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#### REVIEW

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# Treatment of moderate to severe dyspareunia with intravaginal prasterone therapy: a review

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#### ABSTRACT

The loss of sex steroids (e.g. estradiol, dehydroepiandrosterone [DHEA], progesterone) that causes menopause commonly affects a woman's general health and produces bothersome physical changes that may interfere with normal sexual and genitourinary functioning. Although both over-the-counter and prescription treatments are available, there remains a large unmet need, as less than 10% of women are treated. Adrenal DHEA and its sulfate are the most abundant steroids in humans. Here we review the development of intravaginal prasterone, the synthetic equivalent to endogenous DHEA. Prasterone is approved by the US Food and Drug Administration for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Prasterone has been shown to decrease the pain associated with dyspareunia, and to improve vaginal pH, as well as superficial and parabasal cell counts, while maintaining serum hormone levels within the range of those seen in normal postmenopausal women. Unlike other menopausal prescription therapies, intravaginal prasterone does not carry a boxed warning, thus allowing the clinician and patient to engage in meaning-ful and reassuring discussion around a new approach that treats this common, debilitating condition.

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#### Introduction

Menopause is associated with an arrest of the ovarian synthesis of estrogen, progesterone, and dehydroepiandrosterone (DHEA), and its sulfate (DHEA-S), which are produced primarily by the adrenal glands, but also by the ovaries (Supplementary Figure 1)<sup>1</sup>. In the first year of menopause, women lose about 80% of their estrogens. Testosterone levels decline by about 50-75% from the early twenties to age 40-45 years but do not change significantly across the menopausal transition<sup>2</sup>. DHEA-S levels decline steadily with age and are not significantly related to menopause. By age 70 years, they are approximately 20-23% of their peak value<sup>3</sup>. Most importantly, serum testosterone simply results from the uncontrolled leakage of some testosterone made intracellularly from DHEA and is not a valid parameter of androgenic activity<sup>4</sup>. Thus, menopause itself is not associated with dramatic decreases in androgens but postmenopausal women can have significantly less endogenous androgens compared with younger women<sup>5</sup>. The loss of these sex steroids causes physical changes that may interfere with normal sexual and genitourinary functioning in a significant number of postmenopausal women<sup>6,7</sup>.

During perimenopause, menopause, and postmenopause, sex steroid-dependent tissues undergo atrophic changes

including epithelium thinning, altered appearance and function of smooth muscle cells, increased density of connective tissue, and fewer blood vessels<sup>8,9</sup>. Changes in vaginal flora associated with the loss of superficial cells, glycogen, and lactobacilli result in increased pH and the increased potential for vaginal and urinary tract infections and inflammation<sup>10</sup>. Decreases in vaginal blood flow and lubrication often result in dryness and dyspareunia<sup>11,12</sup>. In the vaginal epithelium, a lack of sex steroids causes a decrease in the proportion of superficial cells and an increase in the proportion of immature parabasal cells<sup>13</sup>. There is also less elasticity and vulvovaginal tissue is prone to petechiae, injury, and pain<sup>11</sup>.

#### Menopausal symptoms

A 2013 position statement by the North American Menopause Society (NAMS)<sup>14</sup> cited the REal Women's Vlews of Treatment Options for Menopausal Vaginal ChangEs (REVIVE) survey in which the impact of vulvovaginal atrophy (VVA) symptoms is described in more than 3000 postmeno-pausal women: 85% of partnered women had 'some loss of intimacy'; 59% indicated that VVA symptoms detracted from enjoyment of sex; 47% indicated that VVA interfered with their relationship; 29% reported that VVA had a negative

Supplemental data for this article can be accessed <u>here</u>.

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effect on sleep; and 27% reported that VVA had a negative effect on their general enjoyment of life. Despite this, only 7% of the surveyed women indicated that their health-care professional (HCP) initiated a discussion about VVA.

In 2014, in response to a concern that the term VVA was inadequate to describe the range of menopausal urogenital symptoms, the International Society for the Study of Women's Sexual Health and the NAMS proposed a new term – genitourinary syndrome of menopause (GSM)<sup>15</sup>. GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder, including symptomatic VVA<sup>15</sup>. This consensus statement also recognizes that androgen receptors are widely distributed in the vestibule and within its glands, with urogenital tissues responsive to androgens as well as estrogens.

