

# INTROVALE- levonorgestrel and ethinyl estradiol Xiromed, LLC.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INTROVALE safely and effectively. See full prescribing information for INTROVALE.

Introvale®

Levonorgestrel and Ethinyl Estradiol Tablets, USP

0.15 mg/0.03 mg

for oral use

Initial U.S. Approval: 1982

### WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

*See full prescribing information for complete boxed warning.*

- Introvale (levonorgestrel and ethinyl estradiol tablets) is contraindicated in women over 35 years old who smoke. (4)
- Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)

### RECENT MAJOR CHANGES

Warnings and Precautions, Malignant Neoplasms (5.11)

04/2022

### INDICATIONS AND USAGE

Introvale is an estrogen/progestin COC indicated for use by women to prevent pregnancy. (1)

### DOSAGE AND ADMINISTRATION

- Take one tablet daily by mouth at the same time every day for 91 days. (2.1)
- Take tablets in the order directed on the Extended-Cycle Blister Cards. (2.2)

### DOSAGE FORMS AND STRENGTHS

Introvale (levonorgestrel and ethinyl estradiol tablets, USP) consists of 84 round, peach tablets containing 0.15 mg of levonorgestrel and 0.03 mg of ethinyl estradiol, and 7 round, white inert tablets. (3)

### CONTRAINDICATIONS

- A high risk of arterial or venous thrombotic diseases (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations (4)

### WARNINGS AND PRECAUTIONS

- **Thrombotic disorders and other vascular problems:** Stop levonorgestrel and ethinyl estradiol if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- **Liver disease:** Discontinue levonorgestrel and ethinyl estradiol if jaundice occurs. (5.2)
- **High blood pressure:** If used in women with well-controlled hypertension, monitor blood pressure and stop levonorgestrel and ethinyl estradiol if blood pressure rises significantly. (5.4)
- **Carbohydrate and lipid metabolic effects:** Monitor prediabetic and diabetic women taking levonorgestrel and ethinyl estradiol. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- **Headache:** Evaluate significant change in headaches and discontinue levonorgestrel and ethinyl estradiol if indicated. (5.7)
- **Bleeding irregularities and amenorrhea:** Evaluate irregular bleeding or amenorrhea. (5.8)

### ADVERSE REACTIONS

The most common adverse reactions ( $\geq 2\%$ ) reported during clinical trials were headache, menorrhagia, nausea, dysmenorrhea, acne, migraine, breast tenderness, weight increased, and depression. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Xiromed, LLC at 1-844-XIROMED (1-844-947-6633) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

----- **DRUG INTERACTIONS** -----

Drugs or herbal products that induce certain enzymes (for example CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----- **USE IN SPECIFIC POPULATIONS** -----

- **Nursing Mothers:** Advise use of another contraceptive method. Levonorgestrel and ethinyl estradiol can decrease milk production. (8.3)

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

**Revised: 6/2022**

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## **FULL PRESCRIBING INFORMATION**

### **WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS**

**Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke [see Contraindications (4)].**

## **1 INDICATIONS AND USAGE**

Introvale<sup>®</sup> (levonorgestrel and ethinyl estradiol tablets) is indicated for use by females of reproductive potential to prevent pregnancy.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 How to Start Introvale**

Introvale is dispensed in an Extended-Cycle Blister Card [see *How Supplied/Storage and Handling (16)*]. Introvale should be started on a Sunday ( **see Table 1**). For the first cycle of a Sunday Start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

Instruct patients to take Introvale once a day by mouth at the same time every day for 91 days. To achieve maximum contraceptive effectiveness, Introvale should be taken exactly as directed and at intervals not exceeding 24 hours. For patient instructions regarding missed pills, see *FDA-approved patient labeling*.

## 2.2 How to Take Introvale

**Table 1 Instructions for Administration of Introvale**

<p><b>Starting COCs in women not currently using hormonal contraception (Sunday Start)</b></p> <p><b>Important:</b> Consider the possibility of ovulation and conception prior to initiation of this product.</p> <p><b>Tablet Color:</b></p> <ul style="list-style-type: none"><li>• Introvale active tablets are peach (Day 1 to Day 84).</li><li>• Introvale inactive tablets are white (Day 85 to Day 91).</li></ul>	<p><b>Sunday Start:</b> <b>For each 91-day course, take in the following order:</b></p> <ul style="list-style-type: none"><li>• Take the first <b>peach</b> tablet (0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol) on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, take the tablet on that day. <b>Due to the potential risk of becoming pregnant, use additional non-hormonal contraception (such as condoms or spermicide) for the first 7 days of treatment.</b></li><li>• Take subsequent <b>peach</b> tablets once daily at the same time each day for a total of 84 days.</li><li>• Take one <b>white</b> tablet (inert) daily for the following 7 days and at the same time of day that active tablets were taken. A scheduled period should occur during the 7 days that the white tablets are taken.</li><li>• Begin the next and all subsequent 91-day courses of Introvale without interruption on the same</li></ul>
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	<p>day of the week (i.e., Sunday) on which the patient began her first dose. Follow the same schedule as the initial 91-day course: a peach tablet once a day for 84 days, and a white tablet once a day for 7 days. If the patient does not immediately start her next pill pack, instruct her to protect herself from pregnancy by using a non-hormonal back-up method of contraception until she has taken a peach tablet daily for 7 consecutive days.</p>
<b>Switching to Introvale from another oral contraceptive</b>	Start on the same day that a new pack of the previous oral contraceptive would have started.
<b>Switching from another contraceptive method to Introvale</b>	<b>Start Introvale:</b>
<ul style="list-style-type: none"> <li>• <b>Transdermal patch</b></li> </ul>	<ul style="list-style-type: none"> <li>• On the day when the next application would have been scheduled.</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Vaginal ring</b></li> </ul>	<ul style="list-style-type: none"> <li>• On the day when the next insertion would have been scheduled.</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Injection</b></li> </ul>	<ul style="list-style-type: none"> <li>• On the day when the next injection would have been scheduled.</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Intrauterine contraceptive (IUD)</b></li> </ul>	<ul style="list-style-type: none"> <li>• On the day of removal.</li> <li>• If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraception (such as condoms or spermicide) is needed for the first seven days of the first 91-day course.</li> </ul> <p>days of the first 91-day course.</p>

• <b>Implant</b>	• On the day of removal.
<b>Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-approved patient labeling.</b>	

### ***Starting Introvale after Abortion or Miscarriage***

#### *First-trimester*

- After a first-trimester abortion or miscarriage, Introvale may be started immediately. An additional method of contraception is not needed if Introvale is started immediately.
- If Introvale is not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms or spermicide) for the first seven days of her first 91-day course of Introvale.

