR). Study IVR 1002, the primary Phase III study submitted to support efficacy and safety, was reviewed in its entirety. Safety data from four Phase I studies, two Phase III studies (primary Study IVR 1002 and supportive Study HRT 8), and one ongoing Phase III Study HRT 10 (at the time of the submission) were reviewed. Two additional Phase I studies (HRT 4 and HRT 5) and one Phase II study (HRT 6) were mentioned in the submission. However, because no study reports are available for any of these studies, they are not being considered for review.

The safety data submitted in the 4-Month Safety Update (dated April 18, 2002) and the Second Safety Update (dated September 19, 2002) were reviewed upon receipt.

5.2. Overview of Materials Consulted in Review

Study IVR 1002 was a prospective, double-blind, placebo-controlled, parallel group study conducted in 35 US centers that randomized 333 healthy postmenopausal women to the following three treatment groups:

- 108 subjects to the placebo intravaginal ring,
- 113 subjects to the intravaginal ring delivering estradiol acetate equivalent to 0.05 mg estradiol/day,
- 112 subjects to the intravaginal ring delivering estradiol acetate equivalent to 0.10 mg estradiol/day.

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity

No Division of Safety Inspection (DSI) audit was requested. Generally, "me-too" drug products, with a classification of 2S, do not routinely get DSI inspections unless clinically warranted. Estradiol is an approved drug and longstanding efficacy and safety data are available for vaginal creams, transdermal systems, oral tablets, and a vaginal ring,

5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards

The informed consent document proposed for use in Study IVR 1002 was appropriate. Appropriate standards of patient care were administered during the conduct of the clinical trial in accordance with regulations pertaining to Good Clinical Practice (GCP).

5.5. Evaluation of Financial Disclosure

There were 176 principal investigators and subinvestigators at 35 US sites in Study IVR 1002. FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was submitted by all investigators and subinvestigators. One investigator had disclosable information. — at study site number — Study site — enrolled 11 subjects (3.3%, 11 of 333 subjects) and reported 1 discontinuation and 2 protocol violations. Due to the small number of enrolled subjects at this site, no concerns arise from this financial disclosure information.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

The data presented in NDA 21-367/S-000 provides sufficient evidence from one placebo-controlled clinical trial to support the safety and efficacy of the 0.05 mg estradiol/day intravaginal ring (IVR) and the 0.10 mg estradiol/day IVR for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

6.2. General Approach to Review of the Efficacy of the Drug

Two Phase III clinical trials are included in the submission. Primary Study IVR 1002 was performed to demonstrate the effectiveness of two different intravaginal rings releasing estradiol acetate at rates equivalent to 0.05 mg and 0.10 mg estradiol/day in the treatment of moderate-to-severe vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA) associated with the menopause. Phase 3 Study IVR 1002, conducted in the US under IND — met the Division of Reproductive and Urologic Drug Products (DRUDP) recommendations for clinical trials of estrogen-alone drug products for the treatment of VMS and VVA.

Study HRT 8 was also performed to demonstrate the effectiveness of two different intravaginal rings releasing estradiol acetate at rates equivalent to 0.05 mg and 0.10 mg estradiol/day in the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. However, Phase III Study HRT 8 conducted in the UK did not comply with the Division's recommended inclusion criteria for clinical trials of estrogen-alone drug products for the treatment of VMS and VVA. Subjects were included in HRT 8 with an inclusion criterion of at least 20 hot flushes and night sweats per week and not the Division recommended 7 to 8 moderate-to-severe hot flushes per day or 50 to 60 moderate-to-severe hot flushes per week. Therefore, Study HRT 8 is considered supportive and was reviewed only for safety outcomes. No data from Study HRT 8 was considered in the primary efficacy analyses.

6.3. Detailed Review of Trials by Indication

Study IVR 1002 was a perspective, double-blind, randomized, placebo-controlled, parallel group study in which healthy postmenopausal women were treated with intravaginal rings delivering estradiol acetate equivalent to 0.05 mg and 0.10 mg estradiol/day or placebo over a 13 week duration. Subjects meeting the study eligibility criteria had an intravaginal ring placed in the vagina by the study investigator following randomization. At the end-of-study (or early withdrawal), retained intravaginal rings were then removed by the study investigator.

The primary objective of Study IVR 1002 was:

- To assess the efficacy of intravaginal rings releasing two dosage strengths of estradiol acetate (0.05 mg and 0.10 mg estradiol per day) versus placebo with respect to the relief of moderate-to-severe hot flushes in postmenopausal women.

The secondary objectives of Study IVR 1002 were:

- To assess vaginal atrophy by comparing pre- and post-study subject assessment of vaginal symptoms, Maturation Index, and vaginal examination results.
- To assess the efficacy of intravaginal rings releasing two dosage strengths of estradiol acetate versus placebo with respect to relief of menopausal symptoms other than hot flushes in postmenopausal women.
- To assess the safety and acceptability of continuous administration of intravaginal rings releasing two dosage strengths of estradiol acetate versus placebo in postmenopausal women.
- To assess systemic and local vaginal tolerability of continuous administration of intravaginal rings releasing two dosage strengths of estradiol acetate versus placebo in postmenopausal women.

The estradiol acetate and placebo intravaginal rings (batch numbers 00760/01L and E00760-01L1) were manufactured by Galen Ltd., Northern Ireland, UK.

Reviewer's Comments

The Division recommends that postmenopausal women experiencing 7 to 8 moderate-to-severe hot flushes per day or 50 to 60 per week are eligible for inclusion in clinical trials conducted to demonstrate the relief of vasomotor symptoms. In addition, the Division recommends that for estrogen products intended to treat moderate-to-severe vasomotor symptoms (MSVS), the primary efficacy analysis should show both a clinically and a statistically significant reduction in the frequency and severity of hot flushes in the treated groups compared with the control groups. This reduction should occur within 4 weeks of initiation of treatment and should be maintained throughout 12 weeks of treatment. The study should identify the lowest effective dose of the estrogen to support the indication. Subjective measures (e.g., patient diaries) can be used as primary efficacy endpoints.

Study IVR 1002 met the four co-primary endpoints with hypothesis tests versus placebo required for a relief of vasomotor symptoms indication, namely:

- **The mean change in the number of moderate-to-severe vasomotor symptoms from baseline to week 4 and week 12.**
- **The mean change in the severity of vasomotor symptoms from baseline to week 4 and week 12.**

For a treatment of vulvar and vaginal atrophy indication, the Division recommends three primary efficacy variables:

- **The change in the Maturation Index between baseline and week 12 (statistically significant increase in vaginal superficial cells and a statistically significant corresponding decrease in vaginal parabasal cells).**
- **The change in vaginal pH between baseline and week 12 (statistically significant lowering of vaginal pH).**

- **The change in the subject self-assessment of symptoms between baseline and week 12. The primary efficacy analysis should show statistically significant improvement in the moderate-to-severe symptom identified by the subject as the most bothersome. The subject self-assessment should include the following categories:**

  - **vaginal dryness (presence vs. absence)**
  - **vaginal and/or vulvar irritation/itching (none, mild, moderate or severe)**
  - **dysuria (none, mild, moderate or severe)**
  - **vaginal pain associated with sexual activity (none, mild, moderate or severe)**
  - **vaginal bleeding associated with sexual activity (presence vs. absence)**

Study IVR 1002 met two of the three primary efficacy variables for a relief of vulvar and vaginal atrophy indication, namely, the change in the Maturation Index between baseline and week 12, and the change in vaginal pH between baseline and week 13. However, because enrollment for Study IVR 1002 began before the Division's initiation of the third primary efficacy variable in the year 2001 (the change in the "most bothersome" self-assessment of symptoms between baseline and week 12), the information collected from the self-assessment of symptoms in Study IVR 1002 will be considered supportive and will not be considered for efficacy.

Twenty-eight (28) of 35 US centers enrolled a total of 333 subjects in Study IVR 1002. Seven (7) centers enrolled no subjects. A total of 108 subjects were enrolled to the placebo IVR treatment group, 113 subjects were enrolled to 0.05 mg estradiol/day IVR treatment group, and 112 subjects were enrolled to 0.10 mg estradiol/day IVR treatment group. A total of 54 (16.2%) of 333 subjects discontinued from the study. Significantly more subjects in the placebo IVR treatment group discontinued (26.9%, 29 of 108 subjects) than in the 0.5 mg estradiol/day IVR treatment group (12.4%, 14 of 113 subjects) and the 0.10 mg estradiol/day IVR treatment group (9.8%, 11 of 112 subjects). Overall, adverse events (5.7%, 19 of 333 subjects) and "other" reasons (5.4%, 18 of 333 subjects) were the most common reason for discontinuation. Eleven percent (11%, 12 of 108 subjects) of subjects in the placebo IVR treatment group listed "other' as the reason for discontinuation compared to 3.5 % (4 of 113 subjects) in the 0.05 mg estradiol/day IVR treatment group and 2% (1.8 of 112 subjects) in the 0.10 mg estradiol/day IVR treatment group. Of the 18 discontinuations due to "other" reasons, 8 were due to lack of relief of MSVS, 6 were due to inability to keep the IVR in place, and 4 subjects could not tolerate the IVR. The disposition of subjects by treatment groups is presented in Table 2.

Table 2: Disposition of Subjects by Treatment Groups for Study IVR 1002

Parameter	Intravaginal Ring Treatment Group			Total
	Placebo	0.05 mg Estradiol	0.10 mg Estradiol	
Randomized Subjects (%)	108 (32)	113 (34)	112 (34)	333 (100)
Completed Study (%)	79 (73.1)	99 (87.6)	101(90.2)	279 (83.7)
Discontinued Early (%)	29 (26.9)	14 (12.4)	11 (9.8)	54 (16.2)
Adverse Event	9 (8.3)	6 (5.3)	4 (3.6)	19 (5.7)
Protocol Violation	3 (2.8)	1 (0.9)	3 (2.7)	7 (2.1)
Loss to Follow-Up	0 (0.0)	1 (0.9)	1 (0.9)	2 (0.6)
Insufficient Product	1 (0.9)	0 (0.0)	1 (0.9)	2 (0.6)
Other	12 (11.1)	4 (3.5)	2 (1.8)	18 (5.4)

Source: Adapted from IVR 1002 Final Study Report, Section 14.1, Tables 1.0 and 4.0.
All percentages are relative to the number of subjects randomized.

Overall, for Study IVR 1002, there were no major differences in the demographics and baseline characteristics (age, race, weight, height, or smoking) among the three treatment groups with one exception. There was a significant difference among the three treatment groups for baseline alcohol consumption. There was a lower number of nondrinkers in the 0.05 mg estradiol/day IVR treatment

group (79.6%) and the 0.10 mg estradiol/day IVR treatment group (79.5%) compared to the placebo IVR treatment group (91.7%). See Table 3.

Table 3: Demographic Information for Study IVR 1002

Subject Characteristics	Intravaginal Ring Treatment Group			All Subjects (n = 333)
	Placebo (n = 108)	0.05 mg Estradiol (n = 113)	0.10 mg Estradiol (n = 112)	
Race, n (%)				
White	87 (80.6)	84 (74.3)	86 (76.8)	257 (77.2)
Black	12 (11.1)	15 (13.3)	14 (12.5)	41 (12.3)
Hispanic	9 (8.3)	11 (9.7)	10 (8.9)	30 (9.0)
Asian/Pacific	0 (0.0)	1 (0.9)	1 (0.9)	2 (0.6)
Native American	0 (0.0)	1 (0.9)	1 (0.9)	2 (0.6)
Other	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.3)
Age (years)				
Mean ± SD	50.7 ± 6.5	52.6 ± 8.3	51.8 ± 6.6	51.7 ± 7.2
Min – Max	29 – 67	29 – 85	33 – 73	29 – 85
Weight (lbs.)				
Mean ± SD	164.7 ± 34.5	167.8 ± 40.0	162.7 ± 36.4	165.1 ± 37.0
Min – Max	109 – 284	85 – 292	76 – 255	76 – 292
Height (inches)				
Mean ± SD	64.1 ± 2.6	64.0 ± 2.6	64.2 ± 3.1	64.1 ± 2.8
Min – Max	56 – 72	58 – 72	54 – 71	54 – 72
Alcohol (drinks/day)* n (%)				
0	99 (91.7)	104 (79.6)	89 (79.5)	292 (87.7)
1	9 (8.3)	5 (4.4)	18 (16.1)	32 (9.6)
2 – 4	0 (0.0)	4 (3.5)	5 (4.5)	9 (2.7)
> 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Smoking (cigarettes per day), n (%)				
0	89 (82.4)	90 (79.6)	91 (81.3)	270 (81.1)
1 – 6	2 (1.9)	7 (6.2)	6 (5.4)	15 (4.5)
7 – 12	16 (14.8)	13 (11.5)	12 (10.7)	41 (12.3)
>12	1 (0.9)	3 (2.7)	3 (2.7)	7 (2.1)

Source: IVR 1002 Final Study Report, Section 14.1, Table 7.0.
SD = standard deviation. lbs. = pounds.
* Denotes statistically significant difference ($p<0.05$) among treatment groups using Cochran-Mantel-Haenszel test.

Reviewer's Comments

Table 3 presents demographic data for all randomized subjects in Study IVR 1002. Overall, subjects were predominately white (77.2%) with an average age of 51.7 years. The majority of subjects were nonsmokers (81.1%) and nondrinkers (87.7%).

There were 52 protocol violations discovered for 48 subjects in Study IVR 1002 (14%, 48 of 333 subjects; 4 subjects had 2 violations). Twenty-eight (28) of 333 treated subjects failed to meet the 7 to 8 MSVS/day or 50 to 60 MSVS/week inclusion criteria at baseline (8%). However, these 28 subjects were equally divided among the three treatment groups (10 in the placebo IVR treatment group [9%],

11 in the 0.05 mg estradiol/day IVR treatment group [10%], and 7 in the 0.10 mg estradiol/day IVR treatment group [6%]). Other protocol violations included taking exclusionary medication (16 of 333 subjects, 4.8%), being less than 75% compliant with study drug (4 of 333 subjects, 1.5%), and unopposed estrogens use > 6 months, vaginal/cervical dysplasia at screening, and failure to be postmenopausal (1 each for a total of 3 of 333 subjects, 0.9%). Please see Table 4.