With the decline of circulating sex steroids and precursors, GSM can start in perimenopause, increase during the early menopausal period, and further increase in the 2–3 years after menopause. The symptoms range in severity from mildly bothersome to unbearable<sup>16</sup>. Unlike vasomotor symptoms, the vaginal symptoms associated with GSM do not resolve spontaneously; rather, there is a progressive and cumulative negative effect over time<sup>9</sup>. Long-term therapy may be necessary to maintain urogenital health<sup>17</sup>.

Women spend more than one-third of their lives in the postmenopausal state. Over half of postmenopausal women report experiencing GSM<sup>18-22</sup>, and more than 75% report an impact on their sexual lives<sup>18</sup>. However, most postmenopausal women do not recognize these symptoms as part of a chronic condition associated with menopause that may require treatment. Many think the symptoms will subside over time or attribute them to a natural part of aging. Surveys have revealed that only 20–25% of women with GSM seek medical attention<sup>23,24</sup>.

The burden of these symptoms is significant. Thinning of the vaginal wall and decreased vaginal secretions may cause vaginal itching, burning, dryness, and even bleeding. Decreased lubrication and associated dryness may lead to dyspareunia often accompanied by associated sexual dysfunction<sup>25</sup>.

Both HCPs and patients find vaginal symptoms to be a sensitive topic that can be difficult to discuss<sup>21</sup>, as evidenced by numerous surveys<sup>21,26,27</sup>. Reasons given for not initiating the discussion included embarrassment (39%), belief that nothing could be done medically (26%), and belief that it is not an appropriate conversation to have with a HCP (23%). Only 36% of HCPs in the Revealing Vaginal Effects at Mid-Life (REVEAL) survey indicated that they 'often' discuss vaginal pain associated with sex with their patients<sup>28</sup>.

#### **Available therapies**

Currently available treatments for the symptoms of GSM include topical over-the-counter lubricants and moisturizers and prescription systemic and vaginal estrogen therapies. Non-hormonal lubricants and moisturizers can ameliorate

dyspareunia, but do not address declining levels of sex steroids or anatomic changes<sup>29</sup>. Although vaginal estrogen therapies can restore estrogen to the vaginal tissue and can reverse some atrophic changes, even low-dose estrogen therapies have been shown to increase serum estradiol above normal levels<sup>30-32</sup>. However, these products carry Food and Drug Administration (FDA) boxed warnings identical to the risks associated with systemic estrogen based on extrapolation of data from trials of either oral estrogen or combined oral estrogen-progestin therapy. Without large, long-term prospective studies that confirm a safer adverse event profile for vaginal estrogen compared to systemic therapies, the class label boxed warning for all estrogenbased products will remain. Thus, patient perceptions of safety based upon class labeling and the time needed by HCPs to convey information about these warnings are obstacles to acceptance and/or adherence to estrogen therapy<sup>28</sup>. The oral selective estrogen receptor modulator ospemifene is another alternative for these symptoms; however, it carries a modified boxed warning<sup>33</sup>.

#### **Compounded hormones**

FDA-approved prescription drugs are required to demonstrate safety and efficacy and to be manufactured according to current Good Manufacturing Practices to help ensure the identity, strength, guality, and purity of drugs by requiring adequate control of manufacturing operations. In contrast, compounded medications are not FDA approved, have not undergone rigorous testing, and do not contain labeling to support the discussion of risks and benefits for informed decision-making. One unintended consequence following the Women's Health Initiative was the rise of compounded hormones, which may appeal to patients because of their perceived lack of risk, as they are not labeled in the same manner as FDA-approved estrogen therapies<sup>34</sup>. Both the American College of Obstetricians and Gynecologists and the NAMS<sup>35</sup> have publicly stated their concerns regarding the use of compounded hormone therapies. Further, the FDA has recently taken steps to regulate this area more aggressively<sup>36</sup>.

