CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210450Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210450
PDUFA Goal Date	07/23/2018
OSE RCM #	2017-1778
Reviewer Name(s)	Courtney Cunningham, PharmD
Acting Team Leader	Laura Zendel, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	July 23, 2018
Subject	Evaluation of Need for a REMS
Established Name	Elagolix
Trade Name	Orilissa
Name of Applicant	AbbVie Inc.
Therapeutic Class	Nonpeptide, gonadotropin-releasing hormone (GnRH) receptor antagonist
Formulation(s)	
Dosing Regimen	150 mg orally once daily; 200 mg orally twice daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Orilissa (elagolix) is necessary to ensure the benefits outweigh its risks. AbbVie Inc. submitted a New Drug Application (NDA 210450) for Orilissa with the proposed indication of management of endometriosis with associated moderate to severe pain. Emergent adverse events of special interest (AESI) were psychiatric events/suicidal ideation, bone mineral density decreases, and hepatocellular transaminase elevations. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Bone, Reproductive, and Urologic Products (DBRUP) agree that a REMS is not needed to ensure the benefits of Orilissa outweigh its risks. Subjects taking both Orilissa doses in the applicant's clinical trials demonstrated statistically significant improvements in dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP) versus placebo. Both clinically and statistically significant were the reduction in subjects' analgesic use and overall pain improvement on the patient global impression of change (PGIC) response scale. Likely prescribers of Orilissa should be familiar with the risks including decrease in bone mineral density, psychiatric events, and suicidal ideation, as other drugs in the class to treat endometriosis have similar risks, and patients are closely monitored for this condition, therefore it could be expected that patients are likely to be monitored for drug-induced liver injury.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Orilissa (elagolix) is necessary to ensure the benefits outweigh its risks. AbbVie Inc. (AbbVie) submitted a New Drug Application (NDA 210450) for Orilissa with the proposed indication of management of endometriosis with associated moderate to severe pain. This application is under review in the Division of Bone, Reproductive, and Urologic Products (DBRUP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Orilissa sodium, a new molecular entity with priority review status, is a gonadotropin-releasing hormone (GnRH) receptor antagonist proposed for the indication of management of endometriosis with associated moderate to severe pain. Orilissa produces a dose-dependent suppression of pituitary secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH). This results in decreases in ovarian production of estradiol and other sex hormones.[1]

Orilissa is proposed as 150 mg and 200 mg oral tablets and is dosed as 150 mg orally once daily or 200 mg orally twice daily in the outpatient setting.[1] It is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210450 relevant to this review:

- 08/23/2017: The Agency received an NDA submission for Orilissa tablets. AbbVie did not submit a proposed REMS.
- (b) (4) NDA 210450.
- 12/11/2017: A Post Mid-cycle teleconference was held between the Agency and AbbVie. The Agency informed AbbVie that based on the currently available data; there are no safety issues that require a REMS for Orilissa.
- 3/1/2018: An Information Request (IR) was sent requesting comprehensive information regarding all findings of elevated liver function tests, potential Hy's Law cases, including complete medical records on a specific subject in question that was improperly noted in trial findings.
- 3/26/18: After reviewing the March 19, 2018 IR amendments from the applicant, a major amendment was issued, and the goal date was extended to July 23, 2018.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Endometriosis affects up to 11% of women in the United States. The exact percentage is unknown, as not all cases are diagnosed.[2] The primary symptom is pelvic pain, which may extend to the back and abdomen, and is typically worse around the time of menstruation. Other symptoms include dysmenorrhea, dyspareunia, menorrhagia and/or menometrorrhagia, dysuria, painful or abnormal bowel movements, bloating and nausea, especially during periods, and is a cause of infertility. Women who have endometriosis also have a higher incidence of ovarian cancer. While exact etiology is unknown, several theories exist, including peritoneal cell transformation, surgical scar implantation, retrograde menstruation, embryonic cell transfer, endometrial cell transport, and immune system disorder. Diagnosis is made either with ultrasound or laparoscopy. Risk factors include low BMI, uterine abnormalities, alcohol consumption, and family history. Any medical condition that prevents normal menstrual flow from the body, or higher exposure to estrogen either through high estrogen levels, short menstrual cycles, early menarche or late menopause also increases the risk of developing endometriosis.[3] An additional report showed that women with endometriosis have a higher risk of preterm birth, miscarriage, placenta previa, infants with low birth weight, and preeclampsia.[4]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Several treatment options, while not curative, exist for patients with endometriosis. Several GnRH agonists, namely leuprolide, nafarelin, and goserelin are available as nasal sprays or injections, are approved for the treatment of endometriosis. Norethindrone is used as a daily oral hormonal addback therapy with leuprolide to minimize its detrimental effects on bone mineral density. Danazol, an oral androgenic steroid that suppresses the pituitary-ovarian axis is also approved for the treatment of endometriosis. None of the FDA approved treatments have a REMS. Other pharmacological therapies