Table 4: Protocol Violations, All Treated Subjects, Study IVR 1002

Protocol Violation	Intravaginal Ring Treatment Group			Total All Subjects (n = 333) n (%)
	Placebo (n = 108) n (%)	0.05 mg Estradiol (n = 113) n (%)	0.10 mg Estradiol (n = 112) n (%)	
Failure to MSVS Criteria at Screening	10 (9.3)	11 (9.7)	7 (6.3)	28 (8.4)
Exclusionary Medications	3 (2.8)	4 (3.5)	9 (8.0)	16 (4.8)
Less than 75% Compliant	3 (2.8)	1 (0.8)	0 (0.0)	5 (1.5)
Unopposed Estrogen Use for > 6 Months	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)
Vaginal/Cervical Dysplasia at Screening	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)
Failure to be Postmenopausal	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)

Source: Adapted from NDA 21-367, Volume 46, Section 14.1, Table 5.0.

Reviewer's Comments

Per the submission, some centers incorrectly counted mild vasomotor symptoms toward the required number of MSVS at baseline (Center # 19 had nine such violations; 3 in the placebo IVR treatment group, 4 in the 0.05 mg estradiol/day IVR treatment group, and 2 in the 0.10 mg estradiol/day IVR treatment group). It appears, however, that most of the protocol violations for failure to meet the inclusion criteria for MSVS at baseline occurred early in the study, afterwhich, centers were re-instructed on how to count baseline hot flushes.

The blind was not broken for any subject during the conduct of Study IVR 1002. All randomized subjects in Study IVR 1002 are included in the safety analysis.

Effects on Vasomotor Symptoms

Three hundred and thirty-three subjects (333) were randomized and treated (had an intravaginal ring inserted) in Study IVR 1002. The intent-to-treat (ITT) population included all treated subjects who had a baseline measurement of moderate-to-severe vasomotor symptoms (MSVS) (i.e., completed a daily diary for a two week period prior to randomization), and had at least one MSVS evaluation following insertion of the intravaginal ring. Three hundred and twenty-five subjects (325) comprised the ITT population. Eight subjects (8) from the treated population are not included in the ITT population. Six of these 8 subjects discontinued on the first day of treatment (2 subjects discontinued due to an inability to retain the intravaginal ring, 2 due to intolerance to the ring, and 2 subjects experienced adverse events). The other 2 subjects were lost to follow-up prior to having a post-baseline evaluation.

The per protocol population included ITT subjects not wrongly included at randomization and who were compliant up to week 13 or early termination (n = 291). Twenty-eight of the 34 subjects excluded from the per protocol population failed to meet 7 to 8 moderate-to-severe hot flushes per day (or 50 to 60 per week) at baseline. Four of the remaining 6 subjects were less than 75% compliant with study medication, one subject was not menopausal at screening, and one subject had used unopposed estrogen for > 6 months prior to treatment.

In Study IVR 1002, 45 of the 333 treated subjects (13.5%) agreed to have a colposcopy, assessments for chlamydia and a mount for the presence of bacterial vaginosis, and a potassium hydroxide (KOH) prep for candidiasis performed at randomization and at weeks 4 and 13 (referred to as the colposcopy subset, involved subjects at six study centers).

A single IVR containing study medication (releasing either 0.05 mg estradiol per day or 0.10 mg estradiol per day) or placebo was inserted by the investigator at the start of the clinical trial and was removed by the investigator at week 13 or early termination. In instances where the IVR was expelled during the clinical trial, subjects were instructed to clean and re-insert the IVR. Subjects were also provided with a "spare" IVR that was only to be used if the initial IVR was expelled and could not be re-inserted.

Twelve centers were selected to send "used" IVRs to Galen Ltd. to determine the amount of estradiol remaining in the ring after 3 months of usage. However, no results are provided in the submission.

In Study IVR 1002, a reduction in the number and severity of MSVS experienced by the subject was the primary efficacy variable. Subjects recorded all hot flushes (number and severity) on daily diary cards. Vasomotor symptom severity was defined as follows:

- Mild: Sensation of heat without perspiration.
- Moderate: Sensation of heat with perspiration, able to continue activity.
- Severe: Sensation of heat with sweating, causing the woman to stop activity.

Results of the comparison among treatment groups of MSVS at baseline showed that the placebo IVR treatment group had a higher mean number of MSVS at baseline (83.1) compared to the 0.05 mg estradiol/day IVR (73.7) and the 0.10 estradiol/day IVR (74.7). This finding was due, in part, to one subject in the placebo IVR treatment group who reported 630 MSVS during the 2-week screening period.

Reviewer's Comments

The Agency's Statistical Reviewer recalculated the mean number of MSVS at baseline for the placebo IVR treatment group eliminating the one subject reporting 630 MSVS during screening in Study IVR 1002. This recalculated data is used in this review of efficacy.

Mean change from baseline in the number and severity of MSVS at weeks 4, 8, and 12 using the last observation carried forward (LOCF) approach for the ITT population was the primary efficacy measure in Study IVR 1002. As shown in Table 5, the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR are equally effective in reducing the number of moderate-to-severe hot flushes at weeks 4, 8, and 12 as compared to placebo.

Table 5: Change in the Mean Number of Moderate-to-Severe Hot Flushes Per week During Therapy, ITT Population, LOCF

	Intravaginal Ring Treatment Group		
Week	Placebo (n = 104)	Estradiol 0.05 mg/day (n = 111)	Estradiol 0.10 mg/day (n = 109)
Baseline			
Mean Number	78.4	73.8	75.1
Week 4			
Mean Number	48.3	21.6	11.4
Mean Change	-30.0	-52.2	-63.7
p-value vs. Placebo	NA	<0.0001	<0.0001
Week 8			
Mean Number	43.9	15.6	8.4
Mean Change	-34.5	-58.3	-66.7

p-value vs. Placebo	NA	<0.0001	<0.0001
Week 12			
Mean Number	42.2	15.5	8.2
Mean Change	-36.1	-58.4	-66.9
p-value vs. Placebo	NA	<0.0001	<0.0001

Source: Adapted from the Agency's Statistical Reviewer's recalculations and data provided by the Sponsor on April 4, 2002.

NA = not applicable.
ITT = intent-to-treat.
LOCF = last observation carried forward.

Reviewer's Comments

The data presented for Study IVR 1002 shows a statistically and clinically significant difference in the number of MSVS versus placebo for both the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR (p-value of <0.0001 for both dosage strengths at weeks 4, 8, and 12).

In Study IVR 1002, both proposed IVR dosage strengths demonstrated a clinically significant difference of 2 or more MSVS per day (or 14 per week). The 0.05 mg estradiol/day IVR reduced the approximate daily number of MSVS from a baseline of 10.5/day to 3.1/day at week 4, 2.2/day at week 8, and 2.2/day at week 12. The 0.10 mg estradiol/day IVR reduced the approximate daily number of MSVS from a baseline of 10.7/day to 1.6/day at week 4, 1.2/day at week 8, and 1.2/day at week 12. These findings show a stronger initial response for the 0.10 mg estradiol/day IVR over the 0.05 mg estradiol/day IVR at week 4, but similar responses for weeks 8 and 12.

Using a scale of 0 = no flushes, 1 = mild, 2 = moderate, and 3 = severe, the mean severity scores for moderate and severe hot flushes at baseline was calculated for each treatment group. There were no major differences among treatment groups in the severity of MSVS at baseline.

Table 6 shows the analyses of the change from baseline in the mean severity of hot flushes for weeks 4, 8, and 12. The 0.05 mg estradiol/day IVR and the 0.10 estradiol/day IVR are effective in reducing the severity of hot flushes at weeks 4, 8, and 12 as compared to placebo.

Table 6: Change from Baseline in the Mean Severity of Hot Flushes During Therapy, ITT Population, LOCF

	Intravaginal Ring Treatment Group		
Week	Placebo (n = 104)	Estradiol 0.05 mg/day (n = 111)	Estradiol 0.10 mg/day (n = 109)
Baseline			
Mean Severity	2.5	2.5	2.5
Week 4			
Mean Severity	2.23	1.67	1.15
Mean Change	-0.28	-0.79	-1.33
p-value vs. Placebo	NA	=0.0001	<0.0001
Week 8			
Mean Severity	2.05	1.54	0.87
Mean Change	-0.45	-0.92	-1.61
p-value vs. Placebo	NA	=0.0009	<0.0001
Week 12			
Mean Severity	2.00	1.41	0.92
Mean Change	-0.51	-1.06	-1.56
p-value vs. Placebo	NA	=0.0002	<0.0001

Source: Adapted from the Agency's Statistical Reviewer's recalculations and data provided by the Sponsor on April 4, 2002.

NA = not applicable. ITT = intent-to-treat.
LOCF = last observation carried forward.

Reviewer's Comments

Table 6 shows that both IVR dosage strengths are equally effective in relieving the severity of hot flushes at week 4 which is maintained through week 12. Given that the 12-weeks efficacy results with the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR are almost indistinguishable for the relief of the frequency and severity of moderate-to-severe vasomotor symptoms, and that the 0.10 mg estradiol/day IVR contains twice as much estradiol acetate as the 0.05 mg estradiol/day IVR, there appears to be no efficacy justification to approve the latter for a VMS indication.

However, the Agency's Statistical Reviewer analyzed the relief of MSVS for both IVR dosage strengths by age groups (< 50, 50 to 59, > 59 years of age). The results of these observational subgroup analyses by age are presented in Table 7 below.

Table 7: **Mean Change from Baseline in the Frequency and Severity of Moderate-to-Severe Vasomotor Symptoms by Age Group, ITT Population with LOCF, Study IVR 1002**

Study Week	Age Group	Intravaginal Ring Treatment Group		
		Placebo	Estradiol 0.05 mg	Estradiol 0.10 mg
		N = 104	N = 111	N = 109
Mean Change from Baseline in the Number of MSVS				
4	< 50 years of age	n = 38	n = 27	n = 37
	Mean Change	-30.6	-44.7	-68.1
	p-value vs. Placebo	NA	0.104	<0.001*
	50 to 59 years of age	n = 59	n = 68	n = 59
	Mean Change	-27.4	-55.2	-62.4
	p-value vs. Placebo	NA	<0.0001*	<0.0001*
	> 59 years of age	n = 7	n = 16	n = 13
	Mean Change	-49.1	-52.5	-57.5
	p-value vs. Placebo	NA	0.815	0.574
8	< 50 years of age	n = 38	n = 27	n = 37
	Mean Change	-33.5	-55.0	-70.6
	p-value vs. Placebo	NA	0.010*	<0.001*
	50 to 59 years of age	n = 59	n = 68	n = 59
	Mean Change	33.1	-61.5	-65.5
	p-value vs. Placebo	NA	<0.0001*	<0.0001*
	> 59 years of age	n = 7	n = 16	n = 13
	Mean Change	-51.4	-50.2	-60.8
	p-value vs. Placebo	NA	0.937	0.528
12	< 50 years of age	n = 38	n = 27	n = 37
	Mean Change	-39.1	-54.8	-70.5
	p-value vs. Placebo	NA	0.054	<0.001*
	50 to 59 years of age	n = 59	n = 68	n = 59
	Mean Change	32.5	-61.6	-66.3
	p-value vs. Placebo	NA	<0.0001*	<0.0001*
	> 59 years of age	n = 7	n = 16	n = 13
	Mean Change	-49.9	-50.7	-59.2
	p-value vs. Placebo	NA	0.957	0.474
Mean Change from Baseline in Severity of Hot Flushes				
4	< 50 years of age	n = 38	n = 27	n = 37
	Mean Change	-0.3	-0.7	-1.4
	p-value vs. Placebo	NA	0.139	<0.001*
	50 to 59 years of age	n = 59	n = 68	n = 59
	Mean Change	-0.2	-0.8	-1.3
	p-value vs. Placebo	NA	<0.0005*	<0.0001*

	≥ 59 years of age	n = 7	n = 16	n = 13
	Mean Change	-0.9	-1.1	-1.4
	p-value vs. Placebo	NA	0.727	0.411
8	< 50 years of age	n = 38	n = 27	n = 37
	Mean Change	-0.6	-0.8	-1.7
	p-value vs. Placebo	NA	0.547	<0.001*
	50 to 59 years of age	n = 59	n = 68	n = 59
	Mean Change	-0.3	-1.0	-1.6
	p-value vs. Placebo	NA	<0.0007*	<0.0001*
	≥ 59 years of age	n = 7	n = 16	n = 13
	Mean Change	-0.9	-1.1	-1.4
	p-value vs. Placebo	NA	0.716	0.356
12	< 50 years of age	n = 38	n = 27	n = 37
	Mean Change	-0.7	-0.8	-1.5
	p-value vs. Placebo	NA	0.613	0.0012*
	50 to 59 years of age	n = 59	n = 68	n = 59
	Mean Change	-0.4	-1.1	-1.5
	p-value vs. Placebo	NA	<0.0001*	<0.0001*
	≥ 59 years of age	n = 7	n = 16	n = 13
	Mean Change	-0.7	-1.3	-1.7
	p-value vs. Placebo	NA	0.957	0.474

Source: Adapted from Statistical Review.
NA = not applicable.
ITT = intent-to-treat.
LOCF = last observation carried forward.
* Statistically significant difference from placebo at the 0.05 alpha level.

These results show that the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR performed similarly in the 50 to 59 years of age subgroup. Both dosage strengths showed statistically significant differences in the relief of MSVS (frequency and severity) at week 4 that was maintained through week 12 ($p<0.05$ at weeks 4, 8, and 12). However, this was not the case in the < 50 years of age subgroup.

In the < 50 years of age subgroup the 0.10 mg estradiol/day IVR relieved both the frequency and severity of hot flushes at weeks 4, 8, and 12 ($p<0.05$ at all time points) while the 0.05 mg estradiol/day IVR showed a delayed treatment effect that was not sustained. The 0.05 mg estradiol/day IVR did not relieve the number of MSVS compared to placebo until week 8 ($p=0.01$) and this relief was not maintained through week 12. In addition, the 0.05 mg estradiol/day IVR did not relieve the severity of hot flushes at any time in the age subgroup analyses (p-values > 0.05 at weeks 4, 8, and 12). The > 59 years of age subgroup had too few subjects to permit an observational assessment of treatment effect.

