CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219469Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	219469
PDUFA Goal Date	October 26, 2025
Nexus TTT #	2024-10700
Reviewer Name(s)	Christopher Booze, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Deputy Division Director	Suzanne Robottom, PharmD
Review Completion Date	October 17, 2025
Subject	Evaluation of Need for a REMS
Established Name	Elinzanetant
Trade Name	Lynkuet
Name of Applicant	Bayer
Therapeutic Class	Neurokinin 1,3 (NK-1,3) receptor antagonist
Formulation(s)	60 mg oral capsule
Dosing Regimen	120 mg once daily at bedtime

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Lynkuet (elinzanetant) is necessary to ensure the benefits outweigh its risks. Bayer submitted a New Drug Application (NDA) 219469 for elinzanetant with the proposed indication for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. Elinzanetant offers a significant reduction, compared to placebo, in both frequency and severity of hot flashes. Additionally, there is an unmet need for effective alternatives to hormonal therapy (HT), the current standard of care, because HT is contraindicated in many patients.

The risks associated with elinzanetant include: central nervous system (CNS) effects and drug-induced liver injury. The applicant did not submit a proposed REMS or risk management plan with this application. The incidence of serious adverse events in the clinical program was low, and there are no concerning care gaps that have been identified with the intended scope of use and practice. Prescribers of elinzanetant will generally be gynecologists or primary care providers who are familiar with managing medications that require routine laboratory monitoring. DRM and DUOG have determined that a REMS is not needed to ensure the benefits of elinzanetant outweigh its risks, and that all risks can be adequately mitigated through labeling.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lynkuet (elinzanetant) is necessary to ensure the benefits outweigh its risks. Bayer submitted a New Drug Application (NDA) 219469 for Lynkuet with the proposed indication for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. This application is under review in the Division of Urology, Obstetrics, and Gynecology (DUOG). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Lynkuet (elinzanetant), a new molecular entity[a], is a non-hormonal, selective neurokinin 1,3 (NK-1,3) receptor antagonist proposed for treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.[1] Lynkuet is proposed as a 60mg capsule taken orally at a dose of 120mg (two capsules) once daily at bedtime.

Elinzanetant exhibits its clinical effect by blocking neurokinin B (NKB) from binding to the kisspeptin, neurokinin B, dynorphin (KNDy) neuron. The KNDy neuron is associated with thermoregulation and is naturally inhibited by estrogen and stimulated by NKB. As estrogen decreases during menopause, NKB

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

has less opposition, resulting in increased KNDy neuronal activity. Hyperactivation of KNDy neurons results in altered thermoregulation and vasomotor symptoms ("hot flashes").[2]

Elinzanetant is not currently approved in any jurisdiction and would be the first NK-1,3 inhibitor marketed in the US, but is pharmacologically similar to fezolinetant, which is an inhibitor of NK-3 only. Fezolinetant was submitted by Astellas under the trade name Veozah (NDA 216578) for the same indication and was approved in May 2023.[3]

The labeling for Veozah had a warning and precaution for hepatic transaminase elevation at the time of approval. After cases of liver injury were reported in the post-market setting, the agency issued a Drug Safety Communication[4] on September 12, 2024 about the risk of drug-induced liver injury (DILI), and a warning about the risk of liver injury was added to labeling in addition to the existing warning about elevated liver function test values. This warning was upgraded to a Boxed Warning in December 2024 based on additional reported cases of liver injury.[5]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219469 relevant to this review:

- 7/26/2024: NDA 219469 submission received for the treatment of moderate to severe vasomotor symptoms associated with menopause received.
- 1/21/2025: A mid-cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant that the safety review was ongoing and a determination had not yet been made on whether a REMS would be needed.[6]
- 5/8/2025: A late-cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant that there were no plans to require a REMS for elinzanetant.[7]
- 7/11/2025: An information request (IR) was sent by the Agency requesting additional safety data from the Applicant.[8]
- 7/22/2025: The Applicant submitted a response to the IR including the requested information.[9]
- 7/23/2025: The Agency notified the Applicant that the July 22, 2025 submission constituted a major amendment which would result in an extension of the goal date from July 26, 2025 to October 26, 2025.[10]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Vasomotor symptoms (VMS), commonly referred to as hot flashes or night sweats, are a hallmark symptom of menopause in women. VMS are sudden sensations of heat, usually in the upper body, and

can include perspiration, flushing, chills, anxiety, and heart palpitations.[11] Up to 80% of women[b] will experience VMS at some point during the menopausal transition, and those affected by VMS average 10-20 hot flashes and night sweats weekly.[12] Symptoms have an average duration of 7 years.[13c]

VMS are not associated with a risk of mortality, however they may be highly disruptive to a patient's life, affecting sleep, concentration, mood, energy, and/or sexual function.[d]

3.2. Description of Current Treatment Options

The American College of Obstetricians and Gynecologists' (ACOG) 2014 Clinical Guidelines for the management of menopausal symptoms include recommendations for the management of VMS.[14] Systemic estrogen hormone therapy (HT) is considered to be the most effective treatment. Both oral and transdermal HT products are approved for VMS.

HT is generally well-tolerated but is associated with an increased risk of breast cancer and venous thromboembolism (VTE). Because of this, HT is contraindicated in women with a history of breast cancer or other estrogen-dependent neoplasia, or history of VTE. HT is also associated with other adverse effects such as breast tenderness, vaginal bleeding, bloating and headache. Lower doses of HT may alleviate these adverse effects but also appear to be less effective at managing VMS.

Alternatives to HT include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), although only a single SSRI (paroxetine) and no SNRIs are FDA-approved for this indication. Adverse effects of SSRIs and SNRIs include nausea, dizziness, dry mouth, nervousness, constipation, somnolence, sweating, and sexual dysfunction, and these adverse effects often resolve over time.

Fezolinetant (Veozah), a NK-3 inhibitor, was approved in 2023 for the treatment of VMS and is the first in a new class of non-hormonal treatment options with similar pharmacology to elinzanetant. Fezolinetant has a Boxed Warning for the risk of liver toxicity, and due to its recent approval is not yet incorporated into clinical guidelines.

Clonidine and gabapentin are also used off-label for management of VMS. There is limited data for their safety and efficacy for this purpose, and they are generally considered to be less efficacious than FDA-approved treatment options.

Herbal remedies such as phytoestrogen supplements, dong quai, and black cohosh are also used for over-the-counter treatment of hot flashes in some patients. These products are not regulated by the

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

FDA, have limited date to support their use, and have the potential for drug interactions (such as between dong quai and warfarin) or liver toxicity.

Given that HT is contraindicated in a significant portion of menopausal women – those who have a known or suspected history of breast cancer, other estrogen-based cancer, or VTE – there is an unmet medical need for additional non-hormonal treatment options in patients who cannot tolerate or do not respond to currently available therapies.

4. Benefit Assessment

The applicant submitted two pivotal phase 3 studