

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>P</sup>r**ORILISSA™**

elagolix (as elagolix sodium)  
tablets 150 mg and 200 mg

Gonadotropin releasing hormone (GnRH) receptor antagonist

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## RECENT MAJOR LABEL CHANGES

Not applicable.

## TABLE OF CONTENTS

<b>PART I: HEALTH PROFESSIONAL INFORMATION</b> .....	<b>4</b>
<b>1. INDICATIONS</b> .....	<b>4</b>
1.1. Pediatrics (< 18 years of age):.....	4
1.2. Geriatrics (> 65 years of age):.....	4
<b>2. CONTRAINDICATIONS</b> .....	<b>4</b>
<b>3. DOSAGE AND ADMINISTRATION</b> .....	<b>5</b>
3.1. Dosing Considerations.....	5
3.2. Recommended Dose and Dosage Adjustment.....	5
3.3. Administration.....	5
3.4. Missed Dose.....	6
<b>4. OVERDOSAGE</b> .....	<b>6</b>
<b>5. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING</b> .....	<b>6</b>
<b>6. WARNINGS AND PRECAUTIONS</b> .....	<b>7</b>
6.1. Special Populations.....	9
6.1.1. Pregnant Women.....	9
6.1.2. Breast-feeding.....	10
6.1.3. Pediatrics (< 18 years of age).....	10
6.1.4. Geriatrics (> 65 years of age).....	10
<b>7. ADVERSE REACTIONS</b> .....	<b>11</b>
7.1. Adverse Drug Reaction Overview.....	11
7.2. Clinical Trial Adverse Drug Reactions.....	11
7.3. Less Common Clinical Trial Adverse Drug Reactions.....	13
7.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.....	15
7.5. Clinical Trial Adverse Reactions (Pediatrics).....	15
7.6. Post-Market Adverse Drug Reactions.....	15
<b>8. DRUG INTERACTIONS</b> .....	<b>16</b>
8.1. Drug-Drug Interactions.....	16
8.2. Drug-Food Interactions.....	19
8.3. Drug-Herb Interactions.....	19
8.4. Drug-Laboratory Test Interactions.....	19
8.5. Drug-Lifestyle Interactions.....	19
<b>9. ACTION AND CLINICAL PHARMACOLOGY</b> .....	<b>19</b>
9.1. Mechanism of Action.....	19
9.2. Pharmacodynamics.....	20
9.3. Pharmacokinetics.....	20
<b>10. STORAGE, STABILITY AND DISPOSAL</b> .....	<b>22</b>
<b>11. SPECIAL HANDLING INSTRUCTIONS</b> .....	<b>22</b>
<b>PART II: SCIENTIFIC INFORMATION</b> .....	<b>23</b>
<b>12. PHARMACEUTICAL INFORMATION</b> .....	<b>23</b>
<b>13. CLINICAL TRIALS</b> .....	<b>24</b>
13.1. Trial Design and Study Demographics.....	24

13.2. Study Results.....	26
13.3. Comparative Bioavailability Studies .....	30
<b>14. MICROBIOLOGY .....</b>	<b>30</b>
<b>15. NON-CLINICAL TOXICOLOGY.....</b>	<b>30</b>
<b>16. SUPPORTING PRODUCT MONOGRAPHS.....</b>	<b>33</b>
<b>PATIENT MEDICATION INFORMATION .....</b>	<b>34</b>

# ORILISSA

elagolix (as elagolix sodium)

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1. INDICATIONS

ORILISSA (elagolix) is indicated for the treatment of moderate to severe pain associated with endometriosis.

#### 1.1. Pediatrics (< 18 years of age):

Safety and effectiveness of ORILISSA in patients less than 18 years of age has not been established.

#### 1.2. Geriatrics (> 65 years of age):

ORILISSA is not indicated in postmenopausal women and has not been studied in women over 65 years of age.

### 2. CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section.
- Women who are, suspected to be, or may become pregnant during the course of therapy.
- Women with undiagnosed vaginal bleeding.
- Women with known osteoporosis, due to the risk of further bone loss.
- Women with severe hepatic impairment (Child-Pugh C). See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**.
- Concomitant use of ORILISSA and strong organic anion transporting polypeptide (OATP)1B1 inhibitors (e.g., cyclosporine and gemfibrozil), due to the risks of increased ORILISSA plasma concentrations.

### 3. DOSAGE AND ADMINISTRATION

#### 3.1. Dosing Considerations

- Women should use effective methods of contraception not containing estrogen while on treatment with ORILISSA (elagolix).
- Treatment with ORILISSA should be initiated at the time of the menstrual flow to decrease the risk of an undiagnosed pregnancy. Pregnancy should be excluded before starting treatment with ORILISSA.
- Clinical studies with ORILISSA have been limited to a 12-month exposure to the drug and therefore the safety and efficacy of ORILISSA beyond 12 months have not been established. Because of the dose-dependent loss of bone mineral density (BMD) associated with ORILISSA treatment, the use of ORILISSA 200 mg twice daily should be limited to 6 months duration.

#### 3.2. Recommended Dose and Dosage Adjustment

ORILISSA is available as either 150 mg tablets (once daily) or 200 mg tablets (twice daily), to be taken orally.

Based on the severity of symptoms and treatment objectives, use the lowest effective dose (see **CLINICAL TRIALS**). Administration of ORILISSA results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, leading to decreased blood levels of the ovarian sex hormones, estradiol and progesterone. LH and FSH suppression begins within hours of administration and is readily reversible upon discontinuation of ORILISSA (see **ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action**).

Safety and effectiveness of ORILISSA in patients less than 18 years of age has not been established.

ORILISSA is not indicated in postmenopausal women and has not been studied in women over 65 years of age.

No dose adjustment of ORILISSA is required in women with mild hepatic impairment (Child-Pugh A). ORILISSA 150 mg once daily is the recommended dose in women with moderate hepatic impairment (Child-Pugh B), with treatment duration limited to 6 months; the 200 mg twice daily dose is not recommended. ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C). See **CONTRAINDICATIONS** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions**.

No dose adjustment of ORILISSA is required in women with any degree of renal impairment or end-stage renal disease (including women on dialysis). See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions**.

#### 3.3. Administration

ORILISSA may be taken with or without food.

### 3.4. Missed Dose

If a woman misses a dose of ORLISSA she should be instructed to take it as soon as she remembers as long as it is on the same day. She should then resume the regular dosing schedule.

- 150 mg once a day: no more than 1 tablet each day should be taken.
- 200 mg twice a day: no more than 2 tablets each day should be taken.

## 4. OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In case of overdose, monitor the patient for any signs or symptoms of adverse reactions and initiate appropriate symptomatic treatment immediately.

## 5. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

ORLISSA (elagolix) is available as 150 mg and 200 mg film-coated tablets.

ORLISSA 150 mg tablets are light pink, oblong, debossed with EL 150 on one side and available as weekly treatment packs containing 7 tablets for 1 week of treatment. Four weekly treatment packs may be packaged in a carton for a total of 28 tablets.

ORLISSA 200 mg tablets are light orange, oblong, debossed with EL 200 on one side and available as weekly treatment packs containing 14 tablets for 1 week of treatment. Four weekly treatment packs may be packaged in a carton for a total of 56 tablets.

### Listing of Non-Medicinal Ingredients

ORLISSA 150 mg tablets contain 155.2 mg of elagolix sodium equivalent to 150 mg elagolix with the following non-medicinal ingredients: carmine high tint, magnesium stearate, mannitol, polyethylene glycol, polyvinyl alcohol, povidone, pregelatinized starch, sodium carbonate monohydrate, talc, and titanium dioxide.

ORLISSA 200 mg tablets contain 207.0 mg of elagolix sodium equivalent to 200 mg elagolix with the following non-medicinal ingredients: iron oxide red, magnesium stearate, mannitol, polyethylene glycol, polyvinyl alcohol, povidone, pregelatinized starch, sodium carbonate monohydrate, talc, and titanium dioxide.

## 6. WARNINGS AND PRECAUTIONS

### General

ORILISSA (elagolix) is not a contraceptive drug. Therefore, women should use an effective method of contraception not containing an estrogen while being treated with ORILISSA. In case of a suspected pregnancy, treatment with ORILISSA should be interrupted until the diagnosis of pregnancy has been excluded (see **Sexual Health, Reproduction**).

### Endocrine and Metabolism

#### *Decrease in Bone Mineral Density*

ORILISSA causes a dose-dependent decrease in bone mineral density (BMD). BMD loss is greater with increasing duration of use and may not be completely reversible after stopping treatment. The impact of these BMD decreases on long-term bone health and future fracture risk are unknown. Consider assessment of BMD in patients with a history of a low-trauma fracture or other risk factors for osteoporosis or bone loss, and do not use in women with known osteoporosis. Limit the duration of use to reduce the extent of bone loss. See **ADVERSE REACTIONS, Decrease in Bone Mineral Density**.

Clinical trials evaluating the effect of ORILISSA on bone mineral density beyond 12 months are not available. If use of ORILISSA continues for longer than 12 months, it is recommended that BMD be assessed by dual energy x-ray absorptiometry (DXA). Discontinue ORILISSA if BMD Z-score is lower than  $-2.0$ . The loss of BMD in premenopausal women should be considered in the benefit/risk assessment for women receiving ORILISSA.

Consider assessment of BMD sooner than at 12 months in patients who are at greater risk of low BMD. Risk factors include patients taking ORILISSA 200 mg twice daily, prior use of gonadotropin-releasing hormone (GnRH) agonists, metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa, strong family history or osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids.

Although there were no studies addressing whether calcium and vitamin D may lessen BMD loss in women using ORILISSA, all patients should have adequate calcium and vitamin D intake.

### Hepatic/Biliary/Pancreatic

#### *Hepatic Transaminase Elevations*

In clinical trials, dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3 times the upper limit of the reference range occurred with ORILISSA.

Use the lowest effective dose of ORILISSA and instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice. Promptly evaluate patients with elevations in liver tests to determine whether the benefits of continued therapy outweigh the risks (see **ADVERSE REACTIONS, Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data, Hepatic Transaminase Elevations**).

## Monitoring and Laboratory Tests

See **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, *Decrease in Bone Mineral Density*** and **Hepatic/Biliary/Pancreatic, *Hepatic Transaminase Elevations***.

## Renal

No dose adjustment of ORILISSA is required in women with any degree of renal impairment or end-stage renal disease (including women on dialysis). See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions**.

## Sexual Health

### *Reproduction*

Exclude pregnancy before initiating treatment with ORILISSA. Exposure to ORILISSA during pregnancy may increase the risk of early pregnancy loss. ORILISSA is not a contraceptive and women on ORILISSA may ovulate and may become pregnant (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Effect on Ovulation and Estradiol**). Women should use effective methods of contraception. Based on the mechanism of action of ORILISSA, estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA. Therefore, consideration should be given to non-hormonal methods or progestin only containing contraceptives e.g. implants, progestin-coated intrauterine device (IUD), or progestin-only pill (POP). The effect of progestin-only contraceptives on the efficacy of ORILISSA is unknown. Contraception should be continued for one week after ORILISSA discontinuation. Perform testing if pregnancy is suspected during ORILISSA therapy. Advise women to notify their healthcare provider and discontinue treatment if they suspect they may be pregnant. Inform the patient of potential risk to the fetus (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

### *Menstrual Bleeding Pattern*

Women who take ORILISSA may experience changes in their normal menstrual bleeding pattern, most often a decreased amount of menstrual flow or amenorrhea, which may reduce the ability to recognize the occurrence of pregnancy (see **CLINICAL TRIALS, Effects on Bleeding Patterns**). Women should be counseled regarding the bleeding pattern changes they may experience.

Upon stopping ORILISSA therapy, the majority of women reported a menstrual period within 1 month.

### *Fertility*

There are no data available in humans for effects of elagolix on male or female fertility. In a 3-month healthy female volunteer study, ORILISSA did not affect anti-Mullerian hormone (AMH), a biomarker used to estimate ovarian reserve; the effect of ORILISSA on antral follicle count is unknown.

In a 3 months folliculogenesis study in young women who received multiple doses of elagolix, the median number of days from last dose of elagolix to return of light bleeding (menses) was 16 and 21 days for the 150 mg once daily and 200 mg twice daily groups, respectively.

No effect on fertility was observed in the rat fertility study; however, the results from this study are limited, due to relatively low binding affinity of elagolix to rat GnRH receptors (see **NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology**).

## Psychiatric

### ***Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders***

Suicidal ideation and behavior, including one completed suicide, occurred in patients treated with ORILISSA in the endometriosis clinical trials. ORILISSA patients had a higher incidence of depression and mood changes compared to placebo, and ORILISSA patients with a history of suicidality or depression had a higher incidence of depression compared to patients without such a history (see **ADVERSE REACTIONS, Less Common Clinical Trial Adverse Drug Reactions, Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders**). Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits.

## 6.1. Special Populations

### 6.1.1. Pregnant Women

ORILISSA is contraindicated in women who are, suspect that they are, or may become pregnant during the course of therapy. Discontinue ORILISSA if pregnancy occurs during treatment.

Based on mechanism of action of GnRH receptor antagonists in humans, there is a risk that ORILISSA may cause a decrease in luteal progesterone production in early pregnancy and may be associated with potential increased risk of pregnancy complications, such as early pregnancy loss.

In animal studies where pregnant rats and rabbits were dosed with elagolix during the period of organogenesis, there was no evidence of fetal malformations even at the highest, maternally toxic doses. A single total litter loss and three abortions (out of 20 pregnancies) were observed at the maternally toxic dose in rabbits; a single total litter loss was observed at a non-maternally toxic dose. Post-implantation loss and increased incidence of visceral and skeletal variations were observed in rats at maternally toxic doses. The relevance of these findings to humans is uncertain (see **NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology**).

In a rat pre- and postnatal development study, there were no fetal malformations (only external evaluated) at either tested dose where maternal plasma concentrations were less than at the MRHD.

There are no adequate and well-controlled studies related to use of elagolix in pregnant women.

In clinical studies of more than 3500 women (of which more than 2000 women had endometriosis) treated with ORILISSA for up to 12 months, there were 49 pregnancies reported. These 49 women became pregnant while receiving ORILISSA treatment or within 30 days after stopping ORILISSA treatment. Among these 49 pregnancies, 2 major congenital malformations were reported. In one case of infant cleft palate, the mother was treated with ORILISSA 150 mg once daily and the estimated fetal exposure to ORILISSA was the first 30 days of pregnancy. In one case of infant tracheoesophageal fistula accompanied by patent ductus arteriosus, tricuspid valve incompetence, pneumothorax and atelectasis, the mother was treated with ORILISSA 150 mg once daily and the estimated fetal exposure to ORILISSA was the first 15 days of pregnancy. A causality assessment of these malformations suggests that both cases were unlikely related to ORILISSA based on timing of exposure relative to organogenesis, lack of a clustering pattern and lack of mechanism of action based findings. However, whether there is a true relationship remains unknown.

In addition, among these 49 pregnancies, there were 5 cases of spontaneous abortion (miscarriage) compared to 5 cases among the 20 pregnancies that occurred in more than 1100 women treated with placebo. Although the duration of fetal exposure was limited in ORILISSA clinical trials, there were no apparent decreases in birth weights associated with ORILISSA treatment in comparison to placebo.

#### **6.1.2. Breast-feeding**

It is not known whether ORILISSA and its metabolites are present in human breast milk, affect human milk production or have effects on the breastfed infant. Because many drugs are secreted into human milk, a decision should be made to discontinue nursing or delay initiation of ORILISSA until the mother is no longer breastfeeding.

Low amounts of elagolix have been detected in rat pups from maternal exposure (see **NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology**).

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORILISSA and any potential adverse effects on the breastfed child from ORILISSA.

#### **6.1.3. Pediatrics (< 18 years of age)**

Safety and effectiveness of ORILISSA in patients less than 18 years of age has not been established.

#### **6.1.4. Geriatrics (> 65 years of age)**

ORILISSA is not indicated in postmenopausal women and has not been studied in women over 65 years of age.

## 7. ADVERSE REACTIONS

### 7.1. Adverse Drug Reaction Overview

The most frequent ( $\geq 10\%$ ) adverse reactions reported in clinical trials with ORILISSA (elagolix) were hot flush, headache and nausea.

In the two controlled studies (M12-665 and M12-671), serious adverse reactions were reported in 2.7% patients treated with ORILISSA and 3.3% patients treated with placebo.

In the two controlled studies, 5.5% of patients treated with ORILISSA 150 mg once daily and 9.6% of patients treated with 200 mg twice daily discontinued therapy due to adverse reactions. Discontinuations for both dosage forms (150 mg once daily and 200 mg twice daily) were most commonly due to hot flush (0.8% and 2.5%, respectively) and nausea (0.8% and 1.5%, respectively). The majority of discontinuation due to hot flushes and nausea occurred within the first 2 months of therapy. No woman discontinued ORILISSA 150 mg once daily for hot flushes during the extension study after receiving it for 6 months in the controlled study.

### 7.2. Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of ORILISSA was evaluated in two 6-month placebo-controlled clinical studies (M12-665 and M12-671) in which a total of 952 women were treated with 150 mg once daily or with 200 mg twice daily. The population age range was 18 to 49 years old. Women who completed 6 months of treatment and met eligibility criteria would have treatment continue in two blinded 6-month extension studies for a total treatment duration of up to 12 months.

Adverse reactions reported in  $\geq 5\%$  of women in the two placebo controlled studies in either ORILISSA dose group and at a greater frequency than placebo are described in **Table 1**.