Overall, from the data presented in Study IVR 1002, the 0.05 mg estradiol/day IVR is the lowest effective dose shown to reduce the mean frequency and severity of moderate-to-severe vasomotor symptoms associated with the menopause. However, the observational age subgroup analysis, performed by the Agency's Statistical Reviewer, clearly shows that the 0.10 mg estradiol/day IVR demonstrates more consistent effectiveness in the relief of MSVS as compared to the 0.05 mg estradiol/day IVR, especially in the < 50 years of age subgroup. Therefore, this reviewer recommends the approval of both the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause. The 0.05 mg estradiol/day IVR is demonstrated to be the lowest effective dose, and this dose should be the starting dose recommended in labeling. However, the availability of the 0.10 mg estradiol/day IVR will provide the healthcare provider with options to better manage moderate-to-severe vasomotor symptoms unresponsive to the 0.05 mg estradiol/day IVR, especially in the newly menopausal woman.

Effects on Vulvar and Vaginal Atrophy

In Study IVR 1002, vulvar and vaginal atrophy was measured by assessing a pre- and post-treatment Maturation Index (MI) and vaginal pH on all treated subjects. The Maturation Index was determined by establishing the percentage of three vaginal cell types (parabasal, intermediate, and superficial). The Maturation Index was calculated using the following formula:

$$MI = 0.2 \times \text{parabasal (\%)} + 0.6 \times \text{intermediate (\%)} + 1.0 \times \text{superficial (\%)}$$

Maturation Index data collected more than 2 days after the last day of dosing was excluded from all analyses.

In Study IVR 1002, subjects were considered to have atrophy at baseline if 20% or more of the sampled vaginal cells were parabasal cells. A Maturation Index score of ≤ 52 was also considered as evidence of vaginal atrophy. Overall, only 18% of subjects in the ITT population in Study IVR 1002 (60 of 325 subjects) met these criteria (19% in the placebo IVR treatment group [20 of 105 subjects], 19% in the 0.05 mg estradiol/day IVR treatment group [21 of 111 subjects], and 17% in the 0.10 mg estradiol/day IVR treatment group [19 of 109 subjects]).

In the submission, a summary of the mean percentage of vaginal parabasal, intermediate, and superficial cells at baseline and week 13 was presented for the subset of subjects with a Maturation Index score of ≤ 52. The findings are shown in Table 8.

Table 8: Summary of the Mean Percentage of Parabasal, Intermediate, and Superficial Cells for Subjects with a Baseline Maturation Index Score ≤ 52, Study IVR 1002

	Intravaginal Ring Treatment Group		
Cell Type Percentage Study Week	Placebo (n = 20)	Estradiol 0.05 mg/day (n = 21)	Estradiol 0.10 mg/day (n = 19)
Parabasal			
Baseline	73.40	69.52	76.05
Week 13	27.25	0.00	1.05
LS Mean Change[a]	-52.60	-65.77	-77.33
p-value vs. Placebo[b]		0.326	0.060
Intermediate			
Baseline	26.60	30.48	23.95
Week 13	65.75	66.43	68.42
LS Mean Change[a]	48.38	29.00	47.27
p-value vs. Placebo[b]		0.199	0.939
Superficial			
Baseline	0.00	0.00	0.00
Week 13	4.22	33.57	30.53
LS Mean Change[a]		36.77	30.06
p-value vs. Placebo[b]		<0.001	<0.002

Source: Adapted from data provided by the Sponsor on April 4, 2002.

[a] Least Squared mean change from baseline to week13.

[b] P-values are obtained from a two-way ANOVA with factors for treatment and study center.

Reviewer's Comments

Table 8 shows the results of the Maturation Index for the subjects in a subset population with a baseline Maturation Index score of ≤ 52. However, this population represents only 18% of the ITT study population (60 of 325 subjects). It is interesting to note, nonetheless, that while the increase in the percentage of vaginal superficial cells between baseline and final evaluation for both IVR dosage strengths is statistically significant (p-value< 0.05), the corresponding decrease in vaginal parabasal cells, while evident, is not statistically significant.

Currently, per the Division's recommendations, there are three primary efficacy variables considered for a treatment of vulvar and vaginal atrophy indication:

1) The change in the Maturation Index between baseline and week 12 (statistically significant increase in superficial vaginal cells and decrease of parabasal vaginal cells).
2) The change in vaginal pH between baseline and week 12 (statistically significant lowering of vaginal pH).
3) The change in the subject self-assessment of symptoms between baseline and week 12. The primary efficacy analysis should show statistically significant improvement in the moderate-to-severe symptom identified by the subject as the most bothersome.

However, at the time of the submission of the protocol for Study IVR 1002, these Division recommendations had not been fully initiated.

The Sponsor also submitted an analysis of the mean percentage of vaginal parabasal, intermediate, and superficial cells at baseline and week 13 using an inclusion criterion of < 5% superficial cells at baseline. However, this subset analysis only represents 22% (71 of 325 subjects) of the ITT population. Table 9 shows the results of this analysis.

Table 9: Summary of the Mean Percentage of Parabasal, Intermediate, and Superficial Cells for Subjects with < 5% Superficial Cells at Baseline, Study IVR 1002

	Intravaginal Ring Treatment Group		
Cell Type Percentage Study Week	Placebo (n = 22)	Estradiol 0.05 mg/day (n = 23)	Estradiol 0.10 mg/day (n = 26)
Parabasal			
Baseline	67.18	64.35	56.62
Week 13	29.32	0.00	0.77
Mean Change[a]	-48.56	-54.39	-54.54
p-value vs. Placebo[b]		0.697	0.672
Intermediate			
Baseline	32.82	35.65	43.38
Week 13	64.32	68.70	71.15
Mean Change[a]	45.19	21.31	26.43
p-value vs. Placebo[b]		0.133	0.209
Superficial			
Baseline	0.00	0.00	0.00
Week 13	3.37	31.30	28.08
Mean Change[a]		33.08	28.12
p-value vs. Placebo[b]		0.001	0.003

Source: Adapted from data provided by the Sponsor on April 4, 2002.
[a] Least Squared mean change from baseline to week13.
[b] P-values are obtained from a two-way ANOVA with factors for treatment and study center.

Reviewer's Comments

Table 9 shows the results of the Maturation Index for a subset population with < 5% vaginal superficial cells at baseline. However, this population represents only 22% of the ITT population (71 of 325 subjects). Nonetheless, this analysis also shows a statistically significant increase in the percentage of vaginal superficial cells between baseline and final evaluation for both IVR dosage strengths (p-value < 0.05) without the corresponding statistically significant decrease in vaginal parabasal cells.

Comparing Tables 8 and 9, only minor differences in the mean percentages of parabasal, intermediate, and superficial cells between the different analyses are demonstrated.

On September 10, 2002, the Agency requested an analysis of the mean change from baseline to final evaluation for the percentages of vaginal parabasal, intermediate and superficial cells for the total ITT population with LOCF. The analysis received on September 12, 2002 show the results of 191 of 325 ITT subjects (59%), defined by the Sponsor as the All Treated population. In a teleconference on September 13, 2002, the Sponsor confirmed that the data represented the findings for those subjects with vaginal cytology smears that were "evaluable" at baseline and final evaluation, and vaginal smears that were collected within the prescribed period at final evaluation (within 2 days of the last day of dosing). This reviewer feels, however, that this population more closely represents an Evaluable population.

The findings presented in Table 10 show a statistically significant increase in vaginal superficial cells (p-value <0.001) for both IVR dosage strengths. In addition, a corresponding statistically significant decrease of vaginal parabasal cells (p-value 0.015) is shown for the 0.05 mg estradiol/day IVR versus placebo, while the p-value for the 0.10 mg estradiol/day IVR approaches statistical significance (p-value 0.06).

Table 10: Summary of the Mean Percentage of Vaginal Parabasal, Intermediate, and Superficial Cells, Evaluable Population, Study IVR 1002

	Intravaginal Ring Treatment Group		
Cell Type Percentage Study Week	Placebo (n = 63)	Estradiol 0.05 mg/day (n = 58)	Estradiol 0.10 mg/day (n = 70)
Parabasal			
Baseline	23.46	25.52	21.03
Week 13	15.16	0.17	0.29
Mean Change[a]	-8.30	-25.34	-20.74
p-value vs. Placebo[b]	NA	0.015	0.062
Intermediate			
Baseline	66.78	63.71	68.11
Week 13	73.97	73.02	69.93
Mean Change[a]	7.19	9.31	1.81
p-value vs. Placebo[b]	NA	0.761	0.419
Superficial			
Baseline	9.76	10.78	10.86
Week 13	10.87	26.81	29.79
Mean Change[a]	1.11	16.03	18.93
p-value vs. Placebo[b]	NA	<0.001	<0.001

Source: Adapted from data provided by the Sponsor on September 11, 2002 and September 13, 2002.

NA = not applicable.

[a] Mean change from baseline to week13.

[b] P-values are obtained from a one-way ANOVA with treatment as the factor.

Reviewer's Comments

Superficial cells increased by a mean of 16.0% and 18.9% for the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR as compared to 1.11% for placebo. Therefore, both IVR dosage strengths were equally effective in increasing the percentage of superficial cells. In addition, parabasal cells decreased by a mean of 25.3% and 20.7%, respectively, as compared to 8.3% for placebo. However, a statistically significant decrease in parabasal cells was not demonstrated for both IVR dosage strengths. Applying the current Division recommendation for a statistically significant corresponding decrease in parabasal cells, Table 10 shows that the 0.05 mg estradiol/day IVR meets this recommendation (p=0.015) while the 0.10 mg estradiol/day IVR closely approaches this recommendation (p=0.06).

In the Division's experience, as previously stated, clinical trial data usually show a maturation of the vaginal mucosa represented by a mean percent increase in superficial cells with a corresponding mean percent reduction in parabasal cells.

It is interesting to note in Table 10, however, that the baseline mean percentages of superficial cells greatly exceeded the current recommendation of < 5% (9.76, 10.78, and 10.86 for the placebo IVR, 0.05 mg estradiol/day IVR, and 0.10 mg estradiol/day IVR, respectively) which may indicate, overall, an "evaluable" subject population with less vaginal atrophy. The effect of this observation is uncertain. Overall, however, the data from Study IVR 1002 shows a mean percent increase in superficial cells with a corresponding mean percent reduction in parabasal cells for the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR.

The issue of the "missing" data in Study IVR 1002 is a concern, however. Forty-one percent (41%) of treated subjects are not included in the data submitted on September 12, 2002 (134 out of 325 subjects). Upon request, on September 19, 2002, the Sponsor submitted a line listing by reason for the ITT subjects not included in the Maturation Index analysis. A review of the data showed the following:

- **By study site, the number of ITT subjects not included ranged from 1 to 11;**
- **24 subjects had end-of-study vaginal smears performed > 2 days after IVR removal and were therefore excluded per protocol;**
- **56 subjects had screening vaginal smears that could not be read by the pathologist due to the following:**

  1) **inadequate smear (4 subjects);**
  2) **presence of infection and/or inflammation (43 subjects);**
  3) **presence of abnormal cells (7 subjects);**
  4) **presence of obscuring blood (2 subjects).**

  Two additional subjects at screening had missing Maturation Index results (no report received from the laboratory). Overall, these 58 subjects were equally divided across the three treatment groups: 19 in the placebo IVR treatment group, 21 in the 0.05 mg estradiol/day IVR treatment group, and 18 in the 0.10 mg estradiol/day IVR treatment group. Subjects were similarly equally divided for the category of infection and/or inflammation at screening: 14 in the placebo IVR treatment group, 17 in the 0.05 mg estradiol/day IVR, and 12 in the 0.10 mg estradiol/day IVR treatment group.

Overall, the majority of vaginal smears not included at screening (51 of 58 vaginal smears) were due to the presence of obscuring blood, abnormal cells, or infection and/or inflammation. However, these findings are not necessarily unexpected in a symptomatic postmenopausal population. In this instance, however, the finding of infection and/or inflammation on the vaginal smear at baseline resulted in the exclusion of potentially symptomatic women from analysis.

A review of the week 13 (or final evaluation) data showed that 66 subjects had vaginal smears that also could not be read by the pathologist due to infection and/or inflammation. Twelve additional subjects had no recorded final evaluation Maturation Index because either no specimens were collected (6 subjects), the vaginal smear slides were broken (2 subjects), or no report was received from the laboratory (4 subjects).

The finding of infection and/or inflammation in vaginal smears at end-of-study is also not unexpected and is most likely due to the presence of the intravaginal ring over a 90-day wear period. For the currently approved intravaginal ring drug product (Estring®), a placebo treatment group was not included due to concerns for the effect of placement in a non-estrogenic vagina over a 90-day wear period. However, the line listing data for Study IVR 1002 presented two observations of interest:

1) **21 of the excluded subjects had reports of infection and/or inflammation at screening and final evaluation (5 in the placebo IVR treatment group, 9 in the 0.05 mg estradiol/day IVR treatment group, and 7 in the 0.10 mg estradiol/day IVR treatment group), and**
2) **42 of the excluded subjects had "acceptable" Maturation Indexes at screening and a report of infection and/or inflammation at final evaluation. The majority however, were subjects in the estrogen-containing IVR treatment groups and not in the placebo treatment group (9 in the placebo IVR treatment group, 21 in the 0.05 mg estradiol/day IVR treatment group, and 12 in the 0.10 mg estradiol/day IVR treatment group).**

Please see the INTEGRATED REVIEW OF SAFETY section of this review for additional information.

Per the submission, at baseline, 81 of 333 randomized subjects had a vaginal pH of < 4.5 (24.3%) and 252 subjects had a baseline vaginal pH > 4.5 (75.6%). A vaginal pH < 4.5 shows the acidic nature of a well-estrogenized vagina due to lactobacillus-dominant vaginal bacterial flora. A vaginal pH > 4.5 encourages the growth of *Escherichia coli* and may increase the potential for urinary tract infections. An analysis of pH changes from baseline to final evaluation is presented in Table 11.