### FDA approval requirements for treatment of VVA symptoms

In 2003, the FDA published a draft guidance providing recommendations to industry concerning the conduct of clinical studies of estrogen and estrogen/progestin drug products for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of VVA associated with menopause<sup>37</sup>. These recommendations impact product approval and indications. For the treatment of moderate to severe symptoms of VVA, study subjects are required to have  $\leq$ 5% superficial cells on a vaginal smear, to have a vaginal pH >5.0, and to have self-identified one moderate to severe symptom that is the 'most bothersome symptom' (MBS) to her. The MBS must be one of the five symptoms recognized by the FDA: vaginal dryness, vaginal and/or vulvar irritation/



Figure 1. Metabolism of dehydroepiandrosterone (DHEA) after its uptake in vaginal cells<sup>1</sup>. 4-DIONE, androstenedione; A-dione, 5a-androstane-3,17-dione; ADT, androsterone; ADT-G, androsterone glucuronide; ADT-S, androsterone sulfate;  $3\alpha$ -DIOL,  $3\alpha$ -androstanediol;  $3\beta$ -HSD,  $3\beta$ -hydroxysteroid dehydrogenase; DHT, dihydrotestosterone; E<sub>1</sub>, estrone; E<sub>2</sub>, estradiol; Testo, testosterone.

itching, dysuria, vaginal pain associated with sexual activity, or vaginal bleeding associated with sexual activity. As the enrollment criteria were restricted to a single MBS per clinical efficacy study, the indication for medications approved after 2003 have been based on a single symptom. Currently, only Osphena<sup>®33</sup> and Intrarosa<sup>®38</sup> have been approved and are available for prescribing, following release of this guidance for prescribing for moderate to severe dyspareunia. Medications approved prior to 2003 are labeled for 'atrophic vaginitis' or 'vulvar and vaginal atrophy'.

## The role of DHEA in the premenopausal and postmenopausal states

In menopause, approximately 80% of DHEA comes from the adrenals and 20% from the ovaries<sup>4</sup>. DHEA is rapidly transformed into its more stable sulfate, DHEA-S; it is also a precursor for intracellular conversion by dehydrogenases, hydroxylases, aromatase, and other enzymes in specific target tissues into estrone, estradiol, testosterone, and dihydrotestosterone (Figure 1)<sup>39,40</sup>. Final intracellular sex steroid inactivation occurs through glucuronidation by enzymes in the uridine diphosphate-glucuronosyltransferase family<sup>41</sup>. This proposed conversion and inactivation mechanism has been described as intracrinology to distinguish it from other endocrine mechanisms of hormone regulation<sup>1</sup>.

#### Intravaginal prasterone

Prasterone (Intrarosa<sup>®</sup>) is a steroid approved by the US FDA in 2016 at a dose of 6.5 mg and a concentration of 0.50% for

the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause<sup>38</sup>. Prasterone is administered as a vaginal insert once daily at bedtime, does not carry a boxed warning in its label, and has no restrictions on duration of use. Prasterone is contraindicated in the presence of undiagnosed abnormal genital bleeding. Postmenopausal women with undiagnosed, persistent, or recurring genital bleeding should be evaluated before considering treatment with prasterone. Prasterone has not been studied in breast cancer.

#### **Preclinical studies**

Androgens are involved in the regulation of vaginal and vestibular lubrication, smooth muscle activity, and blood flow<sup>42,43</sup>; they are also capable of inducing vaginal mucification in the absence of estrogens<sup>44</sup>. In female rats 9 months post ovariectomy, DHEA (80 mg/kg) was associated with a highly mucified epithelium, and increased muscularis thickness by  $50 \pm 2 \,\mu$ m (mean  $\pm$  standard deviation) and collagen fiber compactness in the lamina propria<sup>45</sup>. Histopathologic examination after application of DHEA (30 mg) to the dorsal skin of ovariectomized rats twice daily for 1, 3, or 6 months showed proliferation and mucification of the vaginal epithelium and complete reversal of the signs of vaginal atrophy. The endometrium remained atrophic at all time intervals during treatment<sup>46</sup>. In another study in ovariectomized rats, 2 weeks of daily intravaginal DHEA (0.33 mg, 0.66 mg, or 1 mg) increased serum DHEA, DHEA-S, and androstenediol; while serum testosterone, estradiol, estrone, and dihydrotestosterone remained below detectable levels<sup>47</sup>.