which are not FDA approved for this indication, but are widely used, are both progestin only and combined oral contraceptives, often used as continuous cycles for pain control.[5] Medroxyprogesterone depot injections are also used. To control pain, oftentimes either prescription or over the counter NSAIDs, or in severe cases, opioids are employed. Laparoscopy can be used to both diagnose and excise endometrial lesions; however, many patients experience regrowth or incomplete removal and will require intervention again within 2 years.[3] Hysterectomy is used as a last resort for patients refractive to other therapies. Table 1 below summarizes available endometriosis treatment options.

Table 1. Summary of Endometriosis Treatment Options

Product Trade Name (Generic)	Drug Class-Approved to Treat Endometriosis or Used in Clinical Practice	Dosing and Administration	Important Safety and Tolerability Issues	Boxed Warning
Lupron[6] (leuprolide acetate) depot injection 3.75 mg, 11.25 mg	GnRH Agonist-approved for endometriosis	-3.75 mg IM (intramuscularly) monthly, 11.25 mg IM once every 3 months -6-month duration of therapy limitation	-Use with norethindrone addback therapy -Use with calcium supplementation	No
Synarel[7] (nafarelin acetate) nasal spray	GnRH Agonist-approved to treat endometriosis	-400 mcg daily-may be increased to 800 mcg daily -6-month duration of therapy recommended	-Nasal decongestants must not be used for 2 hours post nafarelin dose	No
Zoladex[8] (goserelin acetate) implant	GnRH Agonist-approved to treat endometriosis	-3.6 mg subcutaneously once every 28 days -6-month duration of therapy limitation	-Unknown safety profile when used for more than one 6-month course of therapy	No
Danazol[9] (danazol) capsule	Androgenic steroid-approved to treat endometriosis	-200 mg-400 mg daily in 2 divided doses for mild disease states -800 mg daily in 2 divided doses for moderate-severe disease	-Androgen-like adverse effects	Yes (pregnancy contraindicated thrombotic events, peliosis hepatis, benign hepatic adenoma, and intracranial hemorrhage)
Depo Provera[10] (medroxyprogesterone acetate)	Progesterone-not approved, but used clinically to treat endometriosis	-150 mg deep IM once every 13 weeks	-Calcium and Vitamin D intake should be adequate	Yes (BMD loss/length of use)

4 BENEFIT ASSESSMENT

The safety and efficacy of Orilissa for the treatment of pain associated with endometriosis was studied by the applicant in two pivotal Phase 3 trials M12-665 (NCT01620528) and M12-671(NCT01931670), and their respective extension studies M12-667 (NCT01760954) and M12-821(NCT02143713). M-665 and M12-671, the 2 pivotal trials, were both identically designed, randomized, double blind, placebo controlled, multicenter trials of female subjects ages 18-49 years old with moderate to severe endometriosis. Study M12-665 was conducted solely in North America, while M12-671 was global. M12-667 and M12-821, the 2 extension trials, were uncontrolled, randomized, double-blind, and multicenter. Supportive Phase 2 studies NBI-56418-0501(NCT00109512), NBI-56418-0504, NBI-56418-0702 (NCT00619866), NBI-56418-0703 (NCT00797225), and NBI-56418-0901 (NCT00973973), were used for supporting safety data. Subjects who were taking hormonal therapies including estrogen and/or progestin preparations, all hormonal contraceptives, and GnRH agonists were subject to a washout period of 2-6 months, depending on what medication they had been using. A screening period of approximately 100 days then began prior to randomization. The pivotal studies had primary endpoints of dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP), measured at months 3 and 6 of treatment. The extension studies continued treatment for another 6 months. Subjects were instructed to take 400 IU of vitamin D and 500-1,000 mg calcium daily for the 6-month treatment period. Once done with active treatment, patients entered a 12-month Post-Treatment Follow-up period (PTFU). Hormonal medications, nonhormonal estrogen supplements, Cytochrome P450 inducers, bisphosphonates, long and short acting strong opioid analgesics, transdermal and IV opioid analgesics were all prohibited during these studies. Permitted rescue analgesics were naproxen, codeine, or acetaminophen in conjunction with tramadol, codeine, and hydrocodone.