**Table 1. Percentage of Patients in Studies M12-665 and M12-671 with Treatment -Emergent Adverse Reactions Occurring in at Least 5% of Patients (either ORILISSA Dose Group) and Greater than Placebo<sup>1</sup>**

	ORILISSA 150 mg once daily N=475 (%)	ORILISSA 200 mg twice daily N=477 (%)	Placebo N=734 (%)
<b>Gastrointestinal Disorders</b>			
Nausea	11	16	13
<b>Infections and Infestations</b>			
Nasopharyngitis	6	6	4
Sinusitis	5	6	4
Upper Respiratory Tract Infection	6	4	5
<b>Musculoskeletal and Connective Tissue Disorder</b>			
Arthralgia	3	5	3
<b>Nervous System Disorders</b>			
Headache	17	20	12
<b>Psychiatric Disorders</b>			
Anxiety	3	5	3
Insomnia	6	9	3
<b>Reproductive System and Breast Disorders</b>			
Amenorrhoea <sup>2</sup>	4	7	<1
<b>Vascular Disorders</b>			
Hot Flush	23	45	9

1 MedDRA version of 19.1

2 See **CLINICAL TRIALS, Effects on Bleeding Patterns**

Events of hot flushes were dose-dependent and the majority were assessed as mild to moderate. All other adverse events were comparable between both doses of ORILISSA.

The adverse reaction profile in the extension studies was similar to those noted in placebo-controlled studies (**Table 1**) and no additional treatment-emergent adverse reactions were reported.

### 7.3. Less Common Clinical Trial Adverse Drug Reactions

In Studies M12-665 and M12-671, adverse reactions reported in  $\geq 3\%$  and  $< 5\%$  in either ORILISSA dose group and greater than placebo included:

Gastrointestinal Disorders:	diarrhoea, abdominal pain, constipation
Investigations:	weight increased
Nervous System Disorders:	dizziness
Psychiatric Disorders:	depression, irritability, libido decreased, mood swings
Skin and Subcutaneous Tissue Disorders:	night sweats

#### Decrease in Bone Mineral Density

The effect of ORILISSA on BMD was assessed by dual-energy X-ray absorptiometry (DXA).

In the placebo-controlled Phase 3 studies there was a dose-dependent decrease in BMD in ORILISSA-treated patients compared to an increase in placebo-treated patients.

In Study M12-665, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was  $-0.9\%$  (95% CI:  $-1.3, -0.4$ ) with ORILISSA 150 mg once daily and  $-3.1\%$  (95% CI:  $-3.6, -2.6$ ) with ORILISSA 200 mg twice daily (**Table 2**). The percentage of patients with greater than 8% BMD decrease in the lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was 2% with ORILISSA 150 mg once daily, 7% with ORILISSA 200 mg twice daily and  $< 1\%$  with placebo. In the blinded extension, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of patients with greater than 8% BMD decrease in the lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 8% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

In Study M12-671, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was  $-1.3\%$  (95% CI:  $-1.8, -0.8$ ) with ORILISSA 150 mg once daily and  $-3.0\%$  (95% CI:  $-3.5, -2.6$ ) with ORILISSA 200 mg twice daily (**Table 2**). The percentage of patients with greater than 8% BMD decrease in the lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was  $< 1\%$  with ORILISSA 150 mg once daily, 6% with ORILISSA 200 mg twice daily and 0% with placebo. In the blinded extension, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of patients with greater than 8% BMD decrease in the lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 2% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

**Table 2. Percent Change from Baseline in Lumbar Spine BMD at Month 6**

	ORILISSA 150 mg once daily	ORILISSA 200 mg twice daily	Placebo
<b>Study M12-665</b>			
N	183	180	277
Percent Change from Baseline	-0.3	-2.6	0.5
Treatment Difference, % (95% CI)	-0.9 (-1.3, -0.4)	-3.1 (-3.6, -2.6)	
<b>Study M12-671</b>			
N	174	183	271
Percent Change from Baseline	-0.7	-2.5	0.6
Treatment Difference, % (95% CI)	-1.3 (-1.8, -0.8)	-3.0 (-3.5, -2.6)	

To assess for recovery of BMD loss, the change in lumbar spine BMD over time was analyzed for patients who received continuous treatment with ORILISSA 150 mg once daily or ORILISSA 200 mg twice daily for up to 12 months and who were then followed after cessation of therapy for an additional 6 months. Partial recovery of BMD was seen in these patients.

### **Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders**

In the placebo-controlled trials, reports of adverse mood changes (depressed mood, depression, depressive symptoms and/or tearfulness) were numerically more frequent in patients receiving ORILISSA, particularly in those with a history of depression.

Among the 2090 patients exposed to ORILISSA during the Phase 2 and Phase 3 studies, there were 4 reports of suicidal ideation. In 3 cases, there was a history of depression. Two patients discontinued ORILISSA and 2 completed the clinical trial treatment periods. A 44 year old woman committed suicide 2 days after discontinuation of ORILISSA 150 mg once daily, taken for 31 days. She had no relevant past medical history, but was experiencing life stressors.

### **Endometrial Safety**

Endometrial biopsies were performed in patients in Study M12-665 and its extension (M12-667) at Month 6 and Month 12. The results indicate a dose-dependent decrease in proliferative and secretory biopsy patterns and an increase in quiescent/minimally stimulated biopsy patterns. There were no abnormal biopsy findings post-baseline, such as endometrial hyperplasia or cancer.

Based on transvaginal ultrasound, during the course of a 3-menstrual cycle study in healthy women, ORILISSA 150 mg once daily and 200 mg twice daily resulted in a dose-dependent decrease in the mean endometrial thickness compared to the pre-treatment values.

#### **7.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**

##### **Hepatic Transaminase Elevations**

In the placebo-controlled clinical trials, dose-dependent asymptomatic elevations of serum ALT to at least 3 times the upper limit of the reference range occurred during treatment with ORLISSA (150 mg once daily –1/450 [0.2%]; 200 mg twice daily –5/443 [1.1%]; placebo –1/696 [0.1%]). Similar increases were seen in the extension clinical trials.

##### **Lipids**

Dose-dependent increases in total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides were noted during ORLISSA treatment.

Lipid increases typically occurred within 1 to 2 months after the start of ORLISSA therapy and remained stable thereafter over 12 months. Elevated levels of lipids returned to baseline one month after stopping treatment.

The mean increase from pre-treatment baseline in LDL-C was 0.136 mmol/L for 150 mg once daily and 0.339 mmol/L for 200 mg twice daily. The mean increase from pre-treatment baseline in HDL-C was 0.058 mmol/L for 150 mg once daily and 0.108 mmol/L for 200 mg twice daily. The mean increase from pre-treatment baseline in triglycerides was 0.005 mmol/L for 150 mg once daily and 0.125 mmol/L for 200 mg twice daily following 6-month treatment of ORLISSA. Among patients with mildly elevated lipid levels at baseline, further increases in lipid levels occurred more frequently in patients receiving ORLISSA than those in patients receiving placebo.

Changes in lipid ratios were minimal due to increases in both LDL-C and HDL-C.

Lipid profiles should be assessed and managed according to current clinical practice guidelines.

#### **7.5. Clinical Trial Adverse Reactions (Pediatrics)**

Not applicable.

#### **7.6. Post-Market Adverse Drug Reactions**

Not applicable.

## 8. DRUG INTERACTIONS

### 8.1. Drug-Drug Interactions

#### Pharmacokinetic Interactions

##### *Effects of Other Co-administered Drugs on Elagolix*

Elagolix is a substrate for CYP3A; co-administration of elagolix with CYP3A inhibitors, such as ketoconazole, may increase elagolix plasma concentrations (see **Table 3**). Concomitant use of ORILISSA (elagolix) 200 mg twice daily and strong CYP3A inhibitors for more than 1 month is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and strong CYP3A inhibitors to 6 months. Co-administration of ORILISSA with drugs that induce CYP3A may decrease elagolix plasma concentrations. Strong CYP3A inducers are not recommended with ORILISSA.

Elagolix is a substrate for P-glycoprotein (P-gp). The effect of concomitant use of P-gp inhibitors or inducers on the pharmacokinetics of ORILISSA is unknown.

Elagolix is a substrate of organic anion transporting polypeptide (OATP)1B1. Co-administration of ORILISSA with drugs that inhibit OATP1B1 may increase elagolix plasma concentrations. Use of potent OATP1B1 inhibitors is contraindicated with ORILISSA (see **CONTRAINDICATIONS**).

Elagolix pharmacokinetics was not significantly affected with the co-administration of rosuvastatin (20 mg once daily), sertraline (25 mg once daily), and fluconazole (200 mg single dose) in healthy subjects.

**Table 3. Effects of Other Drugs on the Pharmacokinetics of Elagolix**

Co-administered drug	Dose of co-administered drug	Dose of Elagolix	Central Value Ratio <sup>1</sup> (ratio with/without co-administered drug); No effect = 1.00		Clinical comment
			C <sub>max</sub>	AUC	
<b>ANTIFUNGAL</b>					
ketoconazole	400 mg QD, 4 days	150 mg, single dose	1.77	2.20	Concomitant use of ORILISSA 200 mg twice daily and strong CYP3A inhibitors for more than 1 month is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and strong CYP3A inhibitors to 6 months.
<b>ANTIMICOBACTERIAL</b>					
rifampin	600 mg, single dose	150 mg, single dose	4.37	5.58	Concomitant use of elagolix 200 mg twice daily and rifampin should be avoided. Limit concomitant use of ORILISSA 150 mg once daily and rifampin to 6 months.
	600 mg QD, 10 days		2.00	1.65	

1 Ratios indicate C<sub>max</sub> and AUC values for co-administration of the medication with elagolix vs. administration of the medication alone

AUC = area under the plasma concentration-time curve; BID = twice daily; C<sub>max</sub> = peak concentration; QD = once daily

### **Effects of Elagolix on Other Co-administered Drugs**

Elagolix is a weak to moderate inducer of CYP3A enzyme. ORILISSA may decrease plasma concentration of drugs that are substrates of CYP3A (e.g. midazolam, see **Table 4**).