Table 11: Summary of the Change from Baseline to Week 13 for vaginal pH, Study IVR 1002

	Intravaginal Ring Treatment Group		
Study Week	Placebo (n = 95)	Estradiol 0.05 mg/day (n = 104)	Estradiol 0.10 mg/day (n = 104)
Baseline			
Mean (SD)	5.32 (1.17)	5.33 (1.12)	5.32 (1.18)
Week 13			
Mean (SD)	5.07 (1.02)	4.60 (0.75)	4.72 (0.93)
Mean Change (SD)	-0.25 (1.14)	-0.73 (1.26)	-0.60 (1.36)
p-value vs. Placebo[a]	NA	0.007	0.052

Source: Adapted from requested information provided by the Sponsor on September 11, 2002.
NA = not applicable.
[a] p-values for vaginal pH data are from a one-way ANOVA with treatment as the factor.

Reviewer's Comments

From the data presented, both IVR dosage strengths showed similar decreases in vaginal pH (mean decrease of 0.73 for the 0.05 mg estradiol/day IVR and 0.60 for the 0.10 mg estradiol/day IVR). However, the data presented in Table 11 shows that the mean change from baseline for the 0.05 mg estradiol/day IVR is statistically significant (p=0.007) while the mean change from baseline for the 0.10 mg estradiol/day IVR closely approaches statistical significance (p=0.052).

The mean decrease from baseline in vaginal pH in the placebo IVR treatment group in Study IVR 1002 is of interest and is unexplained (mean decrease of 0.25).

Overall, the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR were more effective in decreasing vaginal pH as compared to the placebo IVR.

A subject self-assessment of vaginal symptoms was also completed pre- and post-treatment in Study IVR 1002 that included the following categories:

- vaginal dryness
- vaginal irritation/itching
- difficulty passing urine
- urinary leakage
- pain during intercourse

- pain after intercourse
- bleeding after intercourse

The severity of each of the self-assessed symptoms was calculated using a scale of 0 = not at all, 1 = a little, 2 = quite a bit, and 3 = extremely. A decrease in the severity score was considered an improvement. Per the submission, subjects were included in the analyses of each symptom if they reported the symptom at baseline. Only those symptoms that were present at baseline in at least 15% of subjects are shown in Table 12.

Table 12: Summary of Subject Assessment of Vaginal Symptoms using Last Observation Carried Forward, Intent-to-Treat Population, Study IVR 1002

Symptom[a]	Intravaginal Ring Treatment Group					
	Placebo (n = 105		Estradiol 0.05 mg/day (n = 111)		Estradiol 0.10 mg/day (n = 109)	
Vaginal Dryness	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Mean Baseline	60	1.6 (0.74)	58	1.4 (0.60)	70	1.7 (0.79)
Mean Change/Week 4	56	-0.7 (0.86)	53	-0.9 (0.70)	68	-1.3 (0.92)*
Mean Change/Week 8	59	-0.8 (1.04)	57	-0.8 (0.75)	70	-1.3 (0.87)*
Mean Change/Week 13	60	-0.8 (0.98)	58	-0.9 (0.81)	70	-1.3 (1.03)
Vaginal Irritation/Itching						
Mean Baseline	32	1.3 (0.54)	35	1.1 (0.28)*	29	1.2 (0.49)
Mean Change/Week 4	30	-0.6 (0.81)	32	-0.3 (0.79)	29	-0.6 (0.68)
Mean Change/Week 8	32	-0.7 (1.03)	35	-0.5 (0.78)	29	-0.6 (0.73)
Mean Change/Week 13	32	-0.8 (0.80)	35	-0.5 (0.74)	29	-0.4 (0.82)
Urinary Frequency						
Mean Baseline	60	1.5 (0.62)	54	1.5 (0.67)	53	1.6 (0.60)
Mean change/Week 4	57	-0.6 (0.87)	53	-0.7 (0.94)	52	-0.8 (0.79)
Mean change/Week 8	59	-0.7 (0.76)	54	-0.8 (0.85)	53	-0.9 (0.86)
Mean Change/Week 13	60	-0.7 (0.81)	54	-0.8 (0.95)	53	-1.0 (0.77)
Urinary Leakage						
Mean Baseline	42	1.3 (0.55)	47	1.3 (0.61)	45	1.4 (0.65)
Mean Change/Week 4	40	-0.5 (0.60)	47	-0.6 (0.65)	43	-0.7 (0.81)
Mean Change/week 8	42	-0.5 (0.63)	47	-0.6 (0.85)	45	-0.6 (0.89)
Mean change/Week 13	42	-0.4 (0.67)	47	-0.6 (0.71)	45	-0.5 (0.87)
Pain During Intercourse						
Mean Baseline	25	1.7 (0.80)	19	1.5 (0.61)	24	1.6 (0.83)
Mean Change/Week 4	23	-0.8 (0.85)	18	-1.1 (0.68)*	19	-1.2 (0.96)*
Mean Change/Week 8	25	-0.8 (1.08)	19	-1.1 (0.74)	22	-1.2 (1.01)
Mean Change/Week 13	25	-0.8 (1.01)	19	-1.2 (0.60)	24	-1.3 (1.00)*

Source: NDA 21=367, Volume 46, Table T-24, page 3275.
SD = standard deviation.
[a] Only symptoms present in greater than 15% of subjects at baseline are included.
* Denotes statistical significance at the 0.50 level (comparison of active treatment vs. placebo) using a Cochran-Mantel-Haenszel test for row mean scores with study center as strata.

Reviewer's Comments

Study IVR 1002 began before the Division initiated the current recommendation that the primary efficacy analysis should show statistically significant improvement in the moderate-to-severe symptom identified by the subject as the most bothersome. Therefore, subjects participating in Study IVR 1002 were not asked to identify their "most bothersome" self-reported symptom prior to treatment. In addition, the analysis only includes symptoms present in greater than 15% of subjects at baseline, and even includes symptoms reported as "a little" bothersome, and not only symptoms reported as moderate ("quite a bit" bothersome) or severe ("extremely" bothersome) at baseline. Nonetheless, a few observations can be made from the data presented.

Overall, the findings in Table 12 show that vaginal dryness was the most self-reported vaginal symptom (56%, 188 of 325 subjects) followed by urinary frequency (51%, 167 of 325 subjects) and urinary leakage (41%, 134 of 325 subjects).

As shown in Table 12, the frequency of reported symptoms decreased somewhat in all treatment groups over the 13-week treatment duration. However, differences between the active treatment groups and the placebo group were statistically significant for only two of the self-assessed symptoms. Vaginal dryness was statistically significantly decreased in the 0.10 mg estradiol/day IVR treatment group at weeks 4 and 8 ($p<0.05$), but this decrease was not maintained through week 13. Pain during intercourse was statistically significantly decreased at week 4 for the 0.05 mg estradiol/day IVR treatment group ($p<0.05$), but this decrease was not maintained through weeks 8 and 13. The 0.10 mg estradiol/day IVR treatment group shows a statistically significant decrease for pain during intercourse at weeks 4 and 13 but not for week 8.

Since Study IVR 1002 was initiated prior to the Division's recommendations for the subject self-assessment of vaginal symptoms, the data in Table 12 is considered supportive and is not considered for an efficacy analysis.

In addition to obtaining a Maturation Index and vaginal pH at baseline, during the screening vaginal examination the investigator reported upon the following 11 observed signs: atrophy, pallor, generalized epithelial redness, discrete patches of epithelial redness, inflammation, granulation, ulceration, vaginal discharge, vaginal dryness, friability and petechiae. The investigator scored each sign as follows: none = 0, mild = 1, moderate = 2, severe = 3. A single subject could have none, one or more, or all of the signs upon vaginal examination at baseline.

A review of the baseline findings by the investigators shows that the majority of the treated subjects had no signs or only mild signs observed at baseline (range of 71.8% [none or mild atrophy] to 98.5% [none or mild vaginal ulceration]). However, 26.7% of treated subjects presented with moderate or severe signs of vaginal dryness at baseline (89 of 333 treated subjects) and 28.2% of treated subjects presented with moderate or severe signs of atrophy (94 of 333 treated subjects) at baseline.

Reviewer's Comments

Overall, utilizing the 11 investigator observed and rated signs at baseline, Study IVR 1002 showed that the majority of randomized subjects lacked visual evidence of vulvar and vaginal atrophy at baseline (range of 71.8% to 98.5% across the 11 rated signs). However, generalized epithelial redness, discrete patches of epithelial redness, inflammation, granulation, ulceration, vaginal discharge, friability and petechiae were observed signs on vaginal examination that were rated moderate or severe in up to 5% of the subjects (≥ 95% of subjects were rated none or mild for these 8 signs). Atrophy, pallor, and vaginal dryness were exceptions. Twenty-eight percent, 20%, and 26.7 % of subjects, respectively, were rated moderate or severe for these signs.

In the submission, additional data on the mean change from baseline to final evaluation for the following mild, moderate, and severe vaginal signs is presented: atrophy, pallor, dryness, friability, and petechiae. Table 13 shows these reported findings.

Table 13: Analysis of Mean Change from Baseline to Final Evaluation for Vaginal Examination for Subjects with Signs Present at Baseline (ITT Population), Study IVR 1002

Symptom	Intravaginal Ring Treatment Group		
	Placebo (n = 105)	Estradiol 0.05 mg/day (n = 111)	Estradiol 0.10 mg/day (n = 109)
Atrophy (n)	75	84	84
Baseline Mean (SD)	1.3 (0.47)	1.4 (0.63)	1.4 (0.58)
Mean Change to Final Evaluation (SD)	-0.4 (0.70)	-1.1 (0.65)*	-0.8 (0.70)*
Pallor (n)	64	76	74
Baseline	1.3 (0.47)	1.3 (0.53)	1.3 (0.48)
Mean Change to Final Evaluation (SD)	-0.5 (0.76)	-1.0 (0.65)*	-0.9 (0.55)*
Vaginal Dryness (n)	64	65	73
Baseline Mean (SD)	1.5 (0.59)	1.5 (0.49)	1.3 (0.53)
Mean Change to Final Evaluation (SD)	-0.9 (0.79)	-1.2 (0.72)*	-1.1 (0.74)
Friability (n)	18	14	17
Baseline Mean (SD)	1.1 (0.32)	-1.1 (0.36)	1.2 (0.34)
Mean Change to Final Evaluation (SD)	-0.9 (0.68)	-1.0 (0.55)	-1.2 (0.44)*
Petechiae (n)	16	18	16
Baseline Mean (SD)	1.3 (0.45)	1.2 (0.43)	1.1 (0.34)
Mean Change to Final Evaluation (SD)	-0.7 (0.70)	-1.0 (0.49)	-1.0 (0.52)

Source: NDA 21-367, Volume 34, Section 3.8, page 146 of 243.
ITT = Intent-to-Treat. SD = standard deviation.
Symptom score = 0 = none, 1 = mild, 2 = moderate, 3 = severe.
* Denotes statistical significance at the 0.05 level (comparison of active treatment vs. placebo) using a Cochran-Mantel-Haenszel test for row mean scores with study center as strata.

Reviewer's Comments

Among subjects with mild, moderate, and severe signs present at baseline, atrophy and pallor were statistically significantly improved in both active treatment groups (0.05 mg estradiol/day IVR and 0.10 mg estradiol/day IVR) compared to placebo at final evaluation ($p<0.05$). Vaginal dryness was statistically significantly improved in the 0.50 mg estradiol/day IVR treatment group at final evaluation ($p<0.05$), and friability was statistically significantly improved in the 0.10 mg estradiol/day IVR treatment group at final evaluation. Petechiae were improved in both active treatment groups also, but this improvement was not statistically significant.

Study IVR 1002 is one of only a few studies that have assessed observed signs a baseline for a treatment of vulvar and vaginal atrophy indication. Overall, there was greater improvement in investigator-diagnosed signs at baseline in the active treatment groups compared to the placebo group. However, the results in Study IVR 1002 show that only a few investigator-observed signs contributed useful data for decision. The Division continues to investigate the usefulness of investigator-reported vaginal signs for decision making regarding drug product effectiveness.

Supportive Study HRT 8

Study HRT 8 was a prospective, double-blind, multicenter, randomized, comparator-controlled, parallel group study in which 159 healthy postmenopausal women were initially treated with either an IVR releasing 0.05 mg estradiol/day or a placebo IVR or 1 mg oral estradiol per day or oral placebo for 24 weeks. After the first 12 weeks on study medication, women with inadequately controlled vasomotor symptoms could have their dosage strengths increased to 0.10 mg estradiol per day IVR or 2 mg oral estradiol per day for the remaining 12 weeks. In addition, an open-label extension with active rings only followed for a further 24 weeks. Subjects on 1 and 2 mg oral estradiol per day were switched to 0.05 and 0.10 mg estradiol per day IVRs, respectively.

Study HRT 8 is considered supportive for VMS because subjects were enrolled having at least 20 hot flushes/night sweats (HF/NS) per week and not 50 to 60 moderate-to-severe hot flushes per week as recommended by the Division. Study HRT 8 is also considered supportive for VVA. Although, vaginal cytology assessments were performed at baseline and week 24 (Papanicolaou Classification: 0 = inadequate, I = negative, II = negative, no signs of malignancy but some atypical cells), no Maturation Index was obtained. In addition, the vaginal signs of interest differed from Study IVR 1002 (Study HRT 8 included epithelial redness, inflammation, granulation, ulceration, vaginal discharge, cervical polyp, and cystocele/rectocele).

Reviewer's Comments

At the end of the first 12 weeks of study medication in Study HRT 8, 18 of the 83 subjects (21.6%) randomized to the 0.50 mg estradiol/day IVR increased their treatment dose (they received the 0.10 mg estradiol/day IVR for the next 12 weeks) due to inadequate relief of their baseline hot flushes and night sweats (a similar 21.6% increased their oral estradiol from 1 mg/day to 2 mg/day).