For coprimary efficacy endpoints, DYS and NMPP, subjects were considered responders if there was no increase in endometriosis rescue analgesic use and a clinically meaningful reduction in pain based on daily e-diary scores with anchor, Patient Global Impression of Change assessment forms at 3 months, with a response threshold derived by the applicant using a receiver operating characteristics analysis (ROC). The ROC analysis used Patient Global Impression of Change (PGIC) assessment forms, which measured the subject's perceived change in endometriosis associated pain.

In study M12-665, 249 patients received Orilissa 150 mg daily, 248 patients received Orilissa 200 mg twice daily, and 374 patients received placebo for 6 months, and a PTFU of 12 months ensued. Both doses of Orilissa had a statistically significant proportion of DYS and NMPP responders as compared to placebo at both 3 and 6 months. At month 3 DYS reporting, Orilissa 150 mg daily had 46.4% and Orilissa 200 mg twice daily had 75.8% response versus placebo at 19.6% ($p<0.001$). Month 6 DYS response rates included Orilissa 150 mg once daily 42.1%, Orilissa 200 mg twice daily 75.3%, and placebo 23.1% ($p<0.001$). NNMPP placebo response at month 3 was 36.5%, while Orilissa 150 mg was 50.4% and Orilissa 200 mg twice daily was 54.5% ($p<0.001$). At 6 months, NMPP response was still statistically significant from placebo, (34.9%), with 150 mg daily having 45.7% respond ($p=0.008$), and 200 mg daily showing a 62.1% ($p<0.001$) response.

In study M12-671, 226 patients received Orilissa 150 mg daily, 229 patients received Orilissa 200 mg twice daily, and 360 patients received placebo for 6 months, then began a PTFU of 12 months. Again,

both doses of Orilissa had a statistically significant proportion of DYS and NMPP responders as compared to placebo at both 3 and 6 months. Reporting at month 3 DYS Orilissa 150 mg once daily had 43.4% and Orilissa 200 mg twice daily had 72.4% response versus placebo at 22.7% ($p<0.001$). Month 6 DYS response rates included Orilissa 150 mg once daily 46.2%, Orilissa 200 mg twice daily 76.9%, and placebo 25.4% ($p<0.001$). NNMPP placebo response at month 3 was 36.5%, while Orilissa 150 mg was 49.8% ($p=0.003$) and Orilissa 200 mg twice daily was 57.8% ($p<0.001$). At 6 months, NMPP response was still statistically significant from placebo, (40.6%), with Orilissa 150 mg daily having 51.6% respond ($p=0.010$), and Orilissa 200 mg twice daily showing a 62.2% ($p<0.001$) response.

In study M12-667, patients from study M12-665 were rerandomized in the following breakdown; (pivotal trial dose Orilissa [ELA] or placebo[PBO]/extension dose[ELA/PBO]): ELA /ELA 150 mg once daily (n=149), ELA/ELA 200 mg twice daily(n=138), PBO/ELA 150 mg once daily(n=108), PBO/ELA 200 mg twice daily(n=109) to demonstrate 12-month efficacy of Orilissa. Patients still demonstrated a response at 6 months, greatest with Orilissa 200 mg. This is summarized in Table 2 below.

