A Guide to Talking to Your Healthcare Provider
About Moderate to Severe Painful Sex due to Menopause

1 What could be causing my painful sex?

2 Is this a common problem?

3 Is this serious enough to be considered a medical issue that needs treatment?

4 What are my treatment options?

5 What happens if I choose not to treat it? Will the pain go away on its own or will it get worse?

6 What is INTRAROSA® (prasterone) vaginal inserts 6.5 mg?

7 Would INTRAROSA be a potential treatment option for me?

8 How should I use INTRAROSA and do I use it every day?

9 What are the possible side effects of INTRAROSA?

10 How long should I use INTRAROSA for?

Indication
INTRAROSA (prasterone) is a steroid indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Important Safety Information
INTRAROSA is contraindicated in women with undiagnosed abnormal genital bleeding. Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. INTRAROSA has not been studied in women with a history of breast cancer.

Please see additional Important Safety Information on next page. Please see following pages for full Prescribing Information and Instructions for Use.
It’s good to have your own questions before seeing your healthcare provider; however, these are some questions that may come up during your visit.

1. When did the moderate to severe painful sex begin?

2. Where do you feel the pain?

3. How would you describe the severity of your pain? Moderate? Severe?

4. Is it painful every time you have sex or only in certain situations?

5. Are you able to discuss your concerns with your partner?

Important Safety Information (cont’d)
In four 12-week randomized, placebo-controlled clinical trials, the most common adverse reaction with an incidence ≥2 percent was vaginal discharge. In one 52-week open-label clinical trial, the most common adverse reactions with an incidence ≥2 percent were vaginal discharge and abnormal Pap smear.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see following pages for full Prescribing Information and Instructions for Use.
INTRAROSA™ is a steroidal indication for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. (1)

**INDICATIONS AND USAGE**

**Dosage and Administration**

1. Administer one INTRAROSA vaginal insert once daily at bedtime, using the provided applicator.
2. Administer one INTRAROSA vaginal insert once daily at bedtime.

**DOSAGE FORMS AND STRENGTHS**

Vaginal Insert: 6.5 mg of prasterone. (3)

**CONTRAINDICATIONS**

Undiagnosed abnormal genital bleeding. (4)

**ADVERSE REACTIONS**

In a 52-week clinical trial [92% - White Caucasian non-Hispanic women, 6% - Black or African American women, and 2% - “Other” women, average age 57.9 years of age, 6.1

58.8 years of age (range 40 to 80 years of age)], vaginal discharge is the most frequently reported treatment-emergent adverse reaction in the INTRAROSA treatment group with an incidence of 43 to 75 years of age], vaginal discharge and abnormal Pap smear at 52 weeks were the most frequent adverse reactions in women receiving INTRAROSA™ (range 43 to 75 years of age), with an incidence of

2 percent. There were 74 cases of vaginal discharge (14.2 percent) and 11 cases of abnormal Pap smear at 52 weeks were the most frequently reported treatment-emergent adverse reaction in women receiving INTRAROSA™ treatment group with an incidence of

2 percent. There were 74 cases of vaginal discharge (14.2 percent) and 11 cases of abnormal Pap smear (2.1 percent) in 521 participating postmenopausal women.

Adverse reactions occurring with a frequency of 2 percent or greater in the open-label 52-week clinical trial in postmenopausal women receiving INTRAROSA™ and placebo are listed below:

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Risk Summary

INTRAROSA™ is indicated only in postmenopausal women. There are no data with INTRAROSA™ in pregnancy use regarding any drug-associated risks. Animal reproduction studies have not been conducted with prasterone.

**8.2 Lactation**

Risk Summary

INTRAROSA™ is indicated only in postmenopausal women. There is no information on the presence of prasterone in human milk, the effects on the breastfeeding infant, or the effects on milk production.

**8.3 Pediatric Use**

Safety and effectiveness have not been established in pediatric patients.

**8.4 Geriatric Use**

Of the 1522 prasterone-treated postmenopausal women enrolled in the four placebo-controlled 12-week and one open-label 52-week clinical trial, 19 and 11 percent, respectively, were 65 years of age or older.

**11 DESCRIPTION**

PRASERTONE is an inactive endogenous steroid and is converted into active androgens and/or estrogens. The mechanism of action of INTRAROSA in postmenopausal women with vulvar and vaginal atrophy is not fully established.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Prasterone is an inactive endogenous steroid and is converted into active androgens and/or estrogens. The mechanism of action of INTRAROSA in postmenopausal women with vulvar and vaginal atrophy is not fully established.