Per the submission, in Study HRT 8, the mean change from baseline in the number of HF/NS in the 0.05 mg estradiol/day IVR treatment group and the 1 mg oral estradiol treatment group at weeks 4, 8, and 12 in the ITT population was significant ($p<0.001$ for both treatment groups at all time points). The difference between treatment groups was not significant.

During the first 12 weeks of treatment prior to dose escalation, findings reported in Study HRT 8 show that investigator-diagnosed epithelial redness at baseline (7% for the 0.50 mg estradiol IVR treatment group [6 of 84 subjects], and 19% for the 1 mg oral estradiol treatment group [14 of 75 subjects]) decreased to 0% for both treatment groups at week 12. Although reported at a lower incidence at baseline, investigator-diagnosed inflammation also decreased to 0% at week 12 (from 1% for the 0.50 mg estradiol IVR treatment group [1 of 84 subjects] at baseline, and 3% for the 1 mg oral estradiol treatment group [2 of 75 subjects] at baseline). However, the first 12 weeks of Study HRT 8 shows that investigator-diagnosed vaginal discharge increased at week 12 for the 1 mg oral estradiol treatment group (up to 12% from 4% at baseline) and remained unchanged from baseline for the 0.50 mg estradiol/day IVR treatment group (8% for each time points).

6.4. Efficacy Conclusions

For the treatment of moderate-to-severe vasomotor symptoms associated with the menopause:

From the ITT population (325 subjects) data presented in Study IVR 1002, the 0.05 mg estradiol/day IVR dosage strength and the 0.10 mg estradiol/day IVR dosage strength are effective for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause and both IVR dosage strengths demonstrated a statistically significant reduction in the frequency and severity of hot flushes at weeks 4, 8, and 12 compared to placebo ($p<0.05$ at all time points).

A sub-analysis suggests that the 0.05 mg estradiol/day IVR does not provide consistent relief of moderate-to-severe vasomotor symptoms.

This reviewer fells that the data presented in NDA 21-367/S-00 provides sufficient evidence from one placebo-controlled clinical trial to support the safety and efficacy of the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

For the treatment of vulvar and vaginal atrophy associated with the menopause:

The criteria to establish efficacy for the indication of treatment of vulvar and vaginal atrophy associated with the menopause have evolved since 1999. The current criteria are:

- The change in the Maturation Index between baseline and week 12 (statistically significant increase in superficial vaginal cells and decrease of parabasal vaginal cells).
- The change in vaginal pH between baseline and week 12 (statistically significant lowering of vaginal pH).
- The change in the subject self-assessment of symptoms between baseline and week 12. The primary efficacy analysis should show statistically significant improvement in the moderate-to-severe symptom identified by the subject as the most bothersome.

During the course of drug development of this drug product, the Division accepted that efficacy for VVA would be based on the statistically significant change in vaginal superficial cells in the Maturation Index. This criterion for efficacy was consistent with product approved around or before 1999. Although the Sponsor was asked to look at all three cellular components of the Maturation Index (vaginal superficial, intermediate, and parabasal cells), and the physician-assessed signs (includes vaginal pH) and subject-assessed symptoms, the Division did not specify these as requirements for efficacy.

From an "evaluable" population in Study IVR 1002 (191 of 325 ITT subjects with paired baseline and week 13 [or final evaluation] Maturation Indexes), the 0.05 mg estradiol/day IVR dosage strength and the 0.10 mg estradiol/day IVR dosage strength are effective in increasing the percentages of vaginal superficial cells from baseline at week 13. Superficial cells increased by a mean of 16.0% and 18.9% for the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR, respectively, as compared to 1.11% for placebo. This increase was statistical significance at week 13 ($p<0.001$).

This reviewer feels that the data presented in NDA 21-367/S-000 provides sufficient evidence from one placebo-controlled clinical trial to support the safety and efficacy of the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR for the treatment of vulvar and vaginal atrophy associated with the menopause.

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Conclusions

The safety data presented in the submission shows that the overall safety profile of the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR is acceptable. No deaths occurred during the conduct of 9 completed Phase I, II, and III studies and one completed but blinded study at the time of the NDA submission (Study HRT 10). Overall, a total of 22 subjects reported serious adverse events in 10 completed studies with use of the placebo IVR, 0.05 mg or 0.10 mg estradiol/day IVR (3%, 22 of 642 subjects assigned to placebo IVR or estradiol acetate IVRs).

In Phase III Studies IVR 1002 and HRT 8, a total of 197 subjects were exposed to the 0.05 mg estradiol/day IVR, 112 subjects were exposed to the 0.10 mg estradiol/day IVR (in the initial 12 weeks of study participation), and 108 subjects were exposed to the placebo IVR. Overall, the mean duration of exposure ranged from 11weeks (SD 4.233) for placebo, 15 weeks (SD 6.146) for the 0.05 mg

estradiol/day IVR and 12 weeks (SD 2.925) for the 0.10 mg estradiol/day IVR. Thirty out of 417 subjects (7.2%, study population that excludes 18 dose-escalated subjects in Study HRT 8) discontinued due to an adverse event.

7.2. Materials Utilized in the Review

The data from 9 completed Phase I, II, and III studies, and one on-going Phase 3 study were reviewed for safety outcomes (n = 756 subjects). The safety population includes all subjects who received at least one dose of placebo IVR or estrogen-containing IVR and had at least one follow-up safety evaluation. The safety data presented in the NDA submission includes:

- Phase I studies = HRT 4, HRT 5, HRT 6a, IVR 1001, IVR 1005 and IVR 1006 (n = 77)
- Phase II study = HRT 6 (n = 17)
- Phase III studies = IVR 1002 and HRT 8 (n = 492, includes the oral estradiol treatment group)
- Ongoing Phase III study = an interim analysis of the blinded Phase III Study HRT 10 (n = 170, includes the Estring® treatment group)

The safety data from the above 6 Phase I studies and the Phase II study, while presented in the ISS, are not integrated. As noted, 77 postmenopausal women participated in the 6 Phase I studies for a treatment duration ranging from 3 days to 16 weeks. The most commonly reported adverse events in Phase I studies were vaginal discharge, breast tenderness, headache, occasional vaginal bleeding and spotting, and nausea and vomiting. No serious adverse events (SAEs) occurred in the 6 Phase I studies. Only one subject discontinued from the 6 Phase 1 studies (Pilot Study HRT 4 for vaginal bleeding).

The safety data from the Phase 2 Study HRT 6 showed that 17 subjects over a 28 day treatment duration reported vaginal discharge, breast tenderness, headache, and abdominal cramps/leg cramps. One SAE (angina pectoris) was reported in a Subject 10 using a — mg estradiol/day IVR. Three adverse events led to premature withdrawal from study participation (one subject each with abdominal and leg pain, migraine and rectal bleeding due to hemorrhoids, and vaginal discomfort and dysuria). In addition, one subject withdrew due to ring expulsion during coughing.

In the Integrated Summary of Safety (ISS), the safety data from Study IVR 1002 and the blinded portion of Study HRT 8 (first 24 weeks) have been integrated and is presented for 2 populations:

1) All ISS subjects = all postmenopausal women randomized in the blinded portion of these studies (n = 492, includes the oral estradiol treatment group).
2) ISS Subpopulation = all postmenopausal women in Study IVR 1002 and women without a uterus in Study HRT 8. Per the submission, this subpopulation is justified in order for an assessment of the safety profile of the IVR without the possible confounding effects of intermittent progestin administration. In Study HRT 8, subjects with a uterus were provided with 1mg oral norethisterone daily for the last 12 days of each 28-day cycle.

Reviewer's Comments

Since the postmenopausal use of unopposed estrogen in women with a uterus is known to be associated with an increased incidence of endometrial hyperplasia/cancer, study subjects with a uterus who received cyclic progestin (to reduce the incidence of estrogen-induced hyperplasia/cancer) should be included in the safety analysis (i.e., the "All ISS Subject" population). However, the "All ISS Subject" population in the ISS also includes subjects enrolled to treatment with oral estradiol (Study HRT 8). Therefore, for the Medical Officer's safety review only those postmenopausal women (with and without a uterus) randomized to either placebo IVRs or estrogen-containing IVRs in Studies IVR 1002 and HRT 8 are included (n = 435). Those subjects randomized to oral estradiol in Study HRT 8 are not included in this safety review, although specific oral estradiol safety outcomes are mentioned for comparison. The total number of 435 includes 18 subjects counted twice. These 18 subjects used a 0.05 mg

estradiol/day IVR for 12 weeks in Study HRT 8, afterwhich, they used a 0.10 mg estradiol/day IVR for an additional 12 weeks.

7.3. Description of Patient Exposure

In Phase III Studies IVR 1002 and HRT 8, a total of 197 subjects were exposed to the 0.05 mg estradiol/day IVR, 112 subjects were exposed to the 0.10 mg estradiol/day IVR (in the initial 12 weeks of study participation), and 108 subjects were exposed to the placebo IVR. As noted previously, 18 subjects in Study HRT 8 were exposed to the 0.10 mg estradiol/day IVR for a second 12 weeks after completing 12 weeks of exposure to the 0.05 mg estradiol/day IVR.

Overall, the mean duration of exposure ranged from 11weeks (SD 4.233) for placebo, 15 weeks (SD 6.146) for the 0.05 mg estradiol/day IVR and 12 weeks (SD 2.925) for the 0.10 mg estradiol/day IVR. The baseline demographics were similar between the three treatment groups in Study IVR 1002 (see Table 3 on page 20 of this review). Likewise, the baseline demographics were similar between the two treatment groups in Study HRT 8. The mean age was 51.7 ± 7.2 in Study IVR 1002 and 51.2 ± 5.4 in Study HRT 8. Ninety-nine percent (99%) of subjects were white in Study HRT 8, while in Study IVR 1002 more diversity was present: 77% white, 12% black, 9% Hispanic, 2% "other". Fifty percent (50%, 168 of 333 subjects) and 57% (48 of 84 subjects) of subjects in Study IVR 1002 and Study HRT 8, respectively, had a uterus. The mean years since last menses across both studies ranged from a low of 4.3 years in Study IVR 1002 to a high of 7.4 years in Study HRT 8.

The reasons for discontinuation of IVR study medication in the Medical Officer's modified ISS population are shown in Table 14 below.

Table 14: Disposition of Subjects by Treatment Groups

Parameter	Intravaginal Ring Treatment Group			All Subjects (n= 417)
	Placebo (n = 108)	0.05 mg Estradiol (n = 197)	0.10 mg Estradiol (n – 112)[a]	
Completed Study (%)	79 (73)	162 (82)	101 (90)	342 (78)
Discontinued Early (%)	29 (27)	35 (18)	11 (10)	75 (18)
Adverse Event	9 (8)	17 (9)	4 (4)	30 (7.2)
Consent Withdrawal	4 (4)	6 (3)	0 (0)	10 (2.4)
Failure to Comply	3 (3)	4 (2)	3 (3)	10 (2.4)
Loss to Follow-Up	0 (0)	1 (<1)	1 (<1)	2 (0.5)
Insufficient Product	1 (<1)	0 (0)	1 (<1)	2 (0.5)
Other	12 (11)	7 (4)	2 (1.8)	21 (5.0)

Source: Adapted from NDA 221-367, Volume 94, Test Table 3, page 19986.

[a] Does not include 18 subjects in Study HRT 8 initially randomized to 0.50 mg Estradiol/day IVR for 12 weeks who used a 0.10 mg estradiol/day IVR for an additional 12 weeks.

Reviewer's Comments

The percent of subjects who discontinued study participation in two Phase III studies in the ISS (18%) is similar and even lower than that reported in other 12-week VMS and VVA clinical trials.

7.4. Safety Findings from Clinical Studies

There were no deaths reported in any of the Phase I, Phase II, or Phase III studies presented in the submission. Per the submission, no serious adverse events occurred in any Phase 1 study, and only 1 serious adverse event occurred in the Phase 2 Study HRT 6 (Subject 10, angina pectoris) at a higher IVR dosage strength [redacted] mg estradiol/day IVR).

Eight (8) serious adverse events (SAEs) were reported in Study IVR 1002, 3 in the placebo IVR treatment group (2.8%, 3 of 108 placebo subjects), 2 in the 0.50 mg estradiol/day IVR treatment group (1.8%, 2 of 113 subjects), and 3 in the 0.10 mg estradiol/day treatment group (2.7%, 3 of 112 subjects). Only one of these 8 subjects with SAEs discontinued prematurely.

In the placebo IVR treatment group, one subject had a knee arthroplasty (Subject 332, 70 treatment days, causality reported as unrelated), 1 subject had hallucination (Subject 350, 111 treatment days, causality reported as unlikely), and 1 subject had angina pectoris (Subject 439, 13 treatment days, causality reported as unrelated, subject discontinued).

For the 2 subjects in the 0.50 mg estradiol/day treatment group, 1 subject had cholelithiasis with cholecystectomy (Subject 75, 92 treatment days, causality reported as possible), and the second subject had chronic obstructive airway disease and pneumonia (Subject 412, 29 treatment days, causality reported as unrelated).

For the 3 SAEs reported in the 0.10 mg estradiol IVR treatment group, 1 subject had appendicitis (Subject 172, 28 treatment days, causality reported as unrelated), 1 subject had a hernia (Subject 470, 29 treatment days, causality reported as unrelated), and 1 subject had rectal cancer (Subject 431, 91 treatment days, causality reported as unrelated).

In total, seven SAEs occurred in subjects using an estrogen-containing IVR at some time during the 48 treatment weeks (first 24 weeks blinded and second 24 weeks open-label) in Study HRT 8. Three of these 7 subjects discontinued: one case of muscle weakness (Subject 8160, 23 blinded treatment weeks, causality reported as not related), one case of breast pain (Subject 8117, 24 blinded treatment weeks and approximately 12 weeks open-label, causality reported as possible), and one case of complex endometrial hyperplasia (Subject 8144, 24 weeks blinded oral 1 mg estradiol and approximately 12 weeks open-label 0.05 mg estradiol/day IVR, subject discontinued study medication, 2 endometrial polyps per hysteroscopy, pathology diagnosis of polyps was benign).