#### *Second-trimester*

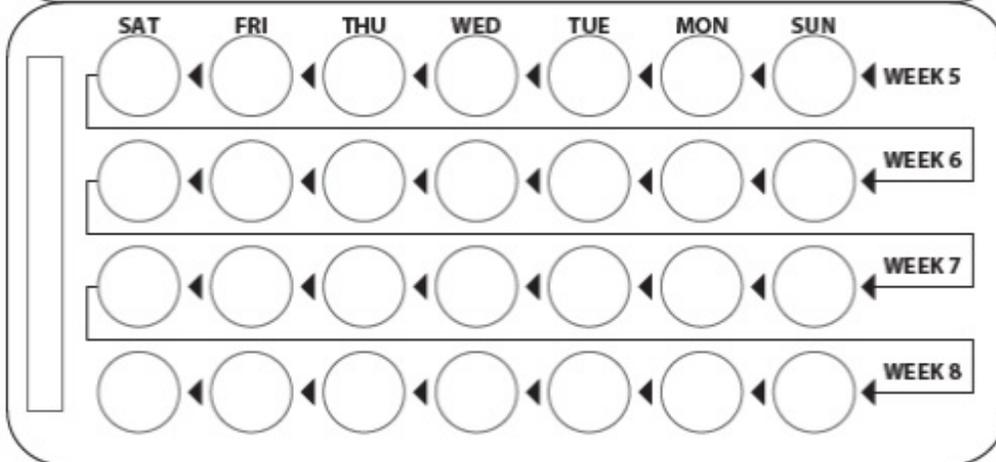
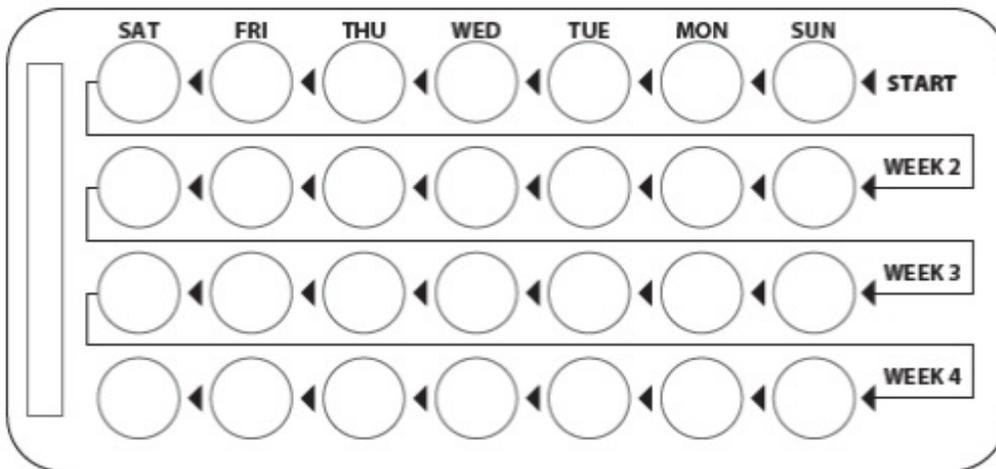
- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start Introvale following the instructions in **Table 1** for Sunday start. Use additional non-hormonal contraception (such as condoms or spermicide) for the first seven days of the patient's first 91-day course of Introvale [see *Contraindications (4), Warnings and Precautions (5.1), and FDA-approved Patient Labeling*].

### ***Starting Introvale after Childbirth***

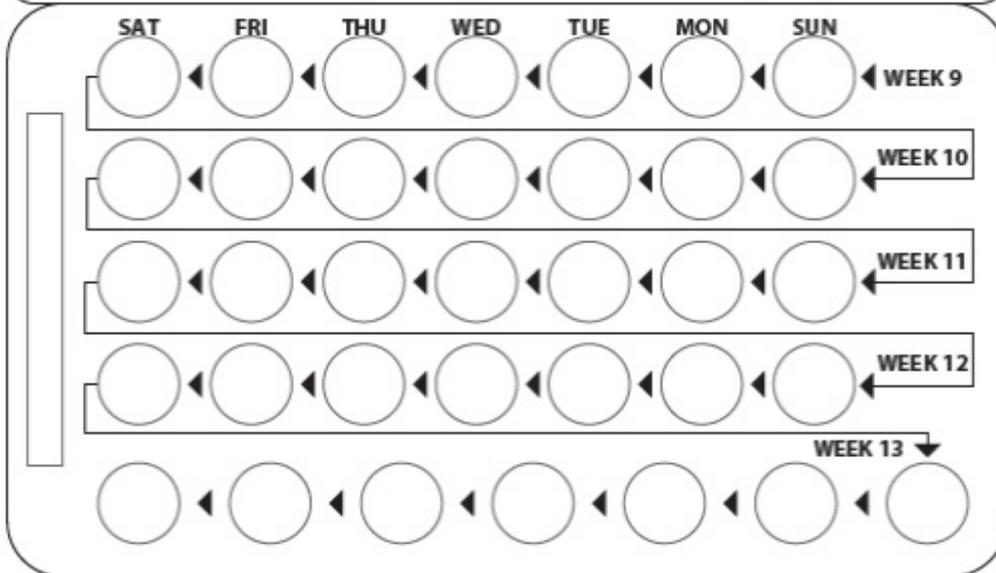
- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with Introvale following the instructions in **Table 1** for women not currently using hormonal contraception.
- Introvale is not recommended for use in lactating women [see *Use in Specific Populations (8.3) and FDA-Approved Patient Labeling*].
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of Introvale [see *Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1 and 8.3), and FDA-approved Patient Labeling*].

### ***Tablet Dispenser Instructions:***

- The Tablet Dispenser consists of a Tri-Fold Blister Card that holds 91 individually sealed pills (a 13-week, or 91-day, cycle). The 91 pills consist of 84 peach pills (active pills with hormones) and 7 white pills (inactive pills without hormone) arranged in 12 rows of 7 tablets each, labeled weeks "**START**" through "**Week 12**" (active pills with hormones) followed by 1 row of 7 white pills, labeled "**Week 13**" (inactive pills without hormone).



**Intended to be use as one unit of 91 tablets.**  
 Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].



- Advise the patient to remove the first pill in the upper left corner by pushing down on the pill. The pill will come out through a hole in the back of the Tablet Dispenser.
- Advise the patient to wait 24 hours to take the next pill, and continue to take one pill each day until all the pills have been taken.
- Advise the patient, after taking the last white pill, to start taking the first peach pill from a new Tablet Dispenser the very next day, regardless of when their period started.

## 2.3 Missed Tablets

**Table 2 Instructions for Missed Introvale Tablets**

<ul style="list-style-type: none"><li>• If one active tablet (peach) is missed in Days 1 through 84</li></ul>	Take the tablet as soon as possible. Take the next tablet at the regular time and continue taking one tablet a day until the 91-day course is finished.
<ul style="list-style-type: none"><li>• If two consecutive active tablets (peach) are missed in Days 1 through 84</li></ul>	Take 2 tablets on the day remembered and 2 tablets the next day. Then continue taking one tablet a day until the 91-day course is finished. <b>Additional non-hormonal contraception (such as condoms or spermicide) should be used as back-up if the patient has sex within 7 days after missing 2 tablets.</b>
<ul style="list-style-type: none"><li>• If three or more consecutive active tablets (peach) are missed in Days 1 through 84</li></ul>	Do not take the missed tablets. Continue taking one tablet a day until the 91-day course is finished. <b>Additional non-hormonal contraception (such as condoms or spermicide) must be used as back-up if the patient has sex within 7 days after missing 3 tablets.</b>

## 2.4 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting or diarrhea occurs within 3 to 4 hours after taking a peach tablet, handle this as a missed tablet [see FDA-approved patient labeling].

## 3 DOSAGE FORMS AND STRENGTHS

Introvale (levonorgestrel and ethinyl estradiol tablets) are available as round, film-coated, debossed “SZ” on one side, packaged in a unit carton, each containing a 13-week supply of tablets in the following order:

- 84 peach tablets, each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol; debossed with “J4” on the other side
- 7 white inert tablets debossed with “J1” on the other side.