Elagolix is an inhibitor of efflux transporter P-gp. ORILISSA may increase plasma concentration of drugs that are substrates of P-gp. Co-administration of elagolix with single dose of digoxin (sensitive P-gp substrate) resulted in approximately 70% increase in digoxin C<sub>max</sub>, relative to digoxin administered alone (see **Table 4**).

In vitro studies suggest that elagolix may inhibit the hepatic uptake transporters OATP1B1 and OAT1B3. However, co-administration of elagolix with multiple doses of rosuvastatin (OATP substrate) resulted in approximately 40% decrease in rosuvastatin AUC, relative to rosuvastatin administered alone.

Elagolix had no clinically relevant effect on the pharmacokinetics of sertraline (25 mg once daily) and fluconazole (200 mg single dose) when co-administered in healthy subjects (see **Table 4**).

**Table 4. Effects of Elagolix on the Pharmacokinetics of Other Drugs**

Co-administered drug	Dose of co-administered drug	Dose of Elagolix	Geometric mean ratio <sup>1</sup> (ratio with/without co-administered drug); No effect=1.00		Clinical comment
			C <sub>max</sub>	AUC	
<b>ANTIARRHYTHMICS</b>					
digoxin	0.5 mg, single dose	200 mg BID, 1 day	1.73	1.32	Clinical monitoring is recommended for digoxin when co-administered with ORILISSA.
		200 mg BID, 10 days	1.71	1.26	
<b>STATINS</b>					
rosuvastatin	20 mg QD, 8 days	300 mg BID, 1 day	1.67	0.88	Consider increasing the dose of rosuvastatin.
		300 mg BID, 7 days	0.99	0.60	
<b>BENZODIAZEPINES</b>					
midazolam	2 mg, single dose	150 mg QD, 13 days	0.81	0.65	Consider increasing the dose of midazolam and individualize therapy based on patient's response.
		300 mg BID, 10 days	0.56	0.46	
<b>ORAL CONTRACEPTIVES</b>					
norethindrone	0.35 mg QD, 4x 28 days	150 mg QD, 2x 28 days	↔	0.88	No dosage adjustment needed.
triphasic oral contraceptive	ethinyl estradiol 0.035 mg, and triphasic norgestimate 0.18/0.215/0.25 mg QD, 3x 28 days	150 mg QD, 2x 28 days	ethinyl estradiol		Although the contraceptive effects of ethinyl estradiol are unlikely to be impacted, the efficacy of ORILISSA may be reduced. See <b>WARNINGS AND PRECAUTIONS, Sexual Health, Reproduction.</b>
			1.15	1.30	
			norgestromin <sup>a</sup>		
			0.87	0.85	
			norgesterel <sup>a</sup>		
↔	↔				

1 Ratios indicate C<sub>max</sub> and AUC values for co-administration of the medication with elagolix versus administration of the medication alone

a. Metabolites of norgestimate

↔ = No change (central value ratio 90% confidence interval 0.80 to 1.25)

AUC = area under the plasma concentration-time curve; BID = twice daily; C<sub>max</sub> = peak concentration; QD = once daily

## 8.2. Drug-Food Interactions

The administration of elagolix with food (high-fat meal) reduced the elagolix area under the plasma concentration-time curve from time 0 to infinity ( $AUC_{inf}$ ) by 24%, reduced the peak plasma concentration ( $C_{max}$ ) by 36%, and delayed the time to  $C_{max}$  ( $T_{max}$ ) from 1.0 to 2.0 hours compared to administration under fasted conditions which is not expected to impact efficacy. ORLISSA may be administered with or without food (see **DOSAGE AND ADMINISTRATION, Administration** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption**).

## 8.3. Drug-Herb Interactions

Interactions with herbal products have not been established.

## 8.4. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 8.5. Drug-Lifestyle Interactions

### Driving and Operating Machinery

ORLISSA is unlikely to affect the ability to drive and use machines as it is not distributed in the central nervous system.

## 9. ACTION AND CLINICAL PHARMACOLOGY

### 9.1. Mechanism of Action

ORLISSA (elagolix) is a novel, orally administered, highly potent, short-acting, selective, non-peptide small molecule GnRH receptor antagonist that blocks endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of ORLISSA results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulation hormone (FSH) levels, leading to decreased blood levels of the ovarian sex hormones, estradiol and progesterone. LH and FSH suppression begins within hours of administration and is readily reversible upon discontinuation of ORLISSA.

## 9.2. Pharmacodynamics

### Effect on Ovulation and Estradiol

During the course of a 3-menstrual cycle study in healthy women, ORILISSA 150 mg once daily and 200 mg twice daily resulted in ovulation rate of approximately 50% and 32%, respectively. In the Phase 3 studies in women with endometriosis, partial suppression of estradiol to approximately 50 pg/mL (183.55 pmol/L) was observed for treatment with ORILISSA 150 mg once daily, whereas nearly full suppression of estradiol to approximately 12 pg/mL (44.05 pmol/L) was observed following treatment with ORILISSA 200 mg twice daily.

### Effect of ORILISSA on QT Interval

The effect of elagolix on the QTc interval was evaluated in a randomized, placebo- and positive-controlled, open-label, single-dose, crossover thorough QTc study in 48 healthy adult premenopausal women. Elagolix concentrations in subjects given a single dose of 1200 mg were 17 times higher than the concentration in subjects given elagolix 200 mg twice daily. There was no clinically relevant prolongation of the QTc interval.

## 9.3. Pharmacokinetics

The steady state pharmacokinetic parameters of ORILISSA in are provided in **Table 5**.

**Table 5. Summary of Elagolix Steady State Pharmacokinetic Parameters**

Dosage	C <sub>max</sub> <sup>1</sup> (ng/mL)	AUC <sub>τ</sub> <sup>1</sup> (ng•hr/mL)	t <sub>1/2</sub> (h)	CL/F <sup>1,2</sup> (L/h)	V <sub>β</sub> /F <sup>1,2</sup> (L)
150 mg QD	574 (29)	1292 (31)	~ 6	123 (21)	1674 (94)
200 mg BID	774 (68)	1725 (57)	~ 4	144 (43)	881 (38)

1 Reported as mean (%CV)

2 Based on population pharmacokinetic analysis

AUC<sub>τ</sub> = area under the plasma concentration-time curve during the dosing interval (τ) i.e., 12 hours for twice daily (BID), 24 hours for once daily (QD); C<sub>max</sub> = peak concentration; CL/F = apparent clearance;

V<sub>β</sub>/F = apparent volume of distribution at the terminal phase; CV = Coefficient of variation; t<sub>1/2</sub> = terminal phase elimination half-life

## Absorption

In healthy premenopausal women, oral administration of elagolix resulted in a rapid absorption with median time to maximum concentration in plasma (T<sub>max</sub>) values of approximately 1 hour. The administration of elagolix with a high-fat meal reduced the elagolix area under the plasma concentration-time curve from time 0 to infinity (AUC<sub>inf</sub>) by 24%, reduced the peak plasma concentration (C<sub>max</sub>) by 36%, and delayed the time to C<sub>max</sub> (T<sub>max</sub>) from 1.0 to 2.0 hours compared to administration under fasted conditions (see **DRUG INTERACTIONS, Drug-Food Interactions**).

## **Distribution**

Elagolix is approximately 80% bound to human plasma proteins. The mean blood-to-plasma ratio was 0.6.

## **Metabolism**

Elagolix is primarily metabolized by CYP3A with minor contributions from CYP2D6, CYP2C8, and uridine glucuronosyltransferases (UGTs). Unchanged elagolix is the major drug-derived material in human plasma (>90%).

## **Excretion**

The major route of elimination is by hepatic metabolism with 90% and <3% of the dose excreted in feces and urine, respectively. O-demethyl metabolite and unchanged elagolix were the major components in the feces (37.6% and 26.3%, respectively). The terminal phase elimination half-life ( $t_{1/2}$ ) is 4 to 6 hours.

## **Special Populations and Conditions**

### ***Pediatrics***

The pharmacokinetics of ORILISSA have not been investigated in women less than 18 years of age.

### ***Geriatrics***

The pharmacokinetics of ORILISSA have not been investigated in women older than 65 years.

### ***Genetic Polymorphism***

Disposition of elagolix involves the OATP1B1 transporter protein. Plasma concentrations of elagolix in patients who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T>C) are expected to be 78% higher than in patients without this genotype. The frequency of this SLCO1B1 521 C/C genotype is generally less than 5% in most racial/ethnic groups. No dose adjustment of ORILISSA is required based on OATP1B1 genotype status.