Three SAEs occurred in subjects who continued an open-label estrogen-containing IVR following completion of 24 blinded weeks of an estrogen-containing IVR: one case of chest pain/palpitations (Subject 8175, approximately 24 treatment weeks, causality reported as unlikely), one case of ovarian cyst (Subject 8122, at 48 treatment weeks, causality reported as possible), and one case of varicose vein (Subject 8151, approximately 28 treatment weeks, causality reported as not related).

The seventh SAE occurred in a subject using an open-label estrogen-containing IVR after completing 24 weeks of blinded treatment on estradiol tablets: one case of arthropathy (Subject 8120, 24 weeks blinded oral estradiol and approximately 12 weeks open-label IVR, causality reported as not related). Subject 8120 completed the study.

Reviewer's Comments

The reported serious adverse events (8 in Study IVR 1002 and 7 in Study HRT 8) do not indicate a higher number of SAEs than observed in other clinical trials with estrogen-alone drug products, and do not present safety-related concerns for this reviewer.

In the ISS, the overall incidence of adverse events was similar between Study IVR 1002 and Study HRT 8 for the placebo IVR, 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR treatment groups. These results are shown in Table 15.

Table 15: Incidence of Adverse Events Occurring in ≥ 2% of Subjects by Preferred Term in Combined Study IVR 1002 and Study HRT 8 for Intravaginal Ring Treatment Groups

Preferred Term[a]	Intravaginal Ring Treatment Group			All Subjects (n= 435)
	Placebo (n = 108)	0.05 mg Estradiol (n = 197)	0.10 mg Estradiol (n = 130)[b]	

Subjects with at least 1 AE	n (%)	n (%)	n (%)	n (%)
Headache (NOS)	10 (9.3)	57 (28.9)	18 (13.8)	85 (19.5)
Breast Tenderness	2 (1.9)	21 (10.7)	12 (9.2)	35 (8.0)
Vaginal Discharge	**9 (8.3)**	**20 (10.2)**	**3 (2.3)**	**32 (7.3)**
Abdominal Distention	3 (2.8)	20 (10.2)	5 (3.8)	28 (6.4)
Back Pain	4 (3.7)	19 (9.6)	5 (3.8)	28 (6.4)
Nausea	5 (4.6)	20 (10.2)	2 (1.50	27 (6.2)
Vaginal Candidiasis	3 (2.8)	10 (5.1)	13 (10.0)	26 (5.9)
Intermenstrual Bleeding	2 (1.9)	11 (5.6)	11 (8.5)	24 (5.5)
Breast Pain	1 (0.9)	13 (6.6)	8 (6.2)	22 (5.0)
Arthralgia	4 (3.7)	13 (6.6)	4 (3.1)	21 (4.8)
Dizziness	1 (0.9)	14 (7.1)	4 (3.1)	19 (4.3)
Insomnia (NEC)	1 (0.9)	11 (5.6)	4 (3.1)	16 (3.6)
Depression (NEC)	2 (1.9)	13 (6.6)	1 (0.8)	16 (3.6)
URT Infection	6 (5.6)	6 (3.0)	4 (3.1)	16 (3.6)
Genital Disorders (NOS)	**9 (8.3)**	**3 (1.5)**	**3 (2.3)**	**15 (3.4)**
Vulvovaginitis (NOS)	**7 (6.5)**	**6 (3.0)**	**1 (0.8)**	**14 (3.2)**
Influenza	1 (1.9)	9 (4.6)	4 (3.1)	14 (3.2)
Abdominal Pain (NOS)	1 (0.9)	9 (4.6)	3 (2.3)	13 (2.9)
Genital Pruritis	3 (2.8)	9 (4.6)	1 (0.8)	13 (2.9)
Abdominal Pain Upper	3 (2.8)	6 (3.0)	2 (1.5)	11 (2.5)
Sore Throat (NOS)	1 (0.9)	7 (3.6)	3 (2.3)	11 (2.5)
Pain in Limb	3 (2.8)	5 (2.5)	3 (2.3)	11 (2.5)
Dysmenorrhea	1 (0.9)	6 (3.0)	3 (2.3)	10 (2.2)
Vulvovaginal Discomfort	1 (0.9)	7 (3.6)	2 (1/5)	10 (2.2)
Cough	1 (0.9)	5 (2.5)	4 (3.1)	10 (2.2)
Sinusitis (NOS)	2 (1.9)	4 (2.0)	4 (3.1)	10 (2.2)
Bronchitis (NOS)	0 (0.0)	4 (2.0)	5 (3.8)	9 (2.0)
Neck Pain	3 (2.8)	3 (1.5)	3 (2.3)	9 (2.0)
Vaginal Irritation	**4 (3.7)**	**3 (1.5)**	**2 (1.5)**	**9 (2.0)**
Dyspepsia	0 (0.0)	6 (3.0)	2 (1.5)	8 (1.8)
Influenza-like Illness	2 (1.9)	5 (2.5)	1 (1.5)	8 (1.8)
Dermatitis	1 (0.9)	6 (3.0)	1 (0.8)	8 (1.6)
Nasopharyngitis	3 (2.8)	3 (1.5)	2 (1.5)	8 (1.6)
Urinary Tract Infection	2 (1.9)	2 (1.0)	4 (3.1)	8 (1.6)
Fatigue	0 (0.0)	7 (3.6)	0 (0.0)	7 (1.6)
Hyperlipidemia	0 (0.0)	7 (3.6)	0 (0.0)	7 (1.6)
Pruritis (NOS)	1 (0.9)	5 (2.5)	1 (0.8)	7 (1.6)
Diarrhea (NOS)	1 (0.9)	6 (3.0)	0 (0.0)	7 (1.6)
Rhinitis (NOS)	0 (0.0)	6 (3.0)	0 (0.0)	6 (1.3)
Irritability	0 (0.0)	4 (2.0)	1 (0.8)	5 (1.1)

Source: Adapted from NDA 21-367, Volume 94, Text Table 10, Page 19995.
AE = adverse event. NOS = not otherwise specified. NEC = not elsewhere classified.
URT = upper respiratory tract.
[a] The order of the preferred terms is determined by the all subjects group.

[b] Includes 18 subjects in Study HRT 8 initially randomized to 0.50 mg Estradiol/day IVR for 12 weeks who used a 0.10 mg estradiol/day IVR for an additional 12 weeks.

Reviewer's Comments

As shown in Table 15, overall, the reported incidences of adverse events for the two estrogen-containing IVRs are higher than that shown for the placebo IVR. There are a few exceptions, however, under reproductive system and breast disorders events, that are noteworthy. The placebo IVR treatment group showed a higher incidence of:

- **vaginal discharge than shown for the combined estrogen-containing IVR treatment groups (8.3 % for placebo IVR, 9 of 108 subjects; 7.0% for the combined estrogen IVR treatment groups, 23 of 327 subjects);**
- **genital disorders than shown for the combined estrogen-containing IVR treatment groups (8.3% for placebo IVR, 9 of 108 subjects; 1.8% for the combined estrogen IVRs, 6 of 327 subjects);**
- **vulvovaginitis than shown for the combined estrogen-containing IVR treatment groups (6.5% for placebo IVR, 7 of 108 subjects; 2.1% for the combined estrogen IVRs, 7 of 327 subjects);**
- **vaginal irritation than shown for the combined estrogen-containing IVR treatment groups (3.7% for placebo IVR, 4 of 108 subjects; 1.5% for the combined estrogen IVRs, 5 of 327 subjects).**

These findings are not unexpected however, and likely show the effect of the placebo IVR in an estrogen-deprived atrophic vagina.

When comparing the two IVR treatment groups in the ISS, the 0.05 mg estradiol/day IVR treatment group generally shows a higher incidence of adverse events than the 0.10 mg estradiol/day IVR treatment group (see Table 15). Per the submission, this finding is due to the higher frequency with which adverse events were reported in the UK Study HRT 8, particularly for the 0.05 mg estradiol/day IVR.

During the 24-week blinded period of Study HRT 8, 84 subjects used the 0.05 mg estradiol/day IVR for the first 12 study weeks, and 66 subjects continued to use the 0.05 mg estradiol/day IVR for the second 12 study weeks. However, eighteen subjects used the 0.05 mg estradiol/day IVR for the first 12 study weeks and the 0.10 mg estradiol/day IVR for the second 12 study weeks. The adverse events reported with the greatest frequency during this blinded 24-week portion of Study HRT 8 were headaches (58.3%, 49 of 84 subjects), breast pain (33.3%, 28 of 84 subjects), vaginal discharge (21.4%, 18 of 84 subjects), nausea (20.2%, 17 of 84 subjects), back pain and dizziness (each 15.5%, 13 of 84 subjects). In comparison, adverse events were similar for the oral estradiol treatment group for the first 12 study weeks: headaches (46.7%, 35 of 75 subjects), back pain (22.6%, 17 of 75 subjects), vaginal discharge (20.0%, 15 of 75 subjects), and breast pain (18.7%, 14 of 75 subjects).

During the 24-week open-label portion of Study HRT 8, a total of 120 subjects received estrogen-containing IVRs (86 subjects received the 0.05 mg estradiol/day IVR and 34 subjects received the 0.10 mg estradiol/day IVR). The adverse events reported with the greatest frequency during this portion of Study HRT 8 were headaches (36.7%, 44 of 120 subjects), back pain (18.3%, 22 of 120 subjects), and breast pain and fatigue (10.8% each, 13 of 120 subjects).

Reviewer's Comments

Overall, similar treatment-emergent adverse events are reported in the blinded 24-week portion and the open-label 24-week portion of Study HRT 8.

In primary, Phase III Study IVR 1002, the majority of subjects in each treatment group had at least 1 treatment-emergent adverse event over the 13-week treatment period, 59.3% of placebo IVR subjects

(64 of 108 subjects), 65.5% of 0.5 mg estradiol/day IVR subjects (74 of 113 subjects), and 68.8% of 0.10 mg estradiol/day IVR subjects (77 of 112 subjects). Overall, the most common adverse event reported in all treatment groups were headaches (8.7%, 29 of 333 treated subjects), vaginal bleeding (6.6%, 22 of 333 treated subjects), vaginal candidiasis (6.6%, 22 of 333 treated subjects), and breast tenderness (6.3%, 21 of 333 treated subjects). Most treatment-emergent adverse events occurred more than 5 days after IVR insertion.

Per the submission, vaginal candidiasis was reported in a higher percentage of subjects in the estrogen-containing IVRs (6.2% in the 0.50 mg estradiol/day IVR and 10.7% in the 0.10 mg estradiol/day IVR) than in the placebo IVR (2.8%). On the other hand, vulvovaginitis was reported in a higher percentage of subjects in the placebo IVR treatment group (6.5%) compared with 5.3% in the 0.50 mg estradiol/day IVR and 0.9% in the 0.10 mg estradiol/day IVR. Vaginal discharge was also more common in placebo IVR subjects (8.3%) compared to 1.8% for the 0.50 mg estradiol/day IVR and 2.7% for the 0.10 mg estradiol/day IVR. See Table 16 for the number and percent of subjects reporting treatment-emergent adverse events that occurred at a rate of ≥ 2% in Study IVR 1002.

Table 16: All Treatment Emergent Adverse Events Regardless of Drug Relationship Reported at a Frequency ≥ 2% in Study IVR 1002

	Intravaginal Ring Treatment Group		
	Placebo (n = 108)	Estradiol 0.05 mg/day (n = 113)	Estradiol 0.10 mg/day (n = 112)
Body System/Preferred Term	N (%)	N (%)	N (%)
Subjects with at least 1 AE	64 (59.3)	74 (65.5)	77 (68.8)
Infections and Infestations			
Bronchitis	0 (0.0)	0 (0.0)	3 (2.7)
Nasopharyngitis	**3 (2.8)**	**2 (1.8)**	**2 (1.8)**
Sinusitis (NOS)	**2 (1.9)**	**2 (1.8)**	**2 (1.8)**
Upper Respiratory Tract (NOS)	6 (5.6)	5 (4.4)	4 (3.6)
Urinary Tract (NOS)	2 (1.9)	1 (0.9)	4 (3.6)
Vaginal Candidiasis	3 (2.8)	7 (6.2)	12 (10.7)
Vulvovaginitis (NOS)	**7 (6.5)**	**6 (5.3)**	**1 (0.9)**
Reproductive System and Breast Disorders			
Breast Tenderness	2 (1.9)	7 (6.2)	12 (10.7)
Genital Disorder (NOS)	9 (8.3)	3 (2.7)	3 (2.7)
Intermenstrual Bleeding	2 (1.9)	9 (8.0)	11 (9.8)
Uterine Pain	1 (0.9)	2 (1.8)	5 (4.5)
Vaginal Discharge	**9 (8.3)**	**2 (1.8)**	**3 (2.7)**
Vaginal Irritation	**4 (3.7)**	**1 (0.9)**	**2 (1.8)**
Vaginal Ulceration	**3 (2.8)**	**0 (0.0)**	**0 (0.0)**
Nervous System Disorders			
Headaches (NOS)	**10 (9.3)**	**8 (7.1)**	**11 (9.8)**
Insomnia (NEC)	1 (0.9)	3 (2.7)	2 (1.8)
Gastrointestinal Disorders			
Abdominal Distention	3 (2.8)	8 (7.1)	3 (2.7)
Abdominal Pain Upper	**3 (2.8)**	**0 (0.0)**	**0 (0.0)**
Nausea	**5 (4.6)**	**3 (2.7)**	**2 (1.8)**
Musculoskeletal Disorders			
Arthralgia	**4 (3.7)**	**2 (1.8)**	**2 (1.8)**
Back Pain	4 (3.7)	7 (6.2)	4 (3.6)
Neck Pain	**3 (2.8)**	**1 (0.9)**	**2 (1.8)**

Pain in Limb	3 (2.8)	1 (0.9)	3 (2.7)
Skin & Subcutaneous Tissue Disorders			
Genital Pruritis	**3 (2.8)**	**2 (1.8)**	**1 (0.9)**

Source: NDA 21-367, Volume 47, Table 18.0, pages 3574 – 3581.
AE = adverse event, NOS = not otherwise specified, NEC = not elsewhere classified.