## 4 CONTRAINDICATIONS

Introvale is contraindicated in females who are known to have or develop the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 [see *Boxed Warning and Warnings and Precautions (5.1)*].
  - Have deep vein thrombosis or pulmonary embolism, now or in the past [see *Warnings and Precautions (5.1)*].
  - Have inherited or acquired hypercoagulopathies [see *Warnings and Precautions (5.1)*].
  - Have cerebrovascular disease [see *Warnings and Precautions (5.1)*].
  - Have coronary artery disease [see *Warnings and Precautions (5.1)*].
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see *Warnings and Precautions (5.1)*].
  - Have uncontrolled hypertension [see *Warnings and Precautions (5.4)*].
  - Have diabetes mellitus with vascular disease [see *Warnings and Precautions (5.6)*].
  - Have headaches with focal neurological symptoms or migraine headaches with aura [see *Warnings and Precautions (5.7)*].
    - Women over age 35 with any migraine headaches [see *Warnings and Precautions (5.7)*].
- Liver tumors, benign or malignant, or liver disease [see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.6)*].
- Undiagnosed abnormal uterine bleeding [see *Warnings and Precautions (5.8)*].
- Pregnancy, because there is no reason to use COCs during pregnancy [see *Warnings and Precautions (5.9)* and *Use in Specific Populations (8.1)*].
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive [see *Warnings and Precautions (5.11)*].
- Use of Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations [see *Warnings and Precautions (5.3)*]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thrombotic Disorders and Other Vascular Problems

- Stop levonorgestrel and ethinyl estradiol if an arterial thrombotic event or venous thromboembolic (VTE) event occurs.
- Stop levonorgestrel and ethinyl estradiol if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.
- If feasible, stop levonorgestrel and ethinyl estradiol at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during and following prolonged immobilization.
- Start levonorgestrel and ethinyl estradiol no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman- years. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued.
- Use of levonorgestrel and ethinyl estradiol provides women with more hormonal exposure on a yearly basis than conventional monthly COCs containing the same strength synthetic estrogens and progestins (an additional 9 weeks of exposure per year). In the clinical trial, one case of pulmonary embolism was reported. Postmarketing adverse reactions of VTE have been reported in women who used levonorgestrel and ethinyl estradiol.
- Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. Stroke has been reported in women associated with the use of levonorgestrel and ethinyl estradiol. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.
- Use COCs with caution in women with cardiovascular disease risk factors.

## **5.2 Liver Disease**

### ***Impaired Liver Function***

Do not use levonorgestrel and ethinyl estradiol in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of the liver [see *Contraindications (4)*]. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue levonorgestrel and ethinyl estradiol if jaundice develops.

### ***Liver Tumors***

Levonorgestrel and ethinyl estradiol is contraindicated in women with benign and malignant liver tumors [see *Contraindications (4)*]. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

## **5.3 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment**

During clinical trial with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl streadiol-containing medications, such as COCs. Discontinue Introvale prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. Introvale can be restarted approximately 2 weeks following completion of treatment with Hepatitis C combination drug regimen.

## **5.4 High Blood Pressure**

Levonorgestrel and ethinyl estradiol is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease [see *Contraindications (4)*]. For women with well-controlled hypertension, monitor blood pressure and stop levonorgestrel and ethinyl estradiol if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

## **5.5 Gallbladder Disease**

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may worsen existing gallbladder disease.

A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC-related cholestasis.

## **5.6 Carbohydrate and Lipid Metabolic Effects**

Carefully monitor prediabetic and diabetic women who are taking levonorgestrel and ethinyl estradiol. COCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

## **5.7 Headache**

If a woman taking levonorgestrel and ethinyl estradiol develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue levonorgestrel and ethinyl estradiol if indicated.

Consider discontinuation of levonorgestrel and ethinyl estradiol in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) [see *Contraindications (4)*].

## **5.8 Bleeding Irregularities and Amenorrhea**

Bleeding and/or spotting that occurs at any time while taking the first 84 tablets of each extended-cycle regimen is considered “unscheduled” bleeding/spotting. Bleeding that occurs during the time a woman takes the seven white inert tablets is considered “scheduled” bleeding.

### ***Unscheduled and Scheduled Bleeding and Spotting***

Unscheduled (breakthrough) bleeding and spotting sometimes occur in patients on COCs, especially during the first 3 months of use. If unscheduled bleeding persists or occurs after previously regular cycles on levonorgestrel and ethinyl estradiol, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Before prescribing levonorgestrel and ethinyl estradiol, advise the woman to weigh the convenience of fewer scheduled menses (4 per year instead of 13 per year) against the inconvenience of increased unscheduled bleeding and/or spotting.

The clinical trial of the efficacy of levonorgestrel and ethinyl estradiol (91-day cycles) in preventing pregnancy also assessed scheduled and unscheduled bleeding. The participants in the study were composed primarily of women who had used oral contraceptives previously as opposed to new users. Women with a history of breakthrough bleeding/spotting  $\geq 10$  consecutive days on oral contraceptives were excluded from the study. More levonorgestrel and ethinyl estradiol subjects, compared to subjects on the comparator 28-day cycle regimen, discontinued prematurely for unacceptable bleeding (7.7% [levonorgestrel and ethinyl estradiol] vs. 1.8% [28-day cycle regimen]).

Unscheduled bleeding and unscheduled spotting decreased over successive 91-day cycles. **Table 3** below presents the number of days with unscheduled bleeding and/or spotting for each respective 91-day cycle.

**Table 3 Number of Unscheduled Bleeding and/or Spotting Days per 91-day Cycle**

Cycle (N)	Days of Unscheduled Bleeding and/or Spotting per 84-Day Interval				Median Days Per Subject- Month
	Mean	Q1	Median	Q3	
1 (446)	15.1	3	12	23	3
2 (368)	11.6	2	6	17.5	1.5
3 (309)	10.6	1	6	15	1.5
4 (282)	8.8	1	4	14	1

Q1=Quartile 1: 25% of women had  $\leq$  this number of days of unscheduled bleeding/spotting

Median: 50% of women had  $\leq$  this number of days of unscheduled bleeding/spotting

Q3=Quartile 3: 75% of women had  $\leq$  this number of days of unscheduled bleeding/spotting

**Table 4** shows the percentages of women with  $\geq 7$  days and  $\geq 20$  days of unscheduled spotting and/or bleeding in the levonorgestrel and ethinyl estradiol and the 28-day cycle treatment groups.

**Table 4 Percentage of Subjects with Unscheduled Bleeding and/or Spotting**

Days of unscheduled bleeding and/or spotting	Percentage of Subjects <sup>a</sup>	
	Cycle 1 (N=385)	Cycle 4 (N=261)
$\geq 7$ days	65%	42%
$\geq 20$ days	35%	15%

<b>28-day regimen</b>	<b>Cycle 1-4 (N=194)</b>	<b>Cycle 10-13 (N=158)</b>
≥7 days	38%	39%
≥20 days	6%	4%

<sup>a</sup>Based on spotting and/or bleeding on days 1 to 84 of a 91 day cycle in the levonorgestrel and ethinyl estradiol subjects and days 1 to 21 of a 28 day cycle over 4 cycles in the 28-day dosing regimen.

Total days of bleeding and/or spotting (scheduled plus unscheduled) were similar over one year of treatment for levonorgestrel and ethinyl estradiol subjects and subjects on the 28-day cycle regimen.

### ***Amenorrhea and Oligomenorrhea***

Women who are not pregnant and use levonorgestrel and ethinyl estradiol may experience amenorrhea. Based on data from the clinical trial, amenorrhea occurred in approximately 0.8% of women during Cycle 1, 1.2% of women during Cycle 2, 3.7% of women during Cycle 3, and 3.4% of women during Cycle 4. Because women using levonorgestrel and ethinyl estradiol will likely have scheduled bleeding only 4 times per year, rule out pregnancy at the time of any missed menstrual period.

Some women may experience amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was pre-existent.

### **5.9 COC Use Before or During Early Pregnancy**

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue levonorgestrel and ethinyl estradiol use if pregnancy is confirmed.

Administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

### **5.10 Depression**

Depression associated with the use of levonorgestrel and ethinyl estradiol has been reported. Carefully observe women with a history of depression and discontinue levonorgestrel and ethinyl estradiol if severe depression recurs.

### **5.11 Malignant Neoplasms**

#### *Breast Cancer*

Introvale is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormonally sensitive [*see Contraindications (4)*].

Epidemiology studies have not found a consistent association between use of combined oral contraceptives (COCs) and breast cancer risk. Studies do not show an association between ever (current or past) use of COCs and risk of breast cancer. However, some

studies report a small increase in the risk of breast cancer among current or recent users (<6 months since last use) and current users with longer duration of COC use [see *Postmarketing Experience (6.2)*].