#### **Clinical development of prasterone**

The intravaginal prasterone clinical trials are detailed in Supplementary Table 1. The bioavailability of DHEA and its metabolites was assessed in a Phase 1/2 randomized, placebo-controlled, double-blind study in postmenopausal women (n = 40) receiving daily intravaginal applications of prasterone (0.5%, 1.0%, or 1.8%) or placebo. After 7 days of treatment, the maturation value of the vaginal epithelial cells was significantly increased, and vaginal pH was significantly decreased at all DHEA doses. Serum concentrations of estradiol and testosterone remained within the values found in normal postmenopausal women<sup>48–50</sup> for the 0.5% and 1. 0% doses<sup>49,51</sup>.

Five randomized, multicenter, double-blind, Phase 3 studies of once-daily intravaginal prasterone were conducted to examine the dose and scheduling in more than 1500 postmenopausal women with VVA. One placebo-controlled trial assessed serum steroid levels in postmenopausal women (n = 218; age 42-74 years) during 12 weeks of daily intravaginal administration of prasterone (0.25%, 0.50%, or 1.0%) or placebo<sup>52</sup>. The serum levels of DHEA and 11 of its metabolites remained at or below the normal postmenopausal limits at day 1 and weeks 2, 4, 8, and 12. At 12 weeks, 0.5% prasterone caused a  $45.9 \pm 5.31\%$  (mean  $\pm$  standard deviation) decrease in parabasal cells, a 6.8 ± 1.29% increase in superficial cells, a  $1.3 \pm 0.13$  unit decrease in vaginal pH, and a  $1.5 \pm 0.14$  score unit decrease in the severity of vaginal symptoms (all p < 0.0001 vs. placebo). Similar changes to vaginal secretions, color, epithelial surface thickness, and epithelial integrity were noted on gynecologic examination. One trial that evaluated a twice-weekly dosing regimen for vaginal dryness failed to meet statistical significance<sup>53</sup>. As a result, the pivotal registration trials focused on daily administration at bedtime.

Two pivotal, Phase 3, randomized, double-blind trials confirmed the efficacy of intravaginal prasterone for moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. In trial 1, postmenopausal women (n = 253; mean age 58.6 years) with the MBS of moderate to severe dyspareunia received prasterone (0.25% and 0.50%) or placebo as a vaginal insert once daily for 12 weeks. The coprimary endpoints were changes from baseline to week 12 in percent vaginal parabasal and superficial cells, vaginal pH, and dyspareunia score. Secondary endpoints included vaginal dryness and vulvovaginal irritation/itching<sup>54</sup>. As the 0.25% dose is not approved or available, we present here only the results for the FDA-approved 0.50% dose. After 12 weeks of daily treatment, 0.50% prasterone significantly decreased the percentage of parabasal cells, increased the percentage of superficial cells, and decreased vaginal pH compared with placebo (all p < 0.0001). By week 12, moderate to severe dyspareunia, self-identified as the MBS, significantly improved by 0.40 severity score units (46%; p = 0.013) versus placebo after treatment with prasterone (Figure 2(a-d)). The secondary endpoint of moderate to severe vaginal dryness improved significantly (p = 0.013); irritation/itching also improved, but the change was not significantly different from placebo. Pelvic examinations that included

Pap smears noted improvements in secretions, epithelial integrity, and epithelial surface thickness and color.

Pivotal trial 2, also in postmenopausal women (n = 554; mean age 59.5 years), employed a similar study design and endpoints as trial 1, except only the 0.5% dose of prasterone and placebo were used<sup>55</sup>. The results were similar to those of trial 1, with significant decreases in the percentage of parabasal cells (p < 0.0001 vs. placebo), increases in superficial cells (p < 0.0001), decreases in vaginal pH (p < 0.0001), and improvement of pain during sexual activity (p = 0.0002) at 12 weeks (Figures 2(a–d)). Although not a primary endpoint in the study, moderate to severe vaginal dryness (present in 84.0% of women) improved by 23% (p = 0.004 vs. placebo). On gynecological physical evaluation, vaginal secretions, epithelial integrity, and epithelial surface thickness and color all improved by 86–121% (p < 0.0001 vs. placebo). This separation of intravaginal prasterone from the placebo group is particularly noteworthy as the vehicle contains Witepsol, a fatty acid glycerol ester base that likely exerted a daily emollient effect in relieving some dyspareunia and dryness symptoms in the vehicle-only arm above and beyond that usually seen with a placebo effect alone. The vehicle alone had minimal effect on the objective parameters of pH and vaginal maturation index.