**12.3 Pharmacokinetics**

In a study conducted in postmenopausal women, administration of the INTRAROSA vaginal insert once daily for 7 days resulted in a mean prasterone Cmax and area under the curve from 0 to 24 hours (AUC0-24) at Day 7 of 4.4 ng/mL and 56.2 ng/hr/mL, respectively, which were significantly higher than those in the group treated with placebo (Table 1). The Cmax and AUC0-24 of the metabolites testosterone and estradiol were also slightly higher in women treated with the INTRAROSA vaginal insert compared to those receiving placebo.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Placebo (N=9)</th>
<th>INTRAROSA (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasterone</td>
<td>Cmax (ng/mL)</td>
<td>1.60 (±0.85)</td>
</tr>
<tr>
<td></td>
<td>AUC0-24 (ng/hr/mL)</td>
<td>24.82 (±14.31)</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Cmax (ng/mL)</td>
<td>0.12 (±0.04)</td>
</tr>
<tr>
<td></td>
<td>AUC0-24 (ng/hr/mL)</td>
<td>2.58 (±0.94)</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Cmax (ng/mL)</td>
<td>3.33 (±1.31)</td>
</tr>
<tr>
<td></td>
<td>AUC0-24 (pg/hr/mL)</td>
<td>66.49 (±20.70)</td>
</tr>
</tbody>
</table>

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**

Vaginal Insert: 6.5 mg of prasterone. (3)

**16.2 Storage and Handling**

Each INTRAROSA (prasterone) vaginal insert contains 6.5 mg of prasterone in 1.3 ml of off-white hard fat (Witepsol).

**17 PATIENT COUNSELING INFORMATION**

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

**FULL PRESCRIBING INFORMATION: CONTENTS**

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2. DOSAGE AND ADMINISTRATION
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
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7. USE IN SPECIFIC POPULATIONS
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10. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
11. DESCRIPTION
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13. NONCLINICAL TOXICOLOGY
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16. PATIENT COUNSELING INFORMATION

Revised: 04/2017
The primary efficacy results obtained in the Intent-to-Treat (ITT) population in Trial 2 are shown in Table 3.

### Table 3: Efficacy Summary in Primary 12-Week Trial 2: ITT Population (LOCF)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>INTRAROSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyspareunia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean Severity</td>
<td>2.56</td>
<td>2.54</td>
</tr>
<tr>
<td>Week 12 Mean Severity</td>
<td>1.30</td>
<td>1.33</td>
</tr>
<tr>
<td>Mean Change in Severity (SD)</td>
<td>-1.06 (1.04)</td>
<td>-1.42 (1.00)</td>
</tr>
<tr>
<td>Difference from Placebo1</td>
<td>-</td>
<td>-0.35</td>
</tr>
<tr>
<td>p-value2</td>
<td></td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td><strong>% Superficial Cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean</td>
<td>1.84</td>
<td>1.02</td>
</tr>
<tr>
<td>Week 12 Mean</td>
<td>2.78</td>
<td>1.22</td>
</tr>
<tr>
<td>Mean Change (SD)</td>
<td>2.75 (3.33)</td>
<td>10.20 (10.35)</td>
</tr>
<tr>
<td>Difference from Placebo1</td>
<td>-</td>
<td>8.46</td>
</tr>
<tr>
<td>p-value2</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>% Parabasal Cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean</td>
<td>3.50</td>
<td>3.74</td>
</tr>
<tr>
<td>Week 12 Mean</td>
<td>3.48</td>
<td>3.79</td>
</tr>
<tr>
<td>Mean Change (SD)</td>
<td>3.52 (3.79)</td>
<td>3.70 (3.95)</td>
</tr>
<tr>
<td>Difference from Placebo1</td>
<td>-</td>
<td>0.68</td>
</tr>
<tr>
<td>p-value2</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Vaginal pH:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>INTRAROSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Mean</td>
<td>4.27</td>
<td>4.57</td>
</tr>
<tr>
<td>Week 12 Mean</td>
<td>4.65</td>
<td>4.79</td>
</tr>
<tr>
<td>Mean Change (SD)</td>
<td>-0.12 (1.06)</td>
<td>-0.35 (1.00)</td>
</tr>
<tr>
<td>Difference from Placebo1</td>
<td>-</td>
<td>-0.22</td>
</tr>
<tr>
<td>p-value2</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

1 Difference from placebo = INTRAROSA (Week 12 mean – Baseline mean) – Placebo (Week 12 mean – Baseline mean).

1 ANCOVA: Treatment as the main factor and Baseline value as the covariate.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis**

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with prasterone. Two metabolites of prasterone, testosterone and estradiol, are carcinogenic in animal studies.