### *Cervical Cancer*

Some studies suggest that COC use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

### **5.12 Effect on Binding Globulins**

The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

### **5.13 Monitoring**

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

### **5.14 Hereditary Angioedema**

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

### **5.15 Chloasma**

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to develop chloasma should avoid prolonged exposure to the sun or ultraviolet radiation while taking levonorgestrel and ethinyl estradiol.

## **6 ADVERSE REACTIONS**

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [see *Warnings and Precautions (5.1)*]
- Liver disease [see *Warnings and Precautions (5.2)*]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

### **6.1 Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The clinical trial that evaluated the safety and efficacy of levonorgestrel and ethinyl estradiol was a 12-month, randomized, multicenter, open-label study, which enrolled women aged 18 to 40, of whom 456 took at least one dose of levonorgestrel and ethinyl estradiol (345.14 woman-years of exposure) [see Clinical Studies (14)].

**Adverse Reactions Leading to Study Discontinuation:** 14.9% of the women discontinued from the clinical trial due to an adverse reaction; the most common adverse reactions ( $\geq 1\%$  of women) leading to discontinuation in the levonorgestrel and ethinyl estradiol group were menorrhagia (5.7%), mood swings (1.9%), weight/appetite increase (1.5%), and acne (1.3%).

**Common Adverse Reactions ( $\geq 2\%$  of women):** headache (20.6%), menorrhagia (11.6%), nausea (7.5%), dysmenorrhea (5.7%), acne (4.6%), migraine (4.4%), breast tenderness (3.5%), weight increased (3.1%), and depression (2.1%).

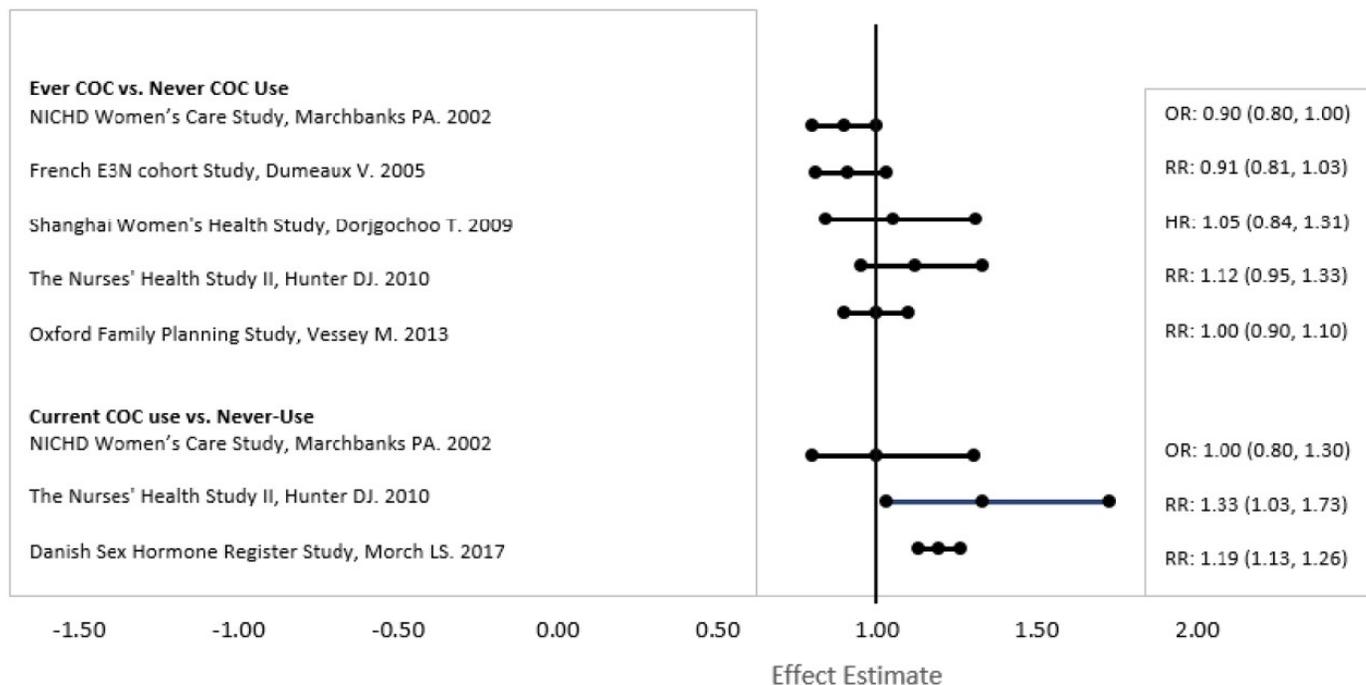
**Serious Adverse Reactions:** pulmonary embolus, cholecystitis.

## 6.2 Postmarketing Experience

Five studies that compared breast cancer risk between ever-users (current or past use) of COCs and never-users of COCs reported no association between ever use of COCs and breast cancer risk, with effect estimates ranging from 0.90 - 1.12 (Figure A).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure A). One of these studies reported no association between breast cancer risk and COC use. The other two studies found an increased relative risk of 1.19 - 1.33 with current or recent use. Both of these studies found an increased risk of breast cancer with current use of longer duration, with relative risks ranging from 1.03 with less than one year of COC use to approximately 1.4 with more than 8-10 years of COC use.

### **Figure A: Relevant Studies of Risk of Breast Cancer with Combined Oral Contraceptives**



RR = relative risk; OR = odds ratio; HR = hazard ratio. "ever COC" are females with current or past COC use; "never COC use" are females that never used COCs.

The following adverse reactions have been identified during post-approval use of levonorgestrel and ethinyl estradiol. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Gastrointestinal disorders:** abdominal distension, vomiting

**General disorders and administration site conditions:** chest pain, fatigue, malaise, edema peripheral, pain

**Immune system disorder:** hypersensitivity reactions, including itching, rash, and angioedema

**Investigations:** blood pressure increased

**Musculoskeletal and connective tissue disorders:** muscle spasms, pain in extremity

**Nervous system disorders:** dizziness, loss of consciousness

**Psychiatric disorders:** insomnia

**Reproductive and breast disorders:** dysmenorrhea

**Skin and subcutaneous tissue disorders:** alopecia

**Vascular disorders:** thrombosis, pulmonary embolism, pulmonary thrombosis

## 7 DRUG INTERACTIONS

Consult the labeling of concurrently used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

## **7.1 Effects of Other Drugs on Combined Oral Contraceptives**

### ***Substances decreasing the plasma concentrations of COCs and potentially diminishing the efficacy of COCs***

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of COCs and potentially diminish the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

#### ***Colesevelam***

Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of EE. The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

### ***Substances increasing the plasma concentrations of COCs***

Co-administration of atorvastatin or rosuvastatin and certain COCs containing ethinyl estradiol (EE) increase AUC values for EE by approximately 20 to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

### ***Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors***

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

## **7.2 Effects of Combined Oral Contraceptives on Other Drugs**

COCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations.

COCs have been shown to decrease plasma concentrations of acetaminophen, clofibrac acid, morphine, salicylic acid, temazepam and lamotrigine. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with

use of COCs [see *Warnings and Precautions (5.12)*].

### **7.3 Concomitant Use with Hepatitis C Vaccine (HCV) Combination Therapy - Liver Enzyme Elevation**

Do not administer Introvale with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations.

### **7.4 Interactions with Laboratory Tests**

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

Do not administer COCs to induce withdrawal bleeding as a test for pregnancy. Do not use COCs during pregnancy to treat threatened or habitual abortion.

### **8.3 Nursing Mothers**

Advise the nursing mother to use other forms of contraception, when possible, until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

### **8.4 Pediatric Use**

Safety and efficacy of levonorgestrel and ethinyl estradiol have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. Use of levonorgestrel and ethinyl estradiol before menarche is not indicated.

### **8.5 Geriatric Use**

Levonorgestrel and ethinyl estradiol has not been studied in postmenopausal women and is not indicated in this population.