While there are no head-to-head trials of intravaginal prasterone versus vaginal estrogen, and cross-trial comparisons have limitations, one review of Phase 3 clinical trials of the effect of daily intravaginal prasterone 6.5 mg (0.50%), daily vaginal conjugated equine estrogens (CEE; 0.3 mg 21 days on/ 7 days off) or twice-weekly 0.3 mg CEE, and vaginal estradiol 10 µg daily for 2 weeks then twice-weekly for 10 weeks on moderate to severe dyspareunia showed a decrease in the total dyspareunia severity score of 1.27–1.63 units with prasterone, 1.4 units with CEE, and 1.23 units with estradiol<sup>56</sup>.

#### Adverse events

In the four placebo-controlled, 12-week clinical trials of intravaginal prasterone, vaginal discharge was the most frequently reported treatment-emergent adverse event in the prasterone treatment group (incidence  $\geq 2\%$  and the only one greater than placebo)<sup>38</sup>.

#### Fifty-two-week, open-label safety study

The fifth trial was a Phase 3, open-label, long-term safety study of intravaginal prasterone in postmenopausal women (n = 530; mean age 57.9 years, range 43–75 years) with mild, moderate, or severe dyspareunia, vaginal dryness, and/or irritation/itch due to VVA associated with menopause. Participants were treated daily with 0.50% intravaginal prasterone for up to 52 weeks. The symptoms and signs of vaginal atrophy were evaluated as a secondary objective<sup>57,58</sup>. A total of 435 women were exposed to prasterone for 52 weeks, 24 women for  $\geq$ 26 weeks but <52 weeks, and 62 women for <26 weeks. Vaginal discharge (74 cases) and abnormal Pap smear at 52 weeks were the most frequently (incidence  $\geq$ 2%) reported treatment emergent adverse



Figure 2. Changes in (a) parabasal cells, (b) superficial cells, (c) vaginal pH, and (d) moderate to severe dyspareunia score in the intent-to-treat population (all women who received at least one dose of the study drug or placebo) using analysis of covariance, with treatment as the main factor and baseline value as the covariate. Score based on severity of dyspareunia: none = 0, mild = 1, moderate = 2, and severe = 3. \*p < 0.0001 vs. placebo; †difference vs. placebo from baseline to week 12; ‡p < 0.05 vs. placebo; §p < 0.001 vs. placebo.

events. An abnormal Pap smear was observed in 11 of 521 subjects (2.1%), with the majority (10 of 11 subjects) being atypical squamous cells of undetermined significance and five subjects being human papilloma virus negative<sup>38</sup>. Improvements in dyspareunia severity score (Supplementary Figure 2), percentage of parabasal cells and superficial cells, and vaginal pH were noted as early as 12 weeks. The improvements continued and were clinically and statistically significant at weeks 26 and 52<sup>57</sup> (p<0.0001 vs. baseline).

#### Serum steroid concentrations

The upper limit for normal postmenopausal estradiol levels<sup>48</sup>, based on validated mass spectrometry, first determined as 9.3 pg estradiol/ml<sup>49</sup>, and similar levels of 10 pg/ml have been recognized by the Mayo Clinical Medical Laboratories<sup>48,59</sup>. Using this parameter as background, there was no meaningful change in the serum levels of estradiol or in the metabolism of the DHEA-derived steroids at 12, 26, or 52 weeks of daily intravaginal administration of 0.50% DHEA compared to baseline. All measurements were done based on sensitive validated liquid chromatography-tandem mass spectrometry<sup>58</sup>.

#### **Endometrial safety**

The endometrial safety of intravaginal prasterone has been examined in three Phase 3, multicenter, placebo-controlled trials and one long-term, open-label safety trial. In total, endometrial biopsies were obtained for 722 women aged 40–75 years who were treated with prasterone (0.25%, 0.50%, or 1.0%) for 12–52 weeks. Atrophic or inactive endometrium was observed in 668 women for whom there was sufficient material for histologic evaluation, with no proliferation or hyperplasia seen, confirming a lack of stimulatory effect due to intravaginal prasterone (Table 1)<sup>54,60</sup>. This is consistent with the absence of aromatase expression in the normal endometrium, which is necessary to convert testosterone into estradiol and androstenedione into estrone, and aligns with the lack of a boxed warning for endometrial hyperplasia or cancer in the prasterone label.