Reviewer's Comments

Similarly to Table 15, Table 16 shows that the reported incidences of adverse events in Study IVR 1002 for the two estrogen-containing IVRs combined are higher than that shown for the placebo IVR with similar exceptions. Under reproductive system and breast disorders, the placebo IVR treatment group shows a higher incidence of vaginal discharge, vaginal irritation, and vaginal ulceration than shown for the estrogen-containing IVRs. Overall, the incidence of vulvovaginitis, nausea, nasopharyngitis, sinusitis, arthralgia, neck pain, and genital pruritis in the placebo IVR treatment group was higher than the combined IVR treatment groups (see bolded adverse events in Table 16).

The findings of an increased incidence of vulvovaginitis, vaginal discharge, irritation, and ulceration in the placebo IVR treatment group is not unexpected, and is most likely a result of the wearing of a placebo ring in an estrogen-deprived atrophic vagina over a 90 day period.

As observed in Table 15 (combined results of US and UK studies) and Table 16 (12 weeks of US study), adverse events reported during the first 12 weeks of treatment are comparable to the summary of all adverse events reported overall, namely, headaches, breast tenderness, and vaginal discharge. Adverse events such as these are commonly associated with estrogen-alone drug products. The reported incidences of these adverse events do not differ from that reported in other similar estrogen-alone clinical trials.

Changes in vaginal examination parameters were also evaluated for safety outcomes in Studies IVR 1002 and HRT 8. As previously noted in the INTEGATED REVIEW OF EFFICACY section of this review, 11 investigator observed and rated signs were assessed during vaginal examination in Study IVR 1002 (please refer to page 31 for a discussion of these outcomes and to Table 13). In summary, for the majority of subjects overall, vaginal signs either stayed the same or improved from baseline to final evaluation (in particular pallor, vaginal dryness, and atrophy). Greater improvement was observed with respect to generalized epithelial redness, vaginal dryness, and friability for the 0.10 mg estradiol/day IVR treatment group, and atrophy and granulation for the 0.05 mg estradiol/day IVR treatment group. Overall, a greater increase in severity of or new signs was observed in the placebo IVR treatment group compared with the estradiol-containing IVR treatment groups. This would be expected of a non-medicated IVR in a postmenopausal population, however.

Two cases of ulceration were reported in Study HRT 8 (1vaginal and 1 vulval) in the 0.05 mg estradiol/day IVR.

In the submission, the incidence of adverse events occurring within the first 5 days following IVR insertion was analyzed to assess the effect of the higher drug concentration seen immediately after IVR insertion. In the modified ISS (excludes the adverse events reported for oral estradiol), 27% of subjects (120 of 435 subjects) reported adverse events within the first five days following IVR insertion. The adverse events reported with the greatest frequency were headaches (6.8%, 30 of 435 subjects), vaginal discharge (3.6%, 16 of 435 subjects), and nausea (2.7%, 12 of 435 subjects). No SAEs occurred during this time period. When the oral estradiol treatment groups are included (ISS population), the adverse events reported with the greatest frequency were also headaches (10.2%, 50 of 492 subjects), vaginal discharge (5.3%, 26 of 492 subjects), and nausea (3.3%, 16 of 492 subjects).

Reviewer's Comments

It is not unexpected that adverse events such as headaches, vaginal discharge, and nausea appeared early after IVR insertion. In fact, looking at the data presented for the 1mg oral estradiol comparator treatment group in Study HRT 8, these adverse events were seen with the same frequency. Therefore, it appears that these adverse events are most likely associated with the initiation of estradiol treatment in general and not necessarily with IVR insertion.

However, adverse events that appeared in this initial 5 day post-insertion period were of particular interest because of the initial serum estradiol concentration burst effects seen with IVRs in Phase 1 studies. In three day Study IVR 1001, the estradiol C_{max} rose to 1664.7 pg/ml in 0.7 hours. In Phase I Study IVR 1006, following administration of the 0.05 mg estradiol/day IVR, day 1 serum estradiol concentration increased rapidly to a C_{max} of 1129 pg/ml in 0.9 hours then decreases to relatively constant serum concentrations for the remaining 13 weeks.

These findings precipitated concern for the effect of the immediate, high concentrations of estradiol on hemostatic parameters and consequent adverse events in a postmenopausal population. As previously stated, however, no serious adverse events were reported during this initial 5-day post-insertion period.

Please see the discussion of clinical laboratory assessments beginning on page 44 of this review.

At each scheduled clinic visit in Study IVR 1002, each subject completed a Ring Acceptability Questionnaire. Questions addressed whether the ring caused discomfort for the subject or her partner, the ease of ring removal and insertion, and the subject's willingness to use the product or recommend the product to a friend. All questions were answered either "yes", "no", or "not applicable" (N/A).

In response to the question, "Did the ring cause discomfort for you during intercourse?", 5% of subjects having intercourse at week 4 said yes (14 of 292 subjects), 4% said yes at week 8 (10 of 266 subjects), and 5 % said yes at week 13 (12 of 251 subjects). Response to the question, "Did the ring cause discomfort for your partner during intercourse?" were somewhat higher, 6% said yes at week 4 (19 of 292 subjects), 6% said yes at week 8 (16 of 266 subjects), and 8% said yes at week 13 (21 of 251 subjects).

In response to the question, "If you removed the ring, was it easy to remove?", 14% of subjects who removed the ring by week 4 said yes (40 of 291 subjects) and 1.4% said no (4 of 291 subjects), 9% said yes at week 8 (24 of 265 subjects) and 1.5% said no (4 of 265 subjects), and 16% said yes at week 13 (40 of 251 subjects) and 3% said no (8 of 251 subjects). Responses to the question, "If you reinserted the ring, was it easy to reinsert?" were higher, 15% said yes at week 4 (43 of 292 subjects) and 2 % said no (5 of 292 subjects), 15% said yes at week 8 (40 of 266 subjects) and 0.7% said no (2 of 266 subjects), and 17% said yes at week 13 (42 of 250 subjects) and 0.8% said no (2 of 250 subjects).

Subjects were also asked the question, "Would you use this product for HRT if it were available?" For the combined estrogen-containing IVRs, yes responses were high: 93% said yes at weeks 4 and 8 (181 of 195 subjects and 173 of 186 subjects, respectively), and 89% said yes at week 13 (160 of 179 subjects). No responses ranged from 7% at weeks 4 and 8 to 11% at week 13. For the placebo IVR, yes responses ranged from 73% at week 4 to 80% at week 13, while no responses ranged from 27% at week 4 to 20% at week 13.

Reviewer's Comments

Overall, study participants who had IVRs inserted by the investigator at randomization had no difficulty removing the IVR or reinserting an IVR. Comparatively, more subjects using estrogen-containing IVRs indicated that use was acceptable than subjects who used placebo IVRs (94% versus 77%, respectively). These findings are not unexpected, however.

Colposcopy Subset

Colposcopy with at least 10X magnification (Site 01 used 16X to 25X magnification and Site 19 used 15X magnification) was performed at randomization, week 4 and week 13 in a subset of 45 subjects enrolled at 5 sites in Study IVR 1002 (14 randomized to the placebo IVR, 15 to the 0.05 mg estradiol/day IVR, and 16 to 0.10 mg estradiol/day IVR). Any findings judged by the investigator to be anything other than normal healthy vaginal epithelium were recorded as a "suspicious area." Each "suspicious area" seen at colposcopy was described by location, appearance, color, character of blood vessels, distinctness of lesion border, depth and size of greatest dimension. A diagnosis (e.g., ecchymosis, petechiae, blister, etc.) was also given to each area.

Sixteen (16) subjects (36%, 16 of 45 subjects) were found to have "abnormal" findings at baseline (including one subject found to have abrasions/lacerations at baseline randomized to the 0.10 mg estradiol/day IVR treatment group). Seventeen (17) subjects (38%, 17 of 45 subjects) were found to have an "abnormal" finding after treatment began that was not there at baseline. The most common diagnoses at baseline and after treatment were petechiae, ecchymosis, erythema and peeling.

"Abnormal" findings noted after treatment were:

- 1 abrasion/laceration after placebo IVR treatment,
- 1 blister/subepithelial hemorrhage after placebo IVR treatment,
- 1 ulcer after placebo IVR treatment,
- 1 excoriation after 0.05 mg estradiol/day IVR treatment
- 1 polyp after 0.05 mg estradiol/day IVR treatment (histologic diagnosis of biopsy revealed normal vaginal mucosa),
- 1 polyp after 0.05 mg estradiol/day IVR treatment (histologic diagnosis of biopsy revealed granulation tissue).
- 1 granulation/erythematous papules after 0.10 mg estradiol/day IVR treatment,

Reviewer's Comments

Some subjects had findings consistent with minor trauma after treatment due to the presence of the IVR. However, the incidence was low and more frequently reported in the placebo IVR treatment group. It is not uncommon, however, to find small vaginal mucosa defects or lacerations (possibly ulcers) in the postmenopausal vagina.

Clinical Laboratory Assessments

In Studies IVR 1002 and HRT 8, only 6 subjects (1.4%, 6 of 435 modified ISS safety subjects) had potentially clinically significant (PCS) hematology values (4 subjects had WBC values ranging from 2.5 to 2.8 thou/*u*L, 1 subject had both hemoglobin and MCH values considered to be low, and 1 subject had a low hemoglobin value). None of these values cause concern, however.

A total of 41 subjects (9%, 41 of 435 subjects) had chemistry values that were considered to be potentially clinically significant in the ISS. The majority of these 41 subjects (88%, 36 of 41 subjects) had cholesterol and triglyceride values that were considered to be PCS. Nine of the 41 subjects participated in Study HRT 8 (4 in the 0.05 mg estradiol/day IVR treatment group and 5 in the 1 mg oral estradiol treatment group). The remaining 32 subjects participated in Study IVR 1002.

In Study IVR 1002, 2 subject had elevated cholesterol and triglycerides levels (Subject 367 in the placebo IVR group and Subject 423 in the 0.05 mg estradiol/day IVR treatment group), and one subject had elevated triglycerides and an increased glucose level (Subject 376). The remaining 29 subjects had either elevated cholesterol levels (2 subjects in the placebo IVR group and 2 subjects in the 0.10 mg estradiol/day IVR group), elevated triglycerides (9 placebo subjects, 5 subjects in the 0.05 mg estradiol/day IVR group and 6 subjects in the 0.10 mg estradiol/day IVR group), elevated GGT (2

subjects in the 0.10 mg estradiol/day IVR group), elevated glucose (1 in the 0.10 mg estradiol/day IVR group), elevated calcium (1 in the placebo group) or elevated total bilirubin (1 in the placebo group).

Reviewer's Comments

Across the two Phase III studies, the number of subjects with chemistry values that were considered to be potentially clinically significant were comparable between the placebo IVR and the 0.05 mg estradiol/day and 0.10 mg estradiol/day IVRs (total number of PCS findings were 15, 13, and 11, respectively). Therefore, no consistent pattern is evident from the chemistry parameters results in the two Phase III clinical trials.

In the colposcopy subset of Study IVR 1002 (5 participating centers) 45 subjects had testing performed for chlamydia, gonorrhea, bacterial vaginosis and candidiasis at baseline and end-of-study. At baseline, one subject had a positive test for bacterial vaginosis (Subject 272 randomized to the 0.05 mg estradiol/day IVR treatment group). No subject had a positive test for any of these vaginal infections at week 13

In Study HRT 8, endometrial biopsies were performed at baseline and week 24. A review of the final study report for evaluable subjects (week 24 endometrial biopsy results available) shows the following:

- 7 subjects assigned to estradiol IVR + placebo tablet had weak/focal secretory endometrium; 5 subjects assigned to estradiol tablet + placebo IVR had weak/focal secretory endometrium.
- 2 subjects assigned to estradiol IVR + placebo tablet had menstrual endometrium,
- 3 subjects assigned to estradiol IVR + placebo tablet had weak/focal proliferative endometrium,
- 1 subject assigned to estradiol IVR + placebo tablet had inactive endometrium,
- 3 subjects assigned to estradiol IVR + placebo tablet had insufficient tissue for diagnosis.

One subject assigned to the estradiol tablet + placebo IVR treatment group in Study HRT 8 had a diagnosis of complex hyperplasia with superimposed secretory change at week 24.

Reviewer's Comments

In Study HRT 8, subjects with a uterus were provided 1 mg norethisterone (Micronor-HRT®) daily for the last 12 days of each 28-day cycle (days 17 to 28) for the study duration. Therefore, the findings reported in Study HRT 8 are not unexpected. Of interest however, are the 3 reported cases of weak/focal proliferative endometrium in the estradiol IVR + placebo tablet treatment group and the one case of complex hyperplasia in the oral estradiol + placebo IVR treatment group given monthly progestin therapy.

In Study IVR 1002, endometrial biopsies were performed as safety assessments at baseline. No endometrial biopsies or transvaginal ultrasounds were performed at end-of-study. Instead, all treated subjects with a uterus were provided a 14-day course of either 2.5 mg norethindrone or 10 mg medroxyprogesterone acetate. These subjects were contacted by telephone after the last clinic visit to determine the outcome of this treatment. Please see section 7.10, Adequacy of Safety Testing for additional information.

As previously mentioned, two Phase I studies collected hemostatic parameters. In Study IVR 1005, the following hemostatic parameters were collected at baseline, 15, 30, 45,and 60 minutes, and at 24 and 72 hours after insertion of the 0.10 mg estradiol/day IVR (14 subjects):

- thrombin-antithrombin complex (TAT)
- prothrombin fragment 1+2 (F1+2)
- von Willebrand factor antigen (vWF Ag)
- Factor VIII coagulant activity (FVIIIC)
- Protein S antigen (PS) (total and free)

- activated protein C sensitivity ratio (APC:SR)

The same hemostatic parameters were collected in Phase I Study IVR 1006 (26 subjects) at baseline, and 1, 24 and 72 hours after IVR insertion in Period 1(0.05 mg estradiol/day IVR inserted and worn for 90 days). In Period 2 (a second 0.05 mg estradiol/day IVR was inserted and worn for 28 days), hemostatic parameters were collected at 1, 24, and 72 hours, and at day 28.