### **8.6 Hepatic Impairment**

The pharmacokinetics of levonorgestrel and ethinyl estradiol have not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function

return to normal and COC causation has been excluded [see *Contraindications (4) and Warnings and Precautions (5.2)*].

## 8.7 Renal Impairment

The pharmacokinetics of levonorgestrel and ethinyl estradiol have not been studied in women with renal impairment.

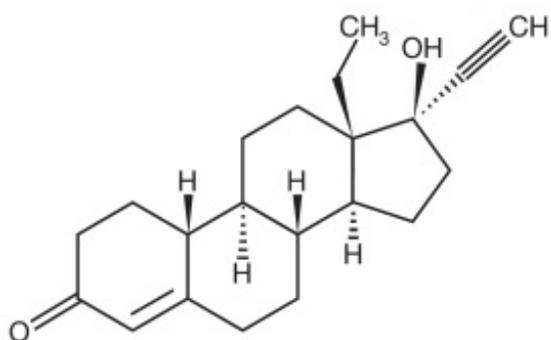
## 10 OVERDOSAGE

There have been no reports of serious ill effects from overdose of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

## 11 DESCRIPTION

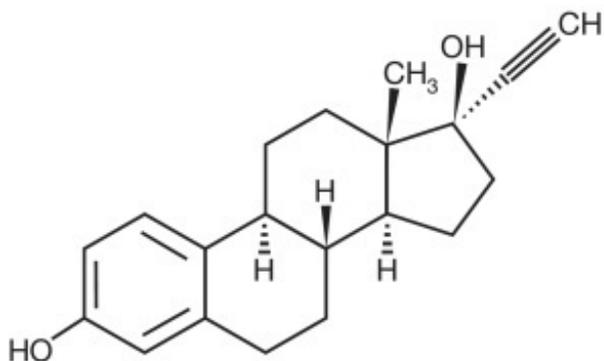
Introvale (levonorgestrel and ethinyl estradiol tablets) is an extended-cycle combination oral contraceptive consisting of 84 peach active tablets each containing 0.15 mg of levonorgestrel, a synthetic progestin and 0.03 mg of ethinyl estradiol, an estrogen, and 7 white inert tablets (without hormones).

The structural formulas for the active components are:



### Levonorgestrel $C_{21}H_{28}O_2$ MW:312.4

Levonorgestrel is chemically 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17 $\alpha$ )-, (-)-.



### Ethinyl Estradiol $C_{20}H_{24}O_2$ MW:296.4

Ethinyl Estradiol is 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 $\alpha$ )-.

- Each peach active tablet contains the following inactive ingredients: lactose anhydrous, magnesium stearate, povidone, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, iron oxide yellow, iron oxide red and iron oxide black.
- Each white inert tablet contains the following inactive ingredients: lactose anhydrous, magnesium stearate, povidone, polyvinyl alcohol, polyethylene glycol, talc and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

### 12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with levonorgestrel and ethinyl estradiol.

### 12.3 Pharmacokinetics

#### **Absorption**

No specific investigation of the absolute bioavailability of levonorgestrel and ethinyl estradiol in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism. EE is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of EE is approximately 43%.

Following continuous dosing with once-daily administration of levonorgestrel and ethinyl estradiol tablets, plasma concentrations of levonorgestrel and EE reached steady-state within 7 days. The mean plasma pharmacokinetic parameters for levonorgestrel and ethinyl estradiol under fasting conditions in normal healthy women following once-daily administration of one levonorgestrel/EE combination tablet for 10 days are summarized in **Table 5**.

**Table 5 Mean  $\pm$ SD Pharmacokinetic Parameters Under Fasting Conditions in Healthy Women Following 10 Days Administration of One Tablet of Levonorgestrel and Ethinyl Estradiol (n=44)**

Analyte	AUC <sub>0-24</sub>	C <sub>max</sub>	C <sub>min</sub>	C <sub>avg</sub> <sup>a</sup>	T <sub>max</sub>
Levonorgestrel	54.6 $\pm$ 16.5 ng*hr/mL	5 $\pm$ 1.5 ng/mL	1.6 $\pm$ 0.5 ng/mL	2.3 $\pm$ 0.7 ng/mL	1.4 $\pm$ 0.7 hours
Ethinyl Estradiol	935.5 $\pm$ 346.9 pg*hr/mL	106.1 $\pm$ 41.2 pg/mL	18.5 $\pm$ 9.4 pg/mL	38.9 $\pm$ 14.4 pg/mL	1.6 $\pm$ 0.6 hours

<sup>a</sup>C<sub>avg</sub> = AUC<sub>0-24</sub>/24

## **Food Effect**

The effect of food on the rate and the extent of levonorgestrel and EE absorption following oral administration of levonorgestrel and ethinyl estradiol has not been evaluated.

## **Distribution**

The apparent volume of distribution of levonorgestrel and EE are reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively. Levonorgestrel is about 97.5 to 99% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. EE is about 95 to 97% bound to serum albumin. EE does not bind to SHBG, but induces SHBG synthesis, which leads to decreased levonorgestrel clearance. Following repeated daily dosing of levonorgestrel/EE oral contraceptives, levonorgestrel plasma concentrations accumulate more than predicted based on single-dose pharmacokinetics, due in part, to increased SHBG levels that are induced by EE, and a possible reduction in hepatic metabolic capacity.

## **Metabolism**

Following absorption, levonorgestrel is conjugated at the 17 $\beta$ -OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3 $\alpha$ ,5 $\beta$ -tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3 $\alpha$ ,5 $\alpha$ -tetrahydrolevonorgestrel and 16 $\beta$ -hydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

First-pass metabolism of EE involves formation of EE-3-sulfate in the gut wall, followed by 2-hydroxylation of a portion of the remaining untransformed EE by hepatic cytochrome P-450 3A4 (CYP3A4). Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of EE hydroxylation. Hydroxylation at the 4-, 6-, and 16- positions may also occur, although to a much lesser extent than 2-hydroxylation. The various hydroxylated metabolites are subject to further methylation and/or conjugation.

## **Excretion**

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The terminal elimination half-life for levonorgestrel after a single dose of levonorgestrel and ethinyl estradiol was about 30 hours.

EE is excreted in the urine and feces as glucuronide and sulfate conjugates, and it undergoes enterohepatic recirculation. The terminal elimination half-life of EE after a single dose of levonorgestrel and ethinyl estradiol was found to be about 15 hours.

## **13 NONCLINICAL TOXICOLOGY**

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

*[see Warnings and Precautions (5.2, 5.10) and Use in Specific Populations (8.1)].*

## 14 CLINICAL STUDIES

In a 12-month, multicenter, randomized, open-label clinical trial, 456 women aged 18 to 40 were studied to assess the safety and efficacy of levonorgestrel and ethinyl estradiol, completing 809 91-day cycles of exposure. The racial demographic of those enrolled was: Caucasian (77%), African-American (11%), Hispanic (7%), Asian (2%), and Other (3%).

There were no exclusions for body mass index (BMI) or weight. The weight range of those women treated was 84 to 304 pounds, with a mean weight of 157 pounds and a median weight of 147 pounds. Among the women in the trial, 63% were current or recent hormonal contraceptive users, 29% were prior users (who had used hormonal contraceptives in the past but not in the 6 months prior to enrollment), and 8% were new starts.

The pregnancy rate (Pearl Index [PI]) in the 397 women aged 18 to 35 years was 1.98 pregnancies per 100 women-years of use (95% CI: 0.54 to 5.03), based on 4 pregnancies that occurred after the onset of treatment and within 14 days after the last combination pill. Cycles in which conception did not occur, but which included the use of back-up contraception, were not included in the calculation of the PI.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

**Introvale** tablets (levonorgestrel and ethinyl estradiol, USP) are available in extended-cycle blister cards (**NDC 70700-117-87**), each containing a 13-week supply of tablets: 84 peach active tablets, each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol, and 7 white inert tablets packaged in a unit carton. The active tablets are peach, round, film-coated, debossed “**SZ**” on one side and “**J4**” on the other side. The inert tablets are white, round, film-coated, debossed with “**SZ**” on one side and “**J1**” on the other side.