#### Summary

For many postmenopausal women, decreased sex steroids leads to a group of genital and urinary symptoms called GSM, which are usually chronic and progressive without

#### Table 1. Endometrial biopsy results in women treated with intravaginal prasterone<sup>60</sup>.

				Віор	Biopsy result	
Study number	Duration (weeks)	Dose	Endometrial biopsy at baseline and EOS (n)	Atrophic/inactive (n)	No/insufficient tissue (n)	
NCT01846442	12	Placebo	25	24	1	
		0.25% (3.25 mg)	27	27	0	
		0.50% (6.5 mg)	29	28	1	
		1.00% (13 mg)	30	30	0	
NCT01256684	12	Placebo	27	25	2	
		0.25% (3.25 mg)	25	23	2	
		0.50% (6.5 mg)	28	23	5	
NCT01358760a	12	Placebo	81b	70	9	
		0.25% (3.25 mg)	74	67	7	
		0.50% (6.5 mg)	72	66	6	
NCT01256671	>12/<52	0.50% (6.5 mg)	15	15	0	
	52		422	389	33	
Total prasterone tr	eated		722	668	54	

EOS, end of study.

<sup>a</sup>Daily for 2 weeks then twice-weekly for 10 weeks.

<sup>b</sup>Two women in the placebo group had weakly proliferative endometrium at week 12. An estrogen signature of serum sex steroids was observed in week 12.

treatment. Many women are unaware of GSM as a condition and assume symptoms are due to aging. Further, they are reluctant to discuss their vaginal health with their HCP and few HCPs initiate the discussion<sup>61</sup>. There is a need for increased awareness and responsiveness on the part of HCPs to educate their patients and to assess, discuss, and adequately treat GSM symptoms in postmenopausal women.

Over-the-counter products can provide temporary relief for the symptoms of GSM, but they do not address the underlying pathophysiology of the condition. Although vaginal estrogen therapy is effective in relieving some of the symptoms of GSM, many women are uncomfortable with or not eligible for vaginal estrogen therapy based upon contraindications for use (e.g. history of thromboembolic disorder, such as stroke or myocardial infarction; history of deep vein thrombosis and/or estrogen-dependent neoplasia).

While not FDA approved, several studies have investigated intravaginal testosterone alone or in combination with CEEs as a potential treatment for VVA, recognizing the role that androgens may play in vaginal health. While some studies' results have shown promise for GSM, studies have been limited. Adequately powered placebo-controlled trials are needed for intravaginal testosterone prior to clinical use<sup>62</sup>.

Intravaginal prasterone provides a treatment for providers and patients that avoids the aforementioned estrogen contraindications, allowing the clinician to focus on counseling without distracting patients with fearful warnings. Moreover, prasterone is novel in its conversion into important androgens, as well as estrogens, and has undergone robust and formal drug development to confirm its efficacy and safety.

The efficacy and safety of prasterone has been evaluated in four placebo-controlled, 12-week trials and one 52-week, open-label safety study in postmenopausal women meeting the FDA criteria for moderate to severe dyspareunia. At a daily bedtime intravaginal dose of 0.50% (6.5 mg), prasterone, a synthetic version of endogenous DHEA, is converted intracellularly at the local tissue level to androgens and estrogens, while sex steroids remain within the normal range of postmenopausal women. Prasterone has shown clinically and statistically significant improvements. In both pivotal trials, treatment with intravaginal prasterone was associated with a significant reduction in moderate to severe dyspareunia due to menopause compared with placebo: -1.27 (0.40 severity score units over placebo, 46%; p = 0.013) and -1.42 (0.36 severity score units over placebo, 34%; p < 0.0002) in pivotal trial 1 and 2, respectively<sup>54,55</sup>.

Many postmenopausal women suffering with GSM symptoms identify painful intercourse as the MBS associated with VVA. Prasterone can provide a safe, effective, and innovative approach to this common and often debilitating condition<sup>62</sup>.

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