### ***Ethnic origin***

No clinically meaningful difference in the pharmacokinetics of ORILISSA between White and Black subjects or between Hispanic and other subjects was observed. There is no clinically meaningful difference in the pharmacokinetics of ORILISSA between Japanese and Han Chinese subjects. No dose adjustment of ORILISSA is required based on race or ethnicity.

### ***Hepatic Insufficiency***

Elagolix exposures ( $C_{max}$  and AUC) are similar between women with normal hepatic function and women with mild hepatic impairment. Elagolix exposures in women with moderate and severe hepatic impairment are approximately 3-fold and 7-fold, respectively, of exposures from women with normal hepatic function. See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**.

### ***Renal Insufficiency***

Elagolix exposures ( $C_{max}$  and AUC) are not altered by renal impairment. The mean exposures are similar for women with moderate to severe or end-stage renal disease (including women on dialysis) compared to women with normal renal function. See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**.

### ***Obesity***

No dose adjustment of ORLISSA is required based on body weight or body mass index.

## **10. STORAGE, STABILITY AND DISPOSAL**

### **Temperature:**

Store between 2 and 30°C.

### **Others:**

Keep out of reach and sight of children.

## **11. SPECIAL HANDLING INSTRUCTIONS**

There are no special handling instructions.

## PART II: SCIENTIFIC INFORMATION

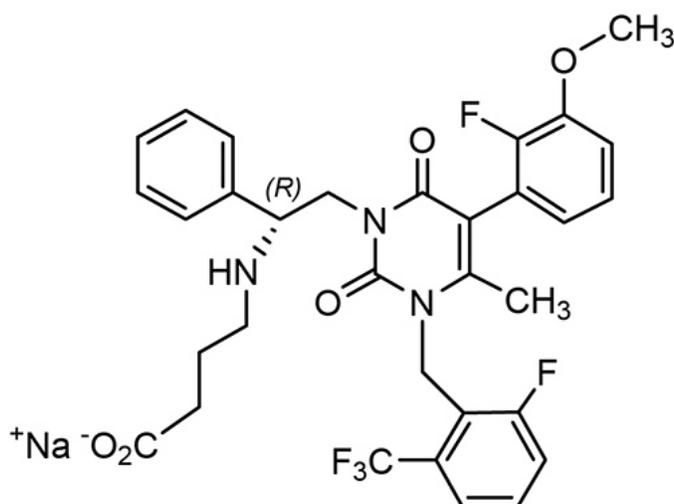
### 12. PHARMACEUTICAL INFORMATION

Common name: elagolix (INN)  
elagolix sodium (USAN)

Chemical name: Sodium 4-(((1*R*)-2-[5-(2-fluoro-3-methoxyphenyl)-3-[[2-fluoro-6-(trifluoromethyl)phenyl]methyl]-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-1-phenylethyl)amino)butanoate

Molecular formula and molecular mass:  $C_{32}H_{29}F_5N_3O_5 \cdot Na$   
653.58 (salt); 631.60 (free form)

Structural formula:



Physicochemical properties: white to off white to light yellow powder and is freely soluble in water

## 13. CLINICAL TRIALS

### 13.1. Trial Design and Study Demographics

The efficacy and safety of ORILISSA (elagolix) 150 mg once daily and 200 mg twice daily in the management of moderate to severe pain associated with endometriosis was demonstrated in two double-blind, randomized, placebo-controlled, multicentre, Phase 3 studies (Study M12-665 and M12-671) and two uncontrolled, blinded extension studies (Study M12-667 and M12-821).

Premenopausal women 18 to 49 years of age with endometriosis were eligible for enrollment if they reported 2 or more days of dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP) scores  $\geq 2$ , a mean daily NMPP score of at least 0.5, and either a mean daily NMPP score of at least 1.0 or at least 4 days of moderate or severe NMPP in the last 35 days of the Screening period.

Each placebo-controlled study assessed the reduction in endometriosis-associated pain over 6 months of treatment. More than 75% of women who completed Study M12-665 and M12-671 enrolled in the extension studies for an additional 6 month treatment period. Patients were followed up for up to 12 months after they completed their treatment.

A total of 872 patients in Study M12-665 and 817 patients in Study M12-671 were randomized to placebo or one of the two elagolix doses. At Baseline, patients were in their 30s and the majority were white in both studies. The majority of patients used NSAIDs and/or opioids for pain management at baseline. There were no significant differences between treatment groups among baseline demographic characteristics in each study (**Table 6**).

**Table 6. Summary of Patient Demographic and Baseline Characteristics from Studies M12-665 and M12-671**

Characteristics	M12-665			M12-671		
	Placebo	ORILISSA		Placebo	ORILISSA	
		150 mg QD	200 mg BID		150 mg QD	200 mg BID
	N = 374	N = 249	N = 248	N = 360	N = 226	N = 229
Median age (Min – Max), y,	31 (18-48)	32 (19-48)	31 (18-47)	33 (18-49)	33 (20-49)	34 (18-47)
Race, %						
White	86.4	88.8	86.7	89.4	87.6	90.4
Black	8.8	7.6	9.7	8.1	11.1	7.9
Other	4.8	3.6	3.6	2.5	1.3	1.7
BMI, kg/m <sup>2</sup> , mean (SD) <sup>a</sup>	28 (6)	28 (6)	28 (6)	27 (6)	27 (7)	27 (7)
Months since surgical diagnosis, mean (SD)	45 (30)	41 (29)	40 (27)	46 (39)	42 (36)	52 (41)
DYS, mean score (SD) <sup>b</sup>	2.2 (0.5)	2.2 (0.5)	2.2 (0.5)	2.2 (0.5)	2.2 (0.5)	2.1 (0.5)
NMPP, mean score (SD) <sup>b</sup>	1.6 (0.5)	1.6 (0.5)	1.6 (0.5)	1.6 (0.5)	1.7 (0.5)	1.6 (0.5)
DYSP, mean score (SD) <sup>b</sup>	1.5 (0.8)	1.5 (0.8)	1.6 (0.9)	1.5 (0.8)	1.5 (0.9)	1.4 (0.9)
NRS, mean score (SD) <sup>c</sup>	5.6 (1.6)	5.7 (1.7)	5.5 (1.6)	5.6 (1.8)	5.7 (1.8)	5.3 (1.8)
BMD, lumbar spine, mean Z-score	0.46	0.49	0.48	0.46	0.26	0.41
BMD, total hip, mean Z-score	0.34	0.44	0.36	0.36	0.23	0.28
BMD, femoral neck, mean Z-score	0.23	0.37	0.26	0.37	0.25	0.33
Analgesic Use, % <sup>d</sup>						
None	7.2	13.7	6.0	9.4	9.3	10.0
NSAID only	36.4	26.1	32.3	28.1	34.1	30.1
Opioid	19.0	18.1	21.4	15.6	14.6	12.2
NSAID and opioid	37.4	42.2	40.3	46.9	42.0	47.6

ANOVA = analysis of variance; BID = twice daily; BMI = body mass index; BMD = bone mineral density; DYS = dysmenorrhea; DYSP = dyspareunia; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; NSAID = anti-inflammatory drug; QD = once daily; SD = standard deviation.

- Heterogeneity among treatment groups was assessed for age and BMI using a one-way ANOVA model with treatment as the main effect, and there were no significant differences.
- Pain scale ranges from 0 (none) to 3 (severe), and was recorded in a daily electronic diary. "Not applicable" was also a choice for dyspareunia; patients who reported "not applicable" for the entire analysis window are excluded from analysis.
- Participants provided daily self-assessments of endometriosis-associated pain (scale of 0 – 10, no pain to worst pain ever).
- Analgesic use for baseline window (i.e., 35 days).

## 13.2. Study Results

### Reduction in Pain

The co-primary efficacy endpoints were the proportion of responders for dysmenorrhea and pelvic pain not related to menses (also known as non-menstrual pelvic pain [NMPP]) at Month 3 compared to placebo. Women used an electronic diary to report daily pain assessments, protocol-specified rescue analgesic use, and uterine bleeding. The portion of the diary assessing dysmenorrhea, non-menstrual pelvic pain, and dyspareunia make up the Endometriosis Daily Pain Impact Diary. The primary analysis independently evaluated these endpoints using the daily diary that asked patients to assess their pain and its impact on their daily activities, over the previous 24 hours. The Daily Endometriosis Pain Impact Scale, consisted of patient reported pain levels of None, Mild, Moderate or Severe (correlating with score of 0 to 3, respectively) and included a functional component for each score.

Women were responders if they experienced clinically meaningful reduction in dysmenorrhea and/or NMPP with no increased analgesic use for endometriosis associated pain. These clinically meaningful reductions corresponded to patients' assessment of pain as "much improved", or "very much improved".

A higher proportion of women treated with ORILISSA 150 mg once daily or 200 mg twice daily were responders for dysmenorrhea and NMPP versus placebo in a dose-dependent manner at Month 3. The persistence of efficacy was observed through Month 6 (**Table 7**).

Dyspareunia was evaluated as a secondary endpoint using the Daily Endometriosis Pain Impact Scale.