Table 2. Extension Study M12-667 Percentage of Subjects Considered Responders to Orilissa at Extension Month 6

Dosing	n	DYS Responder % at Extension Month 6	NMPP Responder % at Extension Month 6
Pivotal Orilissa 150 mg/Extension (Xtn) Orilissa 150 mg	149	52.1	67.5
Pivotal Orilissa 200 mg/(Xtn) Orilissa 200 mg/(Xtn)Orilissa 200 mg	138	78.2	69.1
Pivotal Placebo/(Xtn) Orilissa150 mg	108	32.6	39.5
Pivotal Placebo/(Xtn) Orilissa 200 mg	109	64.4	57.5

In study M12-821, patients from study M12-671 were rerandomized as follows: (pivotal trial dose Orilissa [ELA] or placebo [PBO]/extension dose[ELA/PBO]): ELA /ELA 150 mg once daily(n=142), ELA /ELA 200 mg twice daily (n=140), PBO/ELA 150 mg once daily(n=102), PBO/ELA 200 mg twice daily (n=111), again to study long term efficacy of Orilissa. The clinical reviewer noted the rapid onset of action of Orilissa in regard to DYS response and constancy of responses in the two trials. The results are summarized in Table 3 below.

Table 3. Extension Study M12-821 Percentage of Patients Considered Responders to Orilissa at Extension Month 6

Dosing	n	DYS Responder % at Extension Month 6	NMPP Responder % at Extension Month 6
Pivotal Orilissa 150 mg/Extension Orilissa 150 mg	142	50.8	66.4
Pivotal Orilissa 200 mg/Extension Orilissa 200 mg	140	75.9	67.2
Pivotal Placebo/Extension Orilissa 150 mg	102	37.0	27.2
Pivotal Placebo/Extension Orilissa 200 mg	111	57.1	32.7

5 Risk Assessment & Safe-Use Conditions

Safety data from Phase 3 pivotal studies M12-665, its extension M12-667, and M12-671 and its extension M12-821, were pooled to form the clinical summary of safety along with five Phase 2 supportive studies. 685 women with endometriosis received Orilissa 150 mg daily and 697 women with endometriosis received Orilissa 200 mg twice daily in Phase 3 clinical trials as of June 19, 2017. Long term safety was evaluated in the 6-month extension studies listed above. The most frequently reported adverse events were hot flush, headache, and nausea (all >10%). Mood related adverse event incidence was also higher in Orilissa (10.8%), compared to placebo (6.1%). Adverse events of special interest are bone mineral density decrease, psychiatric events, and suicidal ideations, and hepatocellular transaminase elevations. Characterizations on these safety issues follow.[11]

5.1 DEATH

During the clinical development program there were 4 deaths reported. The first was a suicide during a Phase 3 trial. The subject received Orilissa 150 mg daily for 31 days, and received the last dose of study medication 2 days prior. The death was assessed by the investigator as not reasonably related to study drug, but likely due to life stressors, however, the clinical reviewer cannot exclude Orilissa from association. The second death was a suicide in the Phase 3 fibroid trial. The patient had neither been randomized nor received study drug, and her death was ruled suicide by opioid overdose. The clinical reviewer ruled that due to the patient never receiving Orilissa, this suicide would be ruled unrelated to study drug. The third death was reported in a Phase 1 study. The subject had received a single dose of study drug 20 days prior, and was found deceased on study day 21. The subject had alcoholic cirrhosis, and due to the subject being found with excessive blood in her mouth and nose, investigators believe ruptured esophageal varices could be a possible cause of death. No autopsy was performed. Due to hepatocellular transaminase elevations seen in Orilissa, the clinical reviewer is not able to rule out any role Orilissa may have had in this death. Lastly, the fourth death was included in a 4-month follow-up analysis not included in the original submission. The subject received her last dose of study drug on (b) (6), and died on (b) (6). She reportedly was intoxicated at her home, and then stopped breathing. EMS responded, but the subject was pronounced dead on arrival at the hospital.

5.2 ADVERSE EVENTS OF SPECIAL INTEREST (AESIS)

5.2.1 Psychiatric Events/Suicidal Ideation

In addition to the completed suicide referenced in section 5.1 above, the phase 3 Endo Controlled Analysis Set demonstrated that in subjects with a past medical history of depression, Orilissa therapy increased reported symptoms of depression on Standardized MeDRA Query (SMQ). 16/28 subjects with a history of depression treated with Orilissa reported symptoms of depression, while 8/16 placebo treated subjects with a history of depression reported symptoms. In the depression and suicide/self-injury SMQ, 10.8% of Orilissa subjects reported AE's while only 6.1% of placebo subjects reported AEs. Mood swings were the most commonly reported AE in the depression/suicide/self-injury SMQ, reported by 4.2% of Orilissa subjects compared to 2.5% in placebo. Adverse events in this SMQ led to a 1.5% rate

of discontinuation in Orilissa subjects as compared to 0.7% in placebo. Subjects with a past medical history of depression reported more symptoms than those who did not have a previous diagnosis, and the clinical reviewer noted in the review the data suggest there may be more concern for those with a history of depression. There were 3 total reports of suicidal ideation in subjects taking Orilissa.[11] This AE is seen in other products approved to treat fibroids, and is thought that symptoms may stem from a decrease in estrogen. This will be addressed in the Orilissa label in section 5.3.