**Mutagenesis**

Prasterone was not genotoxic in the in vitro bacterial mutagenesis assay (Ames test), the in vitro chromosomal aberrations assay with human peripheral blood lymphocytes, and in vivo in the mouse bone marrow micronucleus assay.

**Fertility**

Fertility studies were not conducted with prasterone.

### 14 CLINICAL STUDIES

The effectiveness of INTRAROSA on moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause was examined in two primary 12-week placebo-controlled efficacy trials.

The first clinical trial (Trial 1) was a 12-week randomized, double-blind and placebo-controlled trial that enrolled 255 generally healthy postmenopausal women between 40 to 75 years of age (mean 59.5 years) who, at baseline, identified moderate to severe dyspareunia as their most bothersome symptom of vulvar and vaginal atrophy. In addition to moderate to severe dyspareunia, women had ≤ 5% superficial cells on vaginal smear and a vaginal pH > 5. Women were randomized in a 1:1:1 ratio between three treatment groups who received daily INTRAROSA (n=87), one active comparator vaginal insert (n=87), or placebo (n=81). All women were reassessed for improvement from Baseline to Week 12 for four co-primary efficacy endpoints: most bothersome moderate to severe symptom of dyspareunia, the percentage of vaginal superficial cells, the percentage of parabasal cells, and vaginal pH. The primary endpoints and study conduct were the same or similar to those in Trial 1.

The primary efficacy results obtained in the Intent-to-Treat (ITT) population in Trial 1 are shown in Table 2.

### Table 2: Efficacy Summary in Primary 12-Week Trial 1: ITT Population (LOCF)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>INTRAROSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyspareunia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean Severity</td>
<td>2.58</td>
<td>2.63</td>
</tr>
<tr>
<td>Week 12 Mean Severity</td>
<td>1.71</td>
<td>2.36</td>
</tr>
<tr>
<td>Mean Change in Severity (SD)</td>
<td>-0.87 (0.95)</td>
<td>-2.05 (2.00)</td>
</tr>
<tr>
<td>Difference from Placebo1</td>
<td>-</td>
<td>-0.46</td>
</tr>
<tr>
<td>p-value2</td>
<td></td>
<td>0.0032</td>
</tr>
<tr>
<td><strong>% Superficial Cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean</td>
<td>4.73</td>
<td>4.68</td>
</tr>
<tr>
<td>Week 12 Mean</td>
<td>4.64</td>
<td>4.36</td>
</tr>
<tr>
<td>Mean Change (SD)</td>
<td>0.09 (2.00)</td>
<td>0.32 (5.49)</td>
</tr>
<tr>
<td>Difference from Placebo1</td>
<td>-</td>
<td>0.27</td>
</tr>
<tr>
<td>p-value2</td>
<td></td>
<td>0.043</td>
</tr>
<tr>
<td><strong>% Parabasal Cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean</td>
<td>66.48</td>
<td>65.05</td>
</tr>
<tr>
<td>Week 12 Mean</td>
<td>66.66</td>
<td>65.61</td>
</tr>
<tr>
<td>Mean Change (SD)</td>
<td>-0.22 (4.23)</td>
<td>-0.24 (4.67)</td>
</tr>
<tr>
<td>Difference from Placebo1</td>
<td>-</td>
<td>0.28</td>
</tr>
<tr>
<td>p-value2</td>
<td></td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>Vaginal pH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean</td>
<td>4.31</td>
<td>4.47</td>
</tr>
<tr>
<td>Week 12 Mean</td>
<td>4.41</td>
<td>4.43</td>
</tr>
<tr>
<td>Mean Change (SD)</td>
<td>-0.12 (0.69)</td>
<td>-0.12 (0.69)</td>
</tr>
<tr>
<td>Difference from Placebo1</td>
<td>-</td>
<td>0.14</td>
</tr>
<tr>
<td>p-value2</td>
<td></td>
<td>0.0003</td>
</tr>
</tbody>
</table>

1 Difference from placebo = INTRAROSA (Week 12 mean – Baseline mean) – Placebo (Week 12 mean – Baseline mean).

1 ANCOVA: Treatment as the main factor and Baseline value as the covariate.
What is INTRAROSA vaginal inserts?
INTRAROSA vaginal inserts are a prescription medicine used in women after menopause to treat moderate to severe pain during sexual intercourse caused by changes in and around the vagina that happen with menopause.