A higher proportion of women treated with ORILISSA 200 mg twice daily reported clinically meaningful reduction in dyspareunia versus placebo at Month 3 through Month 6.

**Table 7. Proportion and Number of Responders<sup>1</sup> for Dysmenorrhea, Non-Menstrual Pelvic Pain and Dyspareunia at Month 3 and Month 6 in Studies M12-665 and M12-671, using the Daily Endometriosis Pain Impact Scale**

	Study M12-665			Study M12-671		
	ORILISSA		Placebo	ORILISSA		Placebo
	150 mg once daily % (n/N)	200 mg twice daily % (n/N)	% (n/N)	150 mg once daily % (n/N)	200 mg twice daily % (n/N)	% (n/N)
Dysmenorrhea <sup>1</sup> (Month 3)	46.4*** (115/248)	75.8*** (185/244)	19.6 (73/373)	43.4%*** (96/221)	72.4*** (163/225)	22.7 (80/353)
Dysmenorrhea (Month 6) <sup>2</sup>	42.1*** (104/247)	75.3*** (183/243)	23.1 (86/372)	46.2%*** (102/221)	76.9*** (173/225)	25.4 (90/355)
Non-Menstrual Pelvic Pain (Month 3)	50.4*** (125/248)	54.5*** (133/244)	36.5 (136/373)	49.8** (110/221)	57.8*** (130/225)	36.5 (129/353)
Non-Menstrual Pelvic Pain (Month 6) <sup>2</sup>	45.7** (113/247)	62.1*** (151/243)	34.9 (130/372)	51.6%** (114/221)	62.2*** (140/225)	40.6 (144/355)
Dyspareunia <sup>2</sup> (Month 3)	39.6 (74/187)	47.1*** (81/172)	31.9 (90/282)	44.0 (70/159)	53.7** (87/162)	39.5 (101/256)
Dyspareunia <sup>2</sup> (Month 6)	39.6 (74/187)	50.3*** (81/161)	33.3 (90/270)	39.9 (65/163)	55.8*** (92/165)	39.4 (100/254)

1 A responder had a reduction in pain from baseline to the analysis month greater than or equal to a calculated, clinically important threshold of improvement, and also had stable or decreased rescue analgesic use.

2 A secondary endpoint

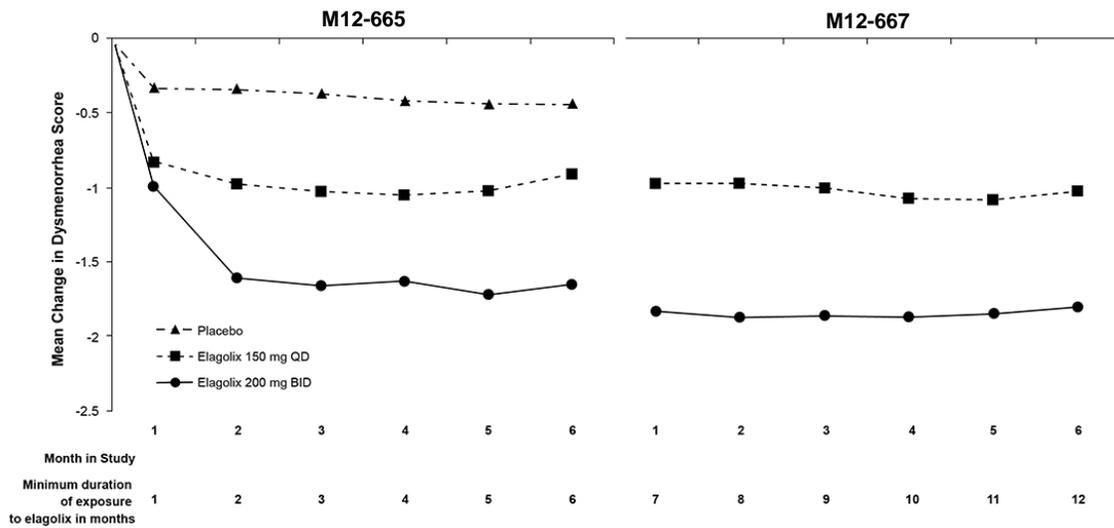
\*\*\*, \*\*, \*  $P \leq 0.001$ ,  $0.01$ , and  $0.05$ , respectively, for test of difference from placebo

Both ORILISSA treatment groups showed mean decreases from Baseline in dysmenorrhea scores that were statistically significantly greater than placebo beginning at Month 1 and persisted through Month 6.

Women in these studies also provided a daily self-assessment of their endometriosis pain using the Numeric Rating Scale (NRS), on a scale ranging from 0 (no pain) to 10 (worst pain ever). Women taking ORILISSA 150 mg once daily and 200 mg twice daily reported a highly statistically ( $p < 0.001$ ) significant reduction in NRS scores compared to placebo at Month 3 and Month 6.

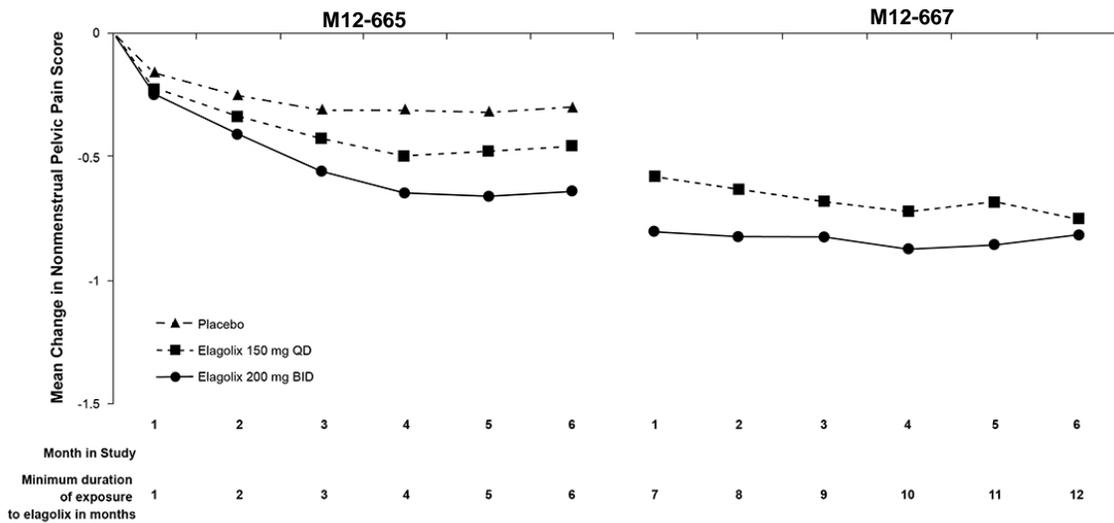
In the two blinded extension studies M12-667 and M12-821, where the patients who were originally on ORILISSA in the controlled studies M12-665 and M12-671 were maintained on their dose, the durability of improvement in dysmenorrhea, NMPP and dyspareunia was demonstrated for a total of 12 months (see **Figure 1**, **Figure 2**, **Figure 3**). In study M12-821, efficacy was maintained when ORILISSA was taken with and without food.

**Figure 1. Mean Change from Baseline in Mean Dysmenorrhea Pain Scores in Study M12-665 and Maintenance of Response in its Extension Study M12-667 over 12 Months**



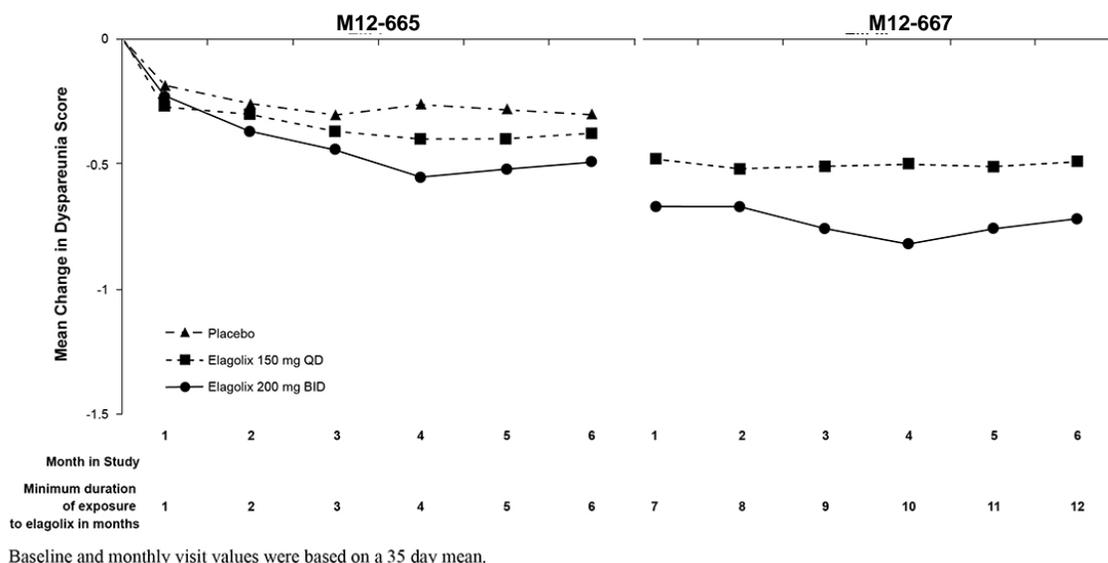
Baseline and monthly visit values were based on a 35 day mean.