5.2.2 Bone Mineral Density Decrease

Orilissa decreased bone mineral density in total hip, lumbar spine, and femoral neck measurements at both 6 months and 12 months of therapy. The decrease was dose and treatment length dependent; the longer the treatment and higher the dose, the greater the bone density decrease. The greatest decrease was seen at the lumbar spine, with a mean decrease of -3.76% (CI -4.19, -3.32). Mean percent decreases in Orilissa subjects at all sites during the pivotal month 6 and extension month 6 measurements were statistically significant. However, the subjects' Z Scores did not see a drop into below normal range accordingly; only 1 patient in the analysis dropped below -2, the lower limit of normal.

3/11 subjects reporting a stress/traumatic fracture had a bone mineral density decrease of $\geq$8% at any point after the pivotal study final assessment, but none had a Z Score $\leq$-1.5. Subjects' whose BMD decrease was $\geq$3% from baseline at post-treatment follow-up month 12 were referred to a bone specialist.[11] The majority received lifestyle alteration, and 1 patient received a prescription calcium/vitamin D supplement. This TEAE is noted in other products used in endometriosis therapy, and the loss may be irreversible. The clinical reviewer concluded that, "Considering the totality of evidence with respect to progressive declines in BMD and lack of full recovery, treatment with Orilissa should be limited." Orilissa labeling is proposed to limit use to 6 months for patients taking 200 mg twice daily and moderately hepatically impaired patients taking 150 mg daily. The label will limit patients of normal hepatic function to 24 months of 150 mg once daily therapy. Labeling will also include a warning that bone mineral density loss may not be completely reversible, and increases with greater duration of use. Decreases in bone mineral density will be addressed in the Orilissa label section 5.3

5.2.3 Hepatocellular Transaminase Elevation

At 125 days after beginning Orilissa 150 mg daily, a subject at a test site in (b) (6) for the trial M12-821 experienced elevated liver enzymes. The subject's values peaked at Day 183, with ALT and AST both at >5 times the upper limit of normal (ULN) and bilirubin >1.5 times ULN. IgM positive serology for acute Hepatitis A infection was received by the Agency from the applicant on February 26, 2018.

The applicant subsequently submitted 40 study subjects who had received at least 1 dose of Orilissa who experienced ALT and/or AST elevations >3 times ULN or were discontinued for elevated liver enzymes, regardless of value in response to an Information Request from the Agency. Alternative etiologies or confounding factors were offered for 31/37 subjects. Of the remaining 6, 2 had >5 times ULN elevations (doses were 150 mg and 600 mg of Orilissa), and 4 had elevations > 3 times ULN (Orilissa doses 75 mg, 150 mg, 200 mg, and 300 mg). 3 of these 6 discontinued treatment due to these

elevations, and the remaining 3 had resolution or decline of transaminase levels despite treatment. In the phase 3 endometriosis studies, dose dependent elevations of serum ALT of at least 3 times ULN were noted with Orilissa; (placebo = 0.1%; 150 mg/day = 0.2%; 200 mg twice daily = 1.1%). Similar dose dependent effects were seen during the extension studies. A consultation from the Division of Gastrointestinal and Inborn Errors Products, (DGIEP) concluded that while they agreed with the applicant that language must be included to warn prescribers of liver transaminase elevations and instruction to discontinue and seek medical advice if symptoms such as jaundice occur in the Warnings and Precautions section of labeling. Elevations in hepatic transaminases will appear in section 5.3 of Orilissa labeling.

6 Expected Postmarket Use

Orilissa is most likely to be prescribed by Obstetricians/Gynecologists. Once prescribed, Orilissa can be dispensed and self-administered orally by patients in the outpatient setting. Prescribers of Orilissa are likely to be familiar with the risks of bone mineral density loss and depression/suicidality as it has been demonstrated with other GnRH agonists approved to treat endometriosis.