Do not use INTRAROSA vaginal inserts if you have vaginal bleeding that has not been checked by your healthcare provider.

Before using INTRAROSA vaginal inserts, tell your healthcare provider about all of your medical conditions, including if you:
• have, have had, or think you may have had breast cancer. Prasterone, an ingredient in INTRAROSA vaginal inserts, is changed in your body to estrogen. Estrogen medicines are not for use in women who have, have had, or think they may have had breast cancer.
• are pregnant or plan to become pregnant. INTRAROSA is only for use in women who are past menopause. It is not known if INTRAROSA vaginal inserts will harm your unborn baby.
• are breastfeeding or plan to breastfeed. INTRAROSA vaginal inserts are only for use in women who are past menopause. It is not known if INTRAROSA passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use INTRAROSA vaginal inserts?
• See the Instructions for Use at the end of this Patient Information for detailed instructions about the right way to use INTRAROSA vaginal inserts.
• Use INTRAROSA vaginal inserts exactly how your healthcare provider tells you to use it.
• Place 1 INTRAROSA vaginal insert in your vagina one time each day at bedtime, using the applicator that comes with INTRAROSA vaginal inserts.

What are the possible side effects of INTRAROSA vaginal inserts?
The most common side effects of INTRAROSA vaginal inserts are vaginal discharge and changes on Pap smear.

These are not all of the possible side effects of INTRAROSA vaginal inserts.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store INTRAROSA vaginal inserts?
• Store INTRAROSA vaginal inserts between 41°F to 86°F (5°C to 30°C).
• INTRAROSA vaginal inserts can be stored at room temperature or in the refrigerator.

Keep INTRAROSA vaginal inserts and all medicines out of the reach of children.

General Information about the safe and effective use of INTRAROSA vaginal inserts.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use INTRAROSA vaginal inserts for a condition for which it was not prescribed. Do not give INTRAROSA vaginal inserts to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about INTRAROSA vaginal inserts that is written for health professionals.

What are the ingredients in INTRAROSA vaginal inserts?
Active ingredient: prasterone
Inactive ingredient: off-white hard fat (Witepsol)

For more information, go to www.intrarosa.com or call 1-877-411-2510.

Instructions for Use

How should I use INTRAROSA vaginal inserts?
• INTRAROSA is a vaginal insert that you place in your vagina with an applicator that comes with INTRAROSA vaginal inserts.
• Use 1 INTRAROSA vaginal insert, one time each day at bedtime.
• Each applicator is for one time use only.
• Empty your bladder and wash your hands before handling the vaginal insert and applicator.
• Tear off 1 vaginal insert along the perforations from the 7-vaginal insert strip.

STEP 1
1a. Remove 1 applicator from the package.
1b. Pull back on the plunger until it stops to activate the applicator. The applicator must be activated before use. Place the applicator on a clean surface.

STEP 2
Slowly pull the plastic tabs on the vaginal insert away from each other while keeping the vaginal insert still between your fingers. Carefully remove the vaginal insert from the plastic wrap. If a vaginal insert falls on an unsanitary surface, replace it with a new one.

STEP 3
Place the flat end of the vaginal insert into the open end of the activated applicator as shown. You are now ready to insert the vaginal insert into your vagina.

STEP 4
Hold the applicator between your thumb and middle finger. Leave your index (pointer) finger free to press the applicator plunger after the applicator is inserted into your vagina.

STEP 5
Select the position for insertion of the vaginal insert that is most comfortable for you.
5a. Lying position
5b. Standing position

STEP 6
Gently slide the vaginal insert end of the applicator into your vagina as far as it will comfortably go.

Do not use force.

STEP 7
Press the applicator plunger with your index (pointer) finger to release the vaginal insert. Remove the applicator and throw it away after use.