### 16.2 Storage Conditions

- Store at 20° to 25° C (68° to 77° F) [see USP Controlled Room Temperature].
- Protect from light.

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

Counsel patients on the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs [see *Boxed Warning*].
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC [see *Warnings and Precautions (5.1)*].
- Introvale does not protect against HIV-infection (AIDS) and other sexually transmitted infections.

- Introvale is not to be used during pregnancy; if pregnancy occurs during use of Introvale, instruct the patient to stop further use [see *Warnings and Precautions (5.8)*].
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed [see *Dosage and Administration (2.3)*].
- Use a back-up or alternative method of contraception when enzyme inducers are used with Introvale [see *Drug Interactions (7.1)*].
- COCs may reduce breast milk production; this is less likely to occur if breastfeeding is well established [see *Use in Specific Populations (8.3)*].
- Women who start on COCs postpartum, and who have not yet had a period, should use an additional method of contraception until they have taken a peach tablet for 7 consecutive days [see *Dosage and Administration (2.2)*].
- Amenorrhea may occur. Because women using Introvale will likely have scheduled bleeding only 4 times per year, rule out pregnancy at the time of any missed menstrual period [see *Warnings and Precautions (5.7)*].

INTROVALE is a registered trademark of Xiromed Pharma España, S.L.

Manufactured by Laboratorios Leon Farma S.A., Spain

For Xiromed LLC, Florham Park NJ 07932

Product of Spain

Rev. 06/2022

PI-117-03

## **PATIENT INFORMATION**

### **Introvale®**

Levonorgestrel and Ethinyl Estradiol Tablets, USP

### **0.15 mg/0.03 mg**

(lee-voe-nor-JES-trel ETH-in-il es-tra-DIE-ole)

### **What is the most important information I should know about Introvale?**

#### **Do not use Introvale if you smoke cigarettes and are over 35 years old.**

Smoking increases your risk of serious cardiovascular side effects from hormonal birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

### **What is Introvale?**

Introvale is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

### **How does Introvale work for contraception?**

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of clinical studies, about 1 to 5 out of 100 women may get pregnant during the first year they use Introvale.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



**Who should not take Introvale?**

**Do not take Introvale if you:**

- smoke and are over 35 years of age
- had blood clots in your arms, legs, lungs, or eyes
- had a problem with your blood that makes it clot more than normal
- have certain heart valve problems or irregular heart beat
- had a stroke
- had a heart attack
- have high blood pressure that cannot be controlled by medicine
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or any migraine headaches if you are over 35 years of age
- have liver problems, including liver tumors
- take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.
- have any unexplained vaginal bleeding
- are pregnant
- had breast cancer or any cancer that is sensitive to female hormones

**If any of these conditions happen while you are taking Introvale, stop taking Introvale right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking Introvale.**

**What should I tell my healthcare provider before taking Introvale?****Tell your healthcare provider if you:**

- are pregnant or think you may be pregnant
- are depressed now or have been depressed in the past
- had yellowing of your skin or eyes (jaundice) caused by pregnancy (cholestasis of pregnancy)
- are breastfeeding or plan to breastfeed. Introvale may decrease the amount of breast milk you make. A small amount of the hormones in levonorgestrel and ethinyl estradiol may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

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

Introvale may affect the way other medicines work, and other medicines may affect how well Introvale works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

**How should I take Introvale?**

**Read the Instructions for Use at the end of this Patient Information.**

**What are the possible serious side effects of Introvale?**

- **Like pregnancy, Introvale may cause serious side effects, including blood clots in your lungs, heart attack, or a stroke that may lead to death. Some other examples of serious blood clots include blood clots in the legs**

## **or eyes.**

Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age. Serious blood clots are more likely to happen when you:

- o first start taking birth control pills
- o restart the same or different birth control pills after not using them for a month or more

## **Call your healthcare provider or go to a hospital emergency room right away if you have:**

- o leg pain that will not go away
- o sudden severe shortness of breath
- o sudden change in vision or blindness
- o chest pain
- o a sudden, severe headache unlike your usual headaches
- o weakness or numbness in your arm or leg
- o trouble speaking

## **Other serious side effects include:**

- **liver problems, including:**
  - o rare liver tumors
  - o jaundice (cholestasis), especially if you previously had cholestasis of pregnancy. Call your healthcare provider if you have yellowing of your skin or eyes.
- **high blood pressure.** You should see your healthcare provider for a yearly check of your blood pressure.
- **gallbladder problems**
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood**
- **new or worsening headaches including migraine headaches**
- **irregular or unusual vaginal bleeding and spotting between your menstrual periods, especially during the first 3 months of taking Introvale.**
- **Depression**
- **possible cancer in your breast and cervix**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider if you have a swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher if you have a history of angioedema.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Women who tend to get chloasma should avoid spending a long time in sunlight, tanning booths, and under sun lamps while taking Introvale. Use sunscreen if you have to be in the sunlight.

## **What are the most common side effects of Introvale?**

- headache (migraine)
- heavier or longer periods, pain with periods
- nausea
- acne
- breast tenderness
- increase in weight

These are not all the possible side effects of Introvale. For more information, ask your healthcare provider or pharmacist.

You may report side effects to the FDA at 1-800-FDA-1088.

### **What else should I know about taking Introvale?**

- **If you are scheduled for any lab tests, tell your healthcare provider you are taking Introvale. Certain blood tests may be affected by Introvale.**
- **Introvale does not protect against HIV infection (AIDS) and other sexually transmitted infections.**

### **How should I store Introvale?**

Store Introvale at room temperature between 68°F to 77°F (20°C to 25°C).

- Protect from light.

### **General information about the safe and effective use of Introvale.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Introvale for a condition for which it was not prescribed. Do not give Introvale to other people, even if they have the same symptoms that you have.

This Patient Information summarizes the most important information about Introvale. You can ask your pharmacist or healthcare provider for information about Introvale that is written for health professionals.

For more information, call Xiromed, LLC. at 1-844-XIROMED (844-947-6633).

### **Do birth control pills cause cancer?**

It is not known if hormonal birth control pills cause breast cancer. Some studies, but not all, suggest that there could be a slight increase in the risk of breast cancer among current users with longer duration of use.

If you have breast cancer now, or have had it in the past, do not use hormonal birth control because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

### **What if I want to become pregnant?**

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

### **What should I know about my period when taking Introvale?**

When you take Introvale, which has a 91-day extended dosing cycle, you should have **4** scheduled periods a year (bleeding when you are taking the **7** white pills). However, you will probably have more bleeding or spotting between your scheduled periods than if you were using a birth control pill with a 28-day dosing cycle. During the first Introvale 91-day treatment cycle, about **1** in **3** women may have **20** or more days of unplanned bleeding or spotting. This bleeding or spotting tends to decrease with time. **Do not** stop taking Introvale because of this bleeding or spotting. If the spotting continues for more than **7** days in a row or if the bleeding is heavy, call your healthcare provider.

## What are the ingredients in Introvale?

**Active ingredients:** Each peach pill contains levonorgestrel and ethinyl estradiol.

### Inactive ingredients:

**Peach pills:** lactose anhydrous, magnesium stearate, povidone, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, iron oxide yellow, iron oxide red and iron oxide black.

**White pills:** lactose anhydrous, magnesium stearate, povidone, polyvinyl alcohol, polyethylene glycol, talc and titanium dioxide.