**Figure 2. Mean Change from Baseline in Mean NMPP Scores in Study M12-665 and Maintenance of Response in its Extension Study M12-667 over 12 Months**



Baseline and monthly visit values were based on a 35 day mean.

**Figure 3. Mean Change from Baseline in Mean Dyspareunia Pain Scores in Study M12-665 and Maintenance of Response in its Extension Study M12-667 over 12 Months**



Results on efficacy endpoints from Study M12-671 were consistent with those observed in Study M12-665.

### Reduction in pain medication use

In these studies, women taking ORILISSA 200 mg twice daily reduced the amount of opioid or NSAID rescue medication used to treat their endometriosis-associated pain compared to the amount required at baseline. In addition, there was a significant reduction in the percentage of days per month of the opioid or NSAID rescue medication use for women taking ORILISSA 200 mg twice daily compared to women taking placebo. These findings were all statistically significant at both Month 3 and Month 6 ( $p < 0.001$ ). These effects were less consistently observed for women taking ORILISSA 150 mg once daily.

### Effects on Bleeding Patterns

The effects of ORILISSA on uterine bleeding were evaluated using electronic daily diaries for up to 12 months. ORILISSA was associated with altered menstrual bleeding patterns compared to placebo. ORILISSA led to a dose-dependent reduction in mean number of days of bleeding and spotting, bleeding intensity and bleeding duration in those patients who reported uterine bleeding.

ORILISSA also demonstrated a dose-dependent increase in the percentage of women with amenorrhea (defined as no bleeding or spotting in a 56-day interval) over the treatment period. The amenorrhea rate ranged from 14 to 32% for 150 mg once daily and 18 to 67% for 200 mg twice daily during the first 6 months of treatment. During the second 6 months of treatment, the amenorrhea rate ranged from 11 to 15% for 150 mg once daily and 46 to 57% for 200 mg twice daily.

Upon stopping ORILISSA therapy, the majority of women reported a menstrual period within 1 month. By Post-treatment Month 2, more than 85% patients had reported at least 1 post-treatment menses in both ORILISSA dose groups.

### **Quality of Life**

Quality of life was assessed with the 30-item Endometriosis Health Profile (EHP-30) conducted at Month 1, 3 and 6 study visits. ORILISSA treatment resulted in a better quality of life than did placebo on the basis of the mean change from baseline to 3 months and 6 months on the EHP-30. The results differed significantly from those with placebo at 3 months and 6 months in all six dimensions (pain, control and powerlessness, emotional well-being, social support, self-image and sexual intercourse) in the 200 mg twice daily dose group in both M12-665 and M12-671. Each dimension was statistically significant ( $p < 0.001$ ) at Month 3 and Month 6 for 200 mg twice daily.

### **13.3. Comparative Bioavailability Studies**

Not applicable.

## **14. MICROBIOLOGY**

Not applicable.

## **15. NON-CLINICAL TOXICOLOGY**

### **General Toxicology**

#### ***Single-Dose Studies***

##### **Rat**

Elagolix sodium (doses: 0, 300, 600, 1200 or 2000 mg/kg) was administered as a single oral dose by gavage to male and female rats (three/sex/group). The maximum tolerated dose (MTD) was the highest dose of 2000 mg/kg.

##### **Monkey**

Elagolix sodium (doses: 0, 300, 600, 1200 or 2000 mg/kg) was administered as a single oral dose by gavage to male and female cynomolgus monkeys (two/sex/group). The MTD was 300 mg/kg. Changes in clinical chemistry parameters (such as, ALT, AST, total bilirubin, blood urea nitrogen, creatinine, glucose) were observed at higher doses.

## **Repeat-Dose Studies**

### **Mouse**

A 15-week dietary study in mice (10 to 15/sex/group) was conducted using elagolix sodium mixed in diet to achieved doses of 0, 30, 500 or 1700 mg/kg/day. A no-observed adverse-effect-level (NOAEL) of 500 mg/kg/day was based on the combination of a decrease in body weight and observation of clinical pathology (up to 3-fold elevation in ALT) and microscopic changes (centrilobular hepatocellular) at the 1700 mg/kg/day dose.

### **Rat**

Elagolix sodium was given in the diet of SD rats (20/sex/group) for 28-weeks to achieved doses of 0, 600, or 800 mg/kg/day. Elagolix was generally well tolerated.

Findings that were considered off-target effects included increase in liver and thyroid gland weights that was associated with microscopic observation of hypertrophy in these tissues that had previously been observed in several repeat-dose toxicity studies in rats. These changes were considered non-adverse and as a consequence of induction of hepatic metabolizing enzymes and increased metabolism and clearance of thyroid hormones. These finding and the mechanism by which they occurred in rat is not relevant to humans. Moderate focal epithelial degeneration/necrosis, edema and erosion were observed in the non-glandular stomach at the limiting ridge. While these findings were adverse for rats, the observation was not considered of significance for humans due to anatomical differences in the stomach.

A NOAEL in the 28-week dietary study in rat was not identified due to the finding of gastric irritation that does not translate to human. At the highest dose of 800 mg/kg/day, an AUC of 29.9 mcg·hr/mL provided a safety margin of 8.5-fold for the maximum recommended human dose (MRHD).

### **Monkey**

Elagolix findings in monkey were observed only in the 6-week study and not in the study of longest duration (13 weeks) most likely due to substantial decline in plasma concentrations due to induction of enzymes responsible for elagolix metabolism. In the 6-week study, cynomolgus monkeys (3 to 5/sex/group) were administered elagolix sodium (doses: 0, 75, 150, 300 or 600 mg/kg/day) by oral gavage. Notable findings included atrophy of the female reproductive organs; of uterus at doses  $\geq 150$  mg/kg/day and of cervix and vagina at all doses. These effects were considered pharmacologically mediated effects and were reversible after a recovery period of 4 weeks. Because a marked body weight loss and reduced food intake were observed at the 600 mg/kg/day dose, the NOAEL was 300 mg/kg/day. The AUC of 24.8 mcg·hr/mL at the NOAEL resulted in a safety margin of approximately 7.1-fold with respect to the AUC at the MRHD.

## **Dog**

Elagolix (as powder in capsule) was administered orally at doses of 0, 10, 30 or 150 mg/kg/day to beagle dogs (6/sex/group) for 39 weeks. The NOAEL was 30 mg/kg/day based on clinical chemistry and gallbladder changes (granulomatous inflammation in the lamina propria of the mucosa) observed at the highest dose of 150 mg/kg/day. The AUC of 26 mcg·hr/mL at the NOAEL resulted in a safety margin of approximately 7.4-fold with respect to the AUC at the MRHD.

## **Carcinogenicity**

The 2-year carcinogenicity studies (conducted in mice and rats) revealed no increase in tumors in mouse at any dose, but an increase in thyroid (male and female) and liver (males only) tumors occurred in rat at the high dose (13-fold margin of safety with respect to 200 mg twice daily in women). The rat tumors were identified as being species-specific and of negligible relevance to humans. This conclusion is based on a follow-on investigative study that demonstrated that tumor formation was related to induction of hepatic drug metabolizing enzymes at the high dose and that the specific mechanism of induction is not relevant for humans.

## **Genotoxicity**

Mutagenicity studies have been performed with elagolix using in vitro and in vivo test systems. These studies provided no evidence of a mutagenic or clastogenic potential.

## **Reproductive and Developmental Toxicology**

In rats there was no effect in the fertility study at doses up to 300 mg/kg/day in males and females (11.9-fold and 4.6-fold the MRHD based on AUC, respectively), however, it must be noted that the lack of effects on reproduction may be due to the low affinity of elagolix for the rat gonadotropin releasing hormone (GnRH) receptors. The affinity of elagolix for the rat GnRH receptor is 650-fold lower than for the human GnRH receptor. In a 6-week monkey repeat-dose study (doses: 0, 75, 150, 300 and 600 mg/kg/day), a reversible atrophy of reproductive organs (cervix, uterus and vagina) was observed at all doses, which is approximately 1-fold the MRHD based on AUC.

Elagolix was administered by oral gavage to pregnant rats (25 animals) at doses of 0, 300, 600 and 1200 mg/kg/day and to rabbits (20 animals) at doses of 0, 100, 150, and 200 mg/kg/day, during the period of organogenesis. No fetal malformations were present at any dose level tested in either species. Maternal toxicity in rats due to treatment with elagolix included 6 deaths and decreases in body weight gain and food consumption. Increased post-implantation losses and visceral and skeletal variations were present at maternally toxic doses. In rabbits, three abortions and a single total litter loss were observed at a maternal toxic dose of 200 mg/kg/day. A single total litter loss at a lower non-maternally toxic dose of 150 mg/kg/day was attributed to the pharmacologic mechanism of elagolix. The exposure of elagolix in the rat embryo-fetal development (EFD) study at the NOAEL of 300 mg/kg/day was 15.8-fold MRHD based on AUC. The affinity of elagolix for the rat GnRH receptor is 650-fold lower than for the human GnRH receptor. The exposure of elagolix in the rabbit EFD study at the NOAEL of 150 mg/kg/day was 6.6-fold MRHD based on AUC. The affinity of elagolix for the rabbit GnRH receptor is 3.8-fold lower than for the human GnRH receptor.