7 Risk Management Activities Proposed by the Applicant

AbbVie proposed the following risk management activities:

- Pharmacovigilance plan including both routine pharmacovigilance in the form of prescriber questionnaires regarding incidences of bone mineral density decreases, psychiatric events, and pregnancy outcomes. AbbVie also proposed enhanced pharmacovigilance by two postmarketing clinical trials focused on long-term exposure, hormonal add-back therapy, and reversibility of bone density changes. AbbVie proposed a pharmacoepidemiology study within the (b) (4) database to provide information on outcomes of women and infants who are exposed to Orilissa during pregnancy.

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of the REMS program and defer to Division of Pharmacovigilance and/or Epidemiology for review and input.*

8 Discussion of Need for a REMS

After thoughtful review, the clinical reviewers recommend approval of Orilissa on the basis of the efficacy and safety information currently available. Orilissa is proposed for the management of pain associated with endometriosis. This condition is most often diagnosed in adult females, and carries a

significant physiological and psychological burden to the patient. While the most common adverse events seen with Orilissa are hot flush, headache, and nausea, three treatment emergent adverse events of special interest occurred during clinical trials; bone mineral density decrease, psychiatric events and suicidal ideations, and hepatocellular transaminase elevations.

Bone mineral density decreases are a common risk in GnRH agonists and medroxyprogesterone, both used as therapies in endometriosis. It is unclear how this potentially cumulative and permanent premenopausal bone loss may affect women as they age in menopause and beyond, especially if a female uses several different therapies over her lifetime. Adequate calcium and vitamin D supplementation is vital, as well as consideration by providers for bone mineral density assessment in patients who have a history of low-trauma bone fracture or other risk factors for bone loss or osteoporosis. This will be noted in labeling warnings and precautions section 5.1. At the time of this review DBRUP recommends setting limitations of therapy at 6 and 24 months dependent upon dose and liver function due to this risk.

Psychiatric events and suicidal ideation are another adverse event of special interest. In a population at risk of diagnosis of depression, caution must be exercised when prescribing to patients who have a past medical history of depression. Prescribers should also monitor patients who are using Orilissa, and promptly refer patients with new or worsening depression or suicidality symptoms to a mental health professional. The risk will be included in section 5.3 of labeling. Instructions for patients who are experiencing suicidal thoughts will be included in the Medication Guide as well.

Due to the increases seen in hepatocellular transaminase in clinical trials, the recommendations from DGIEP's consult are being considered and incorporated into postmarketing requirements as well as warnings and precautions and clinical trials experience in labeling. It is expected that after appropriate counseling by providers as well as reading of the Medication Guide, patients will be able to recognize the symptoms of such as jaundice, stop Orilissa, and return to their providers for follow up care, including liver function testing, as outlined in Orilissa's labeling section 5.4.

Currently approved GnRH agonist products address bone mineral density decreases, suicidal ideation and psychiatric events in the warnings and precautions section of the labeling. A Medication Guide will be used to inform patients on the risks associated with Orilissa. None of the currently approved therapies to treat endometriosis have a REMS, as labeling for these products has, to date, been adequate for risk management. The additional concern of elevations in hepatocellular transaminases will be addressed to both patients and prescribers in labeling and the Medication Guide. Therefore, based on current available data of the risks of Orilissa, risk mitigation beyond labeling will not be necessary.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks of Orilissa. There are safety concerns associated with Orilissa, however, in general, healthcare providers who treat endometriosis should be familiar with the risk of bone mineral density loss and psychiatric events/suicidal ideations, and the importance of patient monitoring as other products commonly used for the treatment of endometriosis are labeled with these risks, so these are not uncommon to encounter in practice. Additionally, Orilissa's labeling warns prescribers of the risks of elevations in hepatic transaminase elevations, and to counsel patients to report symptoms of jaundice, then perform liver function tests on patients who do note any changes. Further, a Medication Guide informs patients about the potential for decreased bone mineral density and what to do if they are experiencing suicidal thoughts or symptoms of jaundice, and should be adequate as patients are closely monitored to mitigate this risk at this time.

Should the Division of Bone, Reproductive, and Urologic Products have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

1. AbbVie Inc. Proposed Elagolix Labeling. August 2017.
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/s/

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07/23/2018

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