## Instructions For Use

### Introvale

**(levonorgestrel and ethinyl estradiol tablets, USP)**

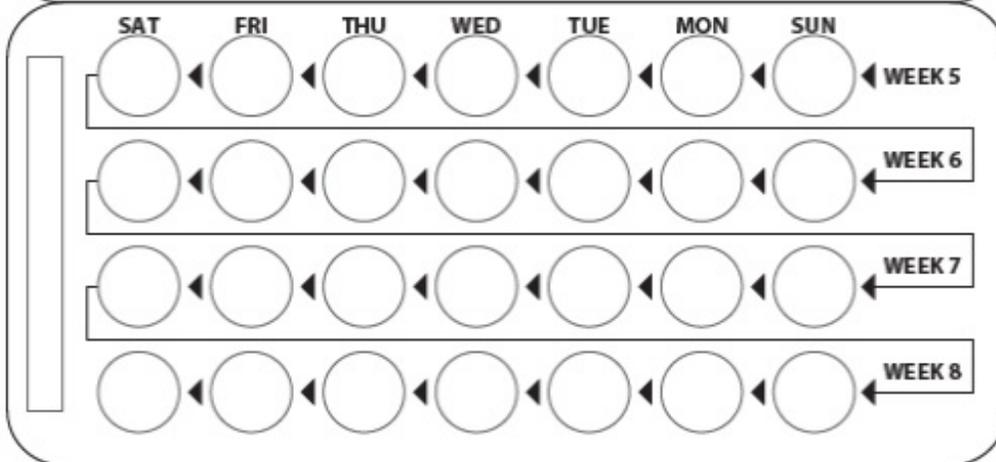
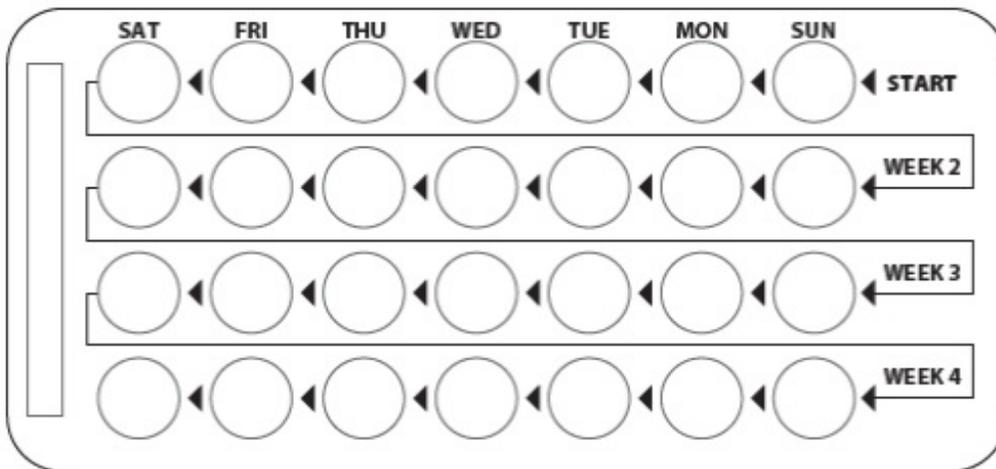
**(lee-voe-nor-JES-trel ETH-in-il es-tra-DIE-ole)**

### Important Information about taking Introvale

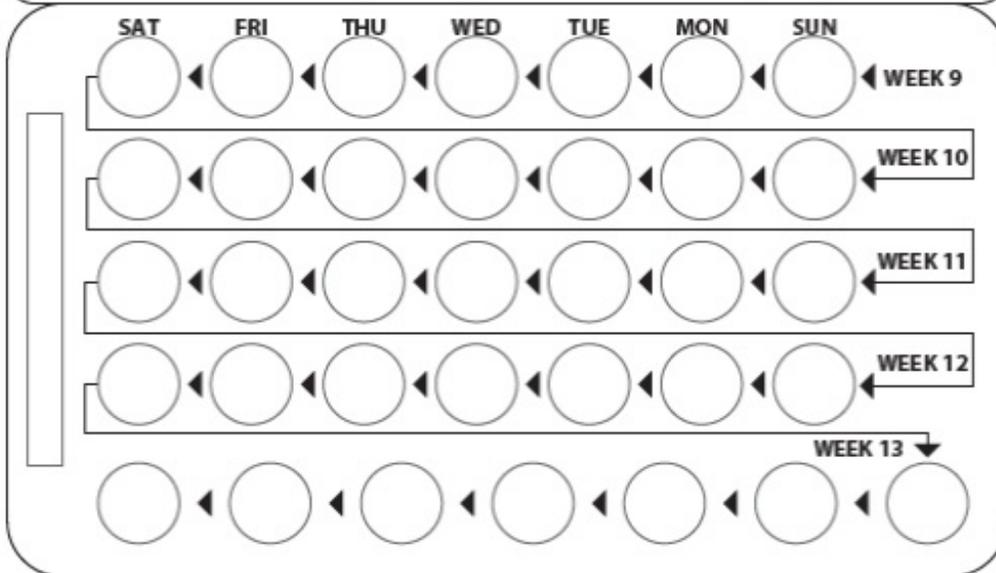
- Take **1** pill every day at the same time. Take the pills in the order directed on your pill dispenser.
- Do not skip your pills, even if you do not have sex often. If you miss pills (including starting the pack late) **you could get pregnant**. The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take Introvale, talk to your healthcare provider.
- When you first start taking Introvale, spotting or light bleeding in between your periods may occur. Contact your healthcare provider if this does not go away after a few months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking Introvale. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If your nausea does not go away, call your healthcare provider.
- Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills (see **What should I do if I miss any Introvale pills?** below), you could also feel a little sick to your stomach.
- It is not uncommon to miss a period. However, if you miss a period and have not taken Introvale according to directions, or feel like you may be pregnant, call your healthcare provider. If you have a positive pregnancy test, you should stop taking Introvale.
- If you have vomiting or diarrhea within **3 to 4** hours of taking a peach pill, take another peach pill as soon as possible. Continue taking one pill a day until the 91-day course is finished.
- If you have vomiting or diarrhea for more than 1 day, your birth control pills may not work as well. Use an additional birth control method, like condoms or spermicide, until you check with your healthcare provider.
- Stop taking Introvale at least **4** weeks before you have major surgery and do not restart after the surgery without asking your healthcare provider. Be sure to use other forms of contraception (like condoms or spermicide) during this time period.

**Before you start taking Introvale:**

- Decide what time of day you want to take your pill. It is important to take it at about the same time every day.
- Look at your Extended-Cycle Blister Cards. Your Tablet Dispenser consists of a Tri-Fold Blister Card that holds 91 individually sealed pills (a 13-week, or 91-day, cycle). The 91 pills consist of 84 peach pills (active pills with hormones) and 7 white pills (inactive pills without hormone) arranged in 12 rows of 7 tablets each, labeled weeks **“START”** through **“Week 12”** (active pills with hormones) followed by 1 row of 7 white pills, labeled **“Week 13”** (inactive pills without hormone).



**Intended to use as one unit of 91 tablets.**  
 Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].



- Also find:
  - o Where on the first tray in the pack to start taking pills (upper left corner) and
  - o In what order to take the pills (follow the weeks)
- Be sure you have ready at all times another kind of birth control (such as condoms or spermicide), to use as a back-up in case you miss pills.

**When should I start taking Introvale?**

**If you start taking Introvale and you have not used a hormonal birth control method before:**

- Take the first peach pill on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the first peach pill that same day.
- Use another method of birth control (such as condoms or spermicides) as a back-up method if you have sex anytime from the Sunday you start your first peach pill until the next Sunday (first 7 days).

**If you start taking Introvale and you are switching from another birth control pill:**

- Start your new Introvale pack on the same day that you would start the next pack of your previous birth control method.
- Do not continue taking the pills from your previous birth control pack.

**If you start taking Introvale and previously used a vaginal ring:**

- Start using Introvale on the day you would have reapplied the next ring.

**If you start taking Introvale and previously used a transdermal patch:**

- Start using Introvale on the day you would have started a new cycle (first patch application).

**If you start taking Introvale and you are switching from a progestin-only method such as an implant or injection:**

- Start taking Introvale on the day of removal of your implant, or on the day when you would have had your next injection.

**If you start taking Introvale and you are switching from an intrauterine device or system (IUD or IUS):**

- Start taking Introvale on the day of removal of your IUD or IUS.
- You do not need back-up contraception if your IUD or IUS is removed on the first day (Day 1) of your period. If your IUD or IUS is removed on any other day, use non-hormonal back-up contraception such as condoms or spermicide for the first 7 days that you take Introvale.

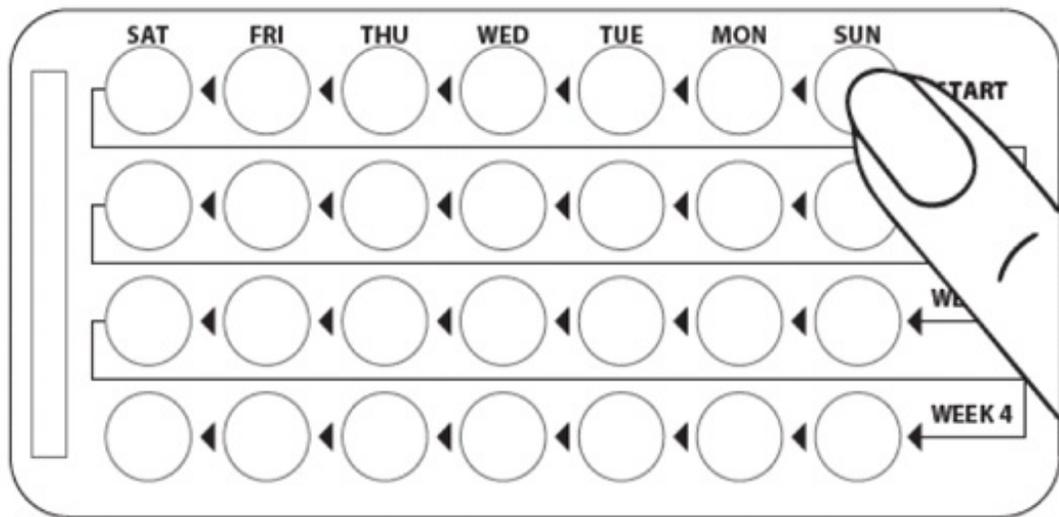
**Keep a calendar to track your period:** If this is the first time you are taking birth control pills, read, “**When should I start taking Introvale ?**” above. Follow these instructions for a **Sunday Start**.

**Instructions for using your Introvale Extended-Cycle Blister Cards:**

**Sunday Start:**

Take pill **1** on the Sunday **after your period starts**. To remove your pill from the dispenser, press the pill through the hole in the bottom of the dispenser. **See Figure C.**

**Figure C**



- If your period starts on a Sunday, take pill “**1**” that same day.
- Take **1** pill at about the same time every day until you have taken the last pill in the tablet dispenser.
- After taking the last white pill on Day 91 from the pill dispenser, start taking the first peach pill from a new Extended-Cycle blister card on the very next day (this should be a Sunday). Take the first pill in the new pack whether or not you are having your period.
- Use non-hormonal back-up contraception such as condoms or spermicide for the first **7** days of the first cycle that you take Introvale.

### What should I do if I miss any Introvale pills?

#### If you miss 1 peach pill, follow these steps:

- Take it as soon as you remember. Take the next pill at your regular time.

This means you may take **2** pills in **1** day.

- Then continue taking **1** pill every day until you finish the pack.
- You do not need to use a back-up birth control method if you have sex.

#### If you miss 2 peach pills in a row, follow these steps:

- Take **2** pills on the day you remember and **2** pills the next day.
- Then continue to take **1** pill every day until you finish the pack.
- You could become pregnant if you have sex in the **7** days after you miss two pills. You **must** use a non-hormonal birth control method (such as a condom or spermicide) as a back-up if you have sex during the first **7** days after you restart your pills.

#### If you miss 3 or more peach pills in a row, follow these steps:

- **Do not** take the missed pills. Keep taking **1** pill every day until you have completed all of the remaining pills in the pack. For example, if you start taking the pill on Thursday, take the pill under “Thursday” and do not take the missed pills. You may have bleeding during the week following the missed pills.
- You could become pregnant if you have sex during the days of missed pills or during the first 7 days after restarting your pills. You **must** use a non-hormonal birth control method (such as a condom or spermicide) as a back-up when you miss pills and for the first **7 days** after you restart your pills. If you do not have your period

when you are taking the white pills, call your healthcare provider because you may be pregnant.

**If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.**

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

INTROVALE is a registered trademark of Xiromed Pharma España, S.L.

Manufactured by Laboratorios Leon Farma S.A., Spain

For Xiromed LLC, Florham Park NJ 07932

Product of Spain

Rev: 06/2022

PIL-117-03

## PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

**Introvale (Levonorgestrel and Ethinyl Estradiol Tablets, USP) 0.15 mg/0.03 mg - NDC 70700-117-87 - Carton Label**





## INTROVALE

levonorgestrel and ethinyl estradiol kit

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:70700-117
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### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70700-117-87	1 in 1 CARTON	02/01/2018	
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

### Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1		84
Part 2		7

## Part 1 of 2

### INTROVALE

levonorgestrel and ethinyl estradiol tablet

#### Product Information

**Item Code (Source)** NDC:70700-825

**Route of Administration** ORAL

#### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>LEVONORGESTREL</b> (UNII: 5W7SIA7YZW) (LEVONORGESTREL - UNII:5W7SIA7YZW)	LEVONORGESTREL	0.15 mg
<b>ETHINYL ESTRADIOL</b> (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.03 mg

#### Inactive Ingredients

Ingredient Name	Strength
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>POVIDONE, UNSPECIFIED</b> (UNII: FZ989GH94E)	
<b>POLYVINYL ALCOHOL</b> (UNII: 532B59J990)	
<b>POLYETHYLENE GLYCOL, UNSPECIFIED</b> (UNII: 3WJQ0SDW1A)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	
<b>TALC</b> (UNII: 7SEV7J4R1U)	
<b>FERRIC OXIDE YELLOW</b> (UNII: EX438O2MRT)	
<b>FERRIC OXIDE RED</b> (UNII: 1K09F3G675)	
<b>FERROSFERRIC OXIDE</b> (UNII: XM0M87F357)	
<b>ANHYDROUS LACTOSE</b> (UNII: 3SY5LH9PMK)	

#### Product Characteristics

<b>Color</b>	BROWN (peach)	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	6mm
<b>Flavor</b>		<b>Imprint Code</b>	SZ;J4
<b>Contains</b>			

#### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079064	02/01/2018	

## Part 2 of 2

### INERT

inert tablet

#### Product Information

**Item Code (Source)** NDC:70700-826

**Route of Administration** ORAL

#### Inactive Ingredients

Ingredient Name	Strength
<b>ANHYDROUS LACTOSE</b> (UNII: 3SY5LH9PMK)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>POVIDONE, UNSPECIFIED</b> (UNII: FZ989GH94E)	
<b>POLYVINYL ALCOHOL</b> (UNII: 532B59J990)	
<b>POLYETHYLENE GLYCOL, UNSPECIFIED</b> (UNII: 3WJQ0SDW1A)	
<b>TALC</b> (UNII: 7SEV7J4R1U)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	

#### Product Characteristics

<b>Color</b>	WHITE	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	6mm
<b>Flavor</b>		<b>Imprint Code</b>	SZ;J1
<b>Contains</b>			

#### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079064	02/01/2018	

#### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079064	02/01/2018	

**Labeler** - Xiromed, LLC. (080228637)

**Registrant** - XIROMED PHARMA ESPANA, S.L. (468835741)

**Establishment**

<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
Aspen Oss B.V.		491013870	api manufacture(70700-117)

## **Establishment**

<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
Aspen Oss B.V.		491017488	api manufacture(70700-117)

Revised: 6/2022

Xiromed, LLC.