In a pre- and post-natal study in rats, elagolix was given in the diet to achieve doses of 0, 100 and 300 mg/kg/day from gestation Day 6 to lactation Day 20. There was no evidence of maternal toxicity. Pup survival was decreased from birth to post-natal day 4. Pups had lower birth weights and lower body weight gains were observed throughout the pre-weaning period only at 300 mg/kg/day. Smaller body size and effect on startle response were associated with lower pup weights at 300 mg/kg/day. Post-weaning growth, development and behavioral endpoints were unaffected by elagolix treatment. Maternal plasma concentrations on lactation Day 21 at 100 and 300 mg/kg/day (47.2 and 125 ng/mL) were 0.06-fold and 0.16-fold the human  $C_{max}$  at the MRHD.

No measurement of elagolix was conducted in the milk of lactating rats. In the range-finding pre- and post-natal study, pregnant rats were given diet containing elagolix throughout the gestation and lactation periods to achieve a daily elagolix dose of 400 mg/kg. During nursing, the dams and litters were divided into restricted feeding and non-restricted groups to determine whether elagolix was secreted in the mother's milk. At post-natal Day 10 and 20, elagolix plasma concentrations in pups of the restricted feeding litters were not measurable. In pups of the non-restricted feeding group, elagolix plasma concentrations were measurable and approximately 1% of the mother's plasma concentrations. Using plasma concentrations in pups as a surrogate of exposure via lactation, elagolix is considered to be minimally secreted in milk.

### **Special Toxicology Studies**

None

### **Juvenile Toxicity**

Not applicable.

## **16. SUPPORTING PRODUCT MONOGRAPHS**

Not applicable.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

**ORILISSA™**

**elagolix (as elagolix sodium) tablets**

**Read this carefully before you start taking ORILISSA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ORILISSA.**

**What is ORILISSA used for?**

- ORILISSA is used to treat the painful symptoms of endometriosis.
- Endometriosis happens when the tissue that forms the lining of the womb grows in other parts the body. This can cause pain when you have your period, during other times of the month or during sex.
- It is not known if ORILISSA is safe and effective in children under 18 years old.

**How does ORILISSA work?**

Estrogen is the hormone that causes the tissues lining your womb to thicken each month. When estrogen levels go down, the tissues break down and you get your period. When this happens to tissues growing outside of your womb, you can bleed inside your body. This causes pain and scars to form. ORILISSA treats endometriosis by lowering the amount of estrogen in your body. The symptoms of endometriosis often get better after 1 month of taking ORILISSA.

ORILISSA improves the symptoms of endometriosis, such as:

- pain during periods
- pain between periods
- heavy bleeding during periods
- pain during sex
- pain or discomfort in the belly or pelvic region

Patients who take ORILISSA are often able to stop taking other kinds of pain medications for endometriosis. Talk to your healthcare professional to see if this is an option for you.

ORILISSA may help you feel better by reducing your pain. It may also improve your emotional well-being, and help you feel like you have more control over your symptoms.

## **What are the ingredients in ORLISSA?**

**Medicinal ingredients:** elagolix (as elagolix sodium)

**Non-medicinal ingredients:** magnesium stearate, mannitol, polyethylene glycol, polyvinyl alcohol, povidone, pregelatinized starch, sodium carbonate monohydrate, talc, and titanium dioxide.

The 150 mg tablet also contains carmine high tint.

The 200 mg tablet also contains iron oxide red.

## **ORLISSA comes in the following dosage forms:**

Tablets: 150 mg and 200 mg elagolix (as elagolix sodium)

## **Do not use ORLISSA if you:**

- are allergic to elagolix or to any of the other ingredients in ORLISSA (see the section **What are the ingredients in ORLISSA?**)
- are pregnant or think you might be pregnant
- have severe liver disease
- know you have osteoporosis
- have unexplained bleeding from your vagina
- are taking cyclosporine, used to prevent organ rejection in people who have had organ transplants, or gemfibrozil, used to lower high cholesterol

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ORLISSA. Talk about any health conditions or problems you may have, including if you:**

- have a history of bone mineral loss. ORLISSA may result in a small loss of minerals from bone. The bone mineral loss may be increased during treatment with ORLISSA if you:
  - use alcohol excessively
  - smoke
  - have a family history of osteoporosis (thinning of the bones with fractures)
  - take other medications that can cause thinning of the bones, for example steroids
- have liver problems

- have a history of mental health problems such as depression or suicidal thoughts
- are pregnant or trying to get pregnant. You should not become pregnant while taking ORILISSA. ORILISSA may affect the way your unborn baby develops or cause early pregnancy loss (miscarriage). If you think you have become pregnant while taking ORILISSA, stop taking ORILISSA and contact your healthcare professional immediately.
- are breastfeeding or plan to breastfeed. The effects of ORILISSA on breast milk and the nursing baby are not known. Talk to your healthcare professional about the best way to feed your baby if you take ORILISSA.

**Other warnings you should know about:**

**Birth control**

ORILISSA is **NOT** birth control. ORILISSA does not prevent pregnancy. You will need to use effective methods of birth control while taking ORILISSA. Talk to your healthcare professional about which birth control to use while taking ORILISSA. Your healthcare professional may change your birth control when you start treatment with ORILISSA as hormonal birth control that contains estrogen can affect how ORILISSA works. You must continue to use effective birth control for one week after stopping treatment with ORILISSA.

**Bleeding changes**

ORILISSA may change your periods. This may lead to:

- irregular bleeding or spotting
- increase or decrease in bleeding
- no bleeding at all

These changes may make it harder to know if you are pregnant. Periods generally come back about 4 weeks after stopping ORILISSA.

**Bone health**

Taking ORILISSA can result in a small loss of minerals from your bones. If you use ORILISSA for a long time, it may increase the risk of weak, porous bones (osteoporosis). This could increase the risk of broken bones, especially after menopause. Your bones may not recover completely when you stop taking ORILISSA. While you are taking ORILISSA, your healthcare professional may tell you to:

- exercise regularly
- eat a healthy diet
- take vitamin D, calcium supplements

Your healthcare professional may order an X-ray test after 1 year of use of ORILISSA or more often, if needed. This test, called DXA, is used to check your bone health.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. The following medicines may interact with ORILISSA:

- digoxin, which is used to treat some heart conditions
- rifampin, which is used to treat certain infections
- midazolam, which is used to treat anxiety
- rosuvastatin, which is used to lower blood cholesterol
- hormonal birth control that contains estrogen, such as “the pill”

### **How to take ORILISSA:**

Take ORILISSA at about the same time each day, even if symptom-free. You may take ORILISSA with or without food.

You should start taking ORILISSA on the day you start your period to ensure you are not pregnant. You must confirm that you are not pregnant before starting treatment with ORILISSA.

### **Usual adult dose:**

Your healthcare professional may prescribe either:

- ORILISSA 150 mg once a day
- ORILISSA 200 mg twice a day

### **Overdose:**

If you think you have taken too much ORILISSA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

### **Missed dose:**

150 mg once a day: take it as soon as you remember, as long as it is on the same day. Do not take more than 1 tablet each day.

200 mg twice a day: take it as soon as you remember, as long as it is on the same day. Do not take more than 2 tablets each day.

## **What are possible side effects from using ORILISSA?**

These are not all the possible side effects you may feel when taking ORILISSA. If you experience any side effects not listed here, contact your healthcare professional.

### **Side effects may include:**

- hot flash
- night sweats
- headache
- dizziness
- feeling sick to the stomach (nausea)
- diarrhea, stomach pain, constipation
- weight increase
- difficulty sleeping
- anxiety, depression, irritability
- mood swing
- decreased sex drive (libido)
- runny, stuffy nose, sore throat, sinus infection, common cold
- joint pain
- menstrual bleeding changes:
  - irregular bleeding or spotting
  - increase or decrease in bleeding
  - no bleeding at all

ORILISSA can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b>			
<b>Mood Changes:</b> feeling sad or depressed, being tearful, loss of interest in daily activities, thoughts of harming yourself (suicidal thoughts)		✓	
<b>VERY RARE</b>			
<b>Liver Disorder:</b> yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p><b>Reporting Side Effects</b></p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> <li>• Visiting the Web page on Adverse Reaction Reporting (<a href="http://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting">www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting</a>) for information on how to report online, by mail or by fax; or</li> <li>• Calling toll-free at 1-866-234-2345.</li> </ul> <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>
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**Storage:**

Store between 2 and 30°C.

Keep out of reach and sight of children.

**If you want more information about ORILISSA:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website ([www.canada.ca/en/health-canada](http://www.canada.ca/en/health-canada)), the manufacturer's website ([www.abbvie.ca](http://www.abbvie.ca)), or by calling 1-888-704-8271.

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