In Study IVR 1005, transient changes in the concentrations of clotting factors were noted: vWF Ag was increased at 24 and 72 hours after IVR insertion and these differences relative to the 0 minutes timepoint were statistically significant, FVIIIC paralleled those of vWF Ag, and mean APC:SR values rose slightly by a statistically significantly increase at 15 minutes only. However, mean TAT complex values were not statistically significantly increased from the 0 minute value at any time point. There were no statistically significant differences between the mean F1+2 values at 0 minutes compared to any timepoint within the 72-hour study. The levels of total and free PS antigen showed no significant changes. All subjects in Study IVR 1005 were exposed to rings manufactured at least 36 months before the start of the study.

In Study IVR 1006, results of the hemostatic parameters measured were similar. Relative to baseline, the levels of vWF Ag were higher at 24 and 72 hours but not at 1 hour after IVR insertion in both Periods 1 and 2. FVIIIC results were inconsistent, lower after the first IVR insertion and higher after the second IVR insertion. APC:SR changes were consistent with those seen for FVIIIC. No conclusions could be drawn from the results of TAT complex and F1+2 since clotting was activated in some of the samples during collection and pre-clinical preparation. All subjects in Study IVR 1006 were exposed to rings manufactured not more than 24 months before the start of the study. As previously discussed in the HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS section of this review, the average serum estradiol concentration (C_{avg}) was 40.6 pg/ml during Period 1 in Study IVR 1006 , the C_{max} was 1129 pg/ml, and the t_{max} was 0.9 hours. The estradiol C_{max} value following insertion of the second IVR was 772 pg/ml and the t_{max} was 1.1 hours. The estradiol C_{avg} was 52.6 pg/ml following dose 2.

Reviewer's Comments

Overall, the analyses of hemostasis parameters in these two Phase 1 studies showed isolated, transient, but statistically significant, changes in the concentrations of some factors, namely, von Willebrand factor antigen (increased at 24 and 72 hours but not at 1 hour), Factor VIII coagulant activity (increased at 24 and 72 hours but not at 1 hour), and activated protein C sensitivity ratio (15 and 45 minutes only) (based on mean levels of each hemostatic parameter and a paired t-test statistical comparison performed at each time point with the baseline value). The interrelationship of the reported hemostasis parameters and serum estradiol concentration levels remained unclear, however.

In Amendment 13 to the NDA, dated October 1, 2002, the Sponsor provided scatter plots for each parameter against estradiol concentration to demonstrate any observable dependence of these hemostatic parameters on effects of estradiol. The analysis showed no evidence of an association between any of these parameters and the simultaneous estradiol concentration, or any late effects of the peak short-term estradiol concentrations.

No clinically evident thromboses were reported in Study IVR 1002 and Study HRT 8. In the absence of clinically evident thrombosis, however, there is no consensus about which clotting factors or combination of clotting factors can be measured as markers of an altered risk of venous thrombosis in postmenopausal women using estrogen therapy.

As previously stated, no serious adverse events were reported in the first 5 days following IVR insertion in the two Phase III studies. Headaches (6.8%, 30 of 435 subjects), vaginal discharge (3.6%, 16 of 435 subjects), and nausea (2.7%, 12 of 435 subjects) were the adverse events reported most frequently during this period.

7.5. Miscellaneous Studies

No additional studies were conducted that contribute to either the historical information regarding the product development or actual safety and efficacy data.

7.6. Literature Review for Safety

The Sponsor conducted a comprehensive search of recent medical literature to assess the safety of local vaginal delivery of estrogen, including vaginal creams, tablets, and intravaginal rings. Approximately 70 publications were compiled and summarized in the submission. No independent literature review was conducted.

7.7. Postmarketing Surveillance – If Applicable

No intravaginal ring containing estradiol-3-acetate is approved for use in the US. On April 3, 2001, marketing authority was authorized in the UK for Menoring® 50 (0.05 mg estradiol/day IVR) for the relief of hot flushes, sweating at night, dryness or soreness of the vagina or pain during sexual intercourse in women who have had a hysterectomy. The Sponsor indicates that Menoring® 50 has been used by approximately 3,650 women since authorization. Per the Sponsor, there have been no reports of any adverse drug reactions due to Menoring® 50 either from the licensing authority, in the literature, or from spontaneous reports.

7.8. Safety Update

4-Month Safety Update

The 4-Month Safety Report, dated April 18, 2002, provided additional information from the non-US supportive, Phase III Study HRT 10. Study HRT 10, which was ongoing at the time of the NDA submission, is now completed. The final report is in preparation. Study HRT 10 was a multicenter, randomized, parallel group, blinded study comparing 0.05 mg estradiol/day IVR, 0.10 mg estradiol/day IVR, and Estring® (single-blind versus Estring® intravaginal ring, 0.008 mg estradiol/day). Each ring was inserted and replaced with a new ring every 12 weeks for a total of 96 weeks. The safety population consists of 170 women ages 31 to 64 (mean age 54.6). Ninety-three subjects completed the study.

There were no deaths reported in Study HRT 10.

Three subjects in the 0.50 mg estradiol/day IVR treatment group (5%, 3 of 57 subjects) experienced eight SAEs during the study. One subject experienced abdominal pain and vomiting (Subject 10624), one subject experienced a malignant breast lump (Subject 10163, discontinued), and one subject experienced lymphadenopathy, Hodgkin's disease, parasitic infection, upper respiratory tract infection and urinary tract infection (Subject 10688, discontinued).

Three subjects (5%, 3 of 56 subjects) in the 0.10 mg estradiol/day IVR treatment group each experienced one SAE (exacerbation of diverticulitis [Subject 10728], rectal polyp [Subject 10162], and osteoporosis of the hip [Subject 10298]).

Four subjects (7%, 4 of 57 subjects) in the Estring® treatment group each experienced one SAE (vulvar cyst [Subject 10353], bacterial infection [Subject 10397], dislocated arm [Subject 10300], and deep vein thrombosis of the left leg [Subject 10574]).

All of the above subjects were initially reported (blinded) in the NDA.

Second Safety Update

The Second Safety Update, dated September 19, 2002, covers the period April 2002 through August 30, 2002. Per the submission, no additional safety information is available to report for Study HRT 10. A copy of the final study report for Study HRT 10 will be submitted to IND ——— upon its availability.

7.9. Drug Withdrawal, Abuse, and Overdose Experience

No serious adverse events were reported as a result of estrogen-containing IVR abuse or overdose during the conduct of any clinical trial. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding in postmenopausal women with a uterus.

7.10. Adequacy of Safety Testing

Physical examinations, including breast and pelvic/Pap smear examination, vital signs and body weight, and laboratory evaluations were completed at screening and week 13 in Study IVR 1002. Mammograms were performed at screening unless documented results of a previous normal mammogram (within the previous 9 months) were available. All treated subjects with a uterus received a 14-day course of either 2.5 mg norethindrone or 10 mg medroxyprogesterone acetate (MPA) (at the discretion of the investigator). These subjects were contacted by telephone 30 days after the last clinic visit to determine the outcome of this treatment.

Reviewer's Comments

The safety assessments conducted in Study IVR 1002 were appropriate and adequate. One hundred and sixty-eight subjects (168) with a uterus, who had taken study medication for at least 4 weeks, were provided post-treatment progestin for 14 days (151 took MPA, 6 took norethindrone, and 1 took another progestin). Thirty-six percent of subjects in the placebo IVR treatment group had a withdrawal bleed (36%, 18 of 50 subjects), 43% of subjects in the 0.05 mg estradiol/day IVR treatment group has a withdrawal bleed (21 of 49 subjects), and 83% of subjects in the 0.10 mg estradiol/day IVR treatment group had a withdrawal bleed (52 of 64 subjects).

From these results we observe that more subjects in the estrogen-containing IVR treatment groups had withdrawal bleeding than the placebo IVR treatment group. This finding is not unexpected and demonstrates the estradiol proliferative effect on the endometrium for the estrogen-containing IVR treatment groups. In addition, twice as many subjects in the 0.10 mg estradiol/day treatment group had withdrawal bleeding than reported for the 0.05 mg estradiol/day IVR treatment group (83% versus 43%, respectively). This suggests a dose-dependent estrogen effect on the endometrium.

7.11. Labeling Safety Issues and Postmarketing Commitments

The proposed labeling for Tradename complies with the Agency's recommendation for estrogen-alone drug products

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

No estradiol acetate IVR is approved for use in the US. The 0.05 mg estradiol/day IVR (Menoring® 50) is approved in the UK for the relief of hot flushes, sweating at night, dryness or soreness of the vagina or pain during sexual intercourse in women who have had a hysterectomy. NDA 21-367/S-000 confirms that the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR are effective in the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. Therefore, labeling should indicate that the 0.05 mg estradiol/day IVR dosage strength is the lowest effective dose for these indications.

9. USE IN SPECIAL POPULATIONS

9.1 Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity. Comment on Adequacy of Applicant's Analyses.

In the submission, the Sponsor examined adverse events by age using two age categories, ≤ 55 years and ≥ 56 years of age. Of the 492 subjects in the ISS population (includes 75 subjects randomized to oral estradiol in Study HRT 8), 75% of subjects (369 of 492 subjects were ≤ 55 years of age and 25% of subjects were ≥ 56 years of age (124 of 492 subjects). Overall, a greater proportion of subjects ≤ 55 years of age reported at least 1 adverse event (78%) compared with 64% subjects ≥ 56 years of age. The adverse event reported most often in both age groups was headaches. Intermenstrual bleeding was reported more often by younger subjects compared with the older subjects while breast pain, back pain, and arthralgia were reported more often by older subjects compared with younger subjects.

There were too few subjects over the age of 65 to permit any assessment of adverse events in a geriatric population.

The majority of subjects in the ISS population (n = 492) were white (84%, 414 of 492 subjects), 16% were non-white (78 of 492 subjects). Among subjects in Study IVR 1002 and HRT 8, 77% and 99% were white. Therefore, it is not possible to adequately compare adverse events by race groups. Nonetheless, in the overall ISS population, the adverse event most often reported in both race groups was headache.

9.2. Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

A request for a pediatric waiver was submitted for NDA 21-367 on February 28, 2002. Tradename™ is only recommended for use in postmenopausal women.

Reviewer's Comments

A pediatric waiver should be granted.

9.3. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

The estrogen-containing IVRs in this submission were investigated in healthy postmenopausal. No data is available for other special populations. Tradename™ should not be used during pregnancy.

10. CONCLUSIONS AND RECOMMENDATIONS, AND LABELING

10.1. Conclusions Regarding Safety and Efficacy

The safety and efficacy data, presented in NDA 21-367/S-000, is adequate to support the approval of the 0.05 mg estradiol/day intravaginal ring (IVR) and the 0.10 mg estradiol/day IVR for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

10.2. Recommendations on Approvability

The data presented in this original NDA provides sufficient evidence from one US Phase III, placebo-controlled clinical trial (Study IVR 1002) and one UK Phase III, double-dummy, active-comparator clinical trial to support the safety and efficacy of two dosage strength intravaginal rings, 0.05 mg estradiol/day and 0.10 mg estradiol/day, for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. From a clinical perspective, the 0.05 mg estradiol/day IVR and the 0.10 mg estradiol/day IVR can be approved.

10.3. Labeling

The proposed labeling for Tradename was modified in accordance with the Division's labeling recommendations for estrogen drug products. In addition, the proposed labeling was revised to include information adapted from the Women's Health Initiative study as reported in JAMA, July 17, 2002, Volume 288, Number 3, pages 321-333.

Two dosage strengths are listed under the **DESCRIPTION** section: Tradename 0.05 mg/day and Tradename 0.10 mg/day.

Please see the attached labeling in **APPENDIX 1**. In summary:

1) Revisions have been made to the **CLINICAL PHARMACOLOGY** section under the **Pharmacokinetic** and **Drug Interactions** subsections to update the text.

2) The following revisions have been made to the **Clinical Studies** subsection:

- Revisions to the text under the **Effects on vasomotor symptoms** and **Effects on vulvar and vaginal atrophy** subsections.
- The Sponsor is requested to add two tables: Table 2 entitled, "Mean Change from Baseline in the Number of Moderate-to-Severe Vasomotor symptoms, ITT Population, LOCF", and Table 3 entitled, "Mean Change from Baseline in the Severity of Moderate-to-Severe Vasomotor Symptoms, ITT Population, LOCF".
- A subsection entitled, **Women's Health Initiative Studies** has been added.

3) Under the **CONTRAINDICATIONS** section, the listed contraindications have been revised and reordered, and the following contraindication has been added, "Active or recent arterial thromboembolic disease (e.g., stroke, myocardial infarction)."

4) Under the **WARNINGS** section, the listed warnings have been revised and reordered, a **Cardiovascular Disorder** subsection has been added including, **a. Coronary heart disease and stroke.** Under the ——— **Malignant Neoplasms** subsection, ——————— has been added. Revised language has been recommended for the following subsections, **Gallbladder Disease,** and Hypercalcemia. A **Visual Abnormalities** subsection has been added.

5) In the **PRECAUTIONS** section, revised language is recommended for the following subsections, **Impaired liver function and past history of cholestatic jaundice** and **Hypothyroidism.** The following subsection have been added, **Fluid retention, Hypocalcemia, Exacerbation of endometriosis,** and **Exacerbation of other conditions.**

6) In the **ADVERSE REACTIONS** section, ——————— under the phrase, "additional adverse reactions have been reported with estrogen ——— have been deleted.

7) Under the **DOSAGE AND ADMINISTRATION** section, the text has been revised to indicate that patients should be started at Tradename™ 0.05 mg/day.

The **PATIENT INFORMATION** insert has been modified in compliance with the plain language initiative and recommendations from the Division of Drug Marketing, Advertising and Communications (DDMAC), and the Division of Surveillance, Research & Communication Support (DSRCS).

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Labeling

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/s/

Theresa Van Der Vlugt
10/18/02 04:19:06 PM
MEDICAL OFFICER

Shelley Slaughter
10/18/02 04:23:01 PM
MEDICAL OFFICER
I have provided comments to this review and concur with the conclusions and recommendations.

Daniel A. Shames
10/21/02 12:01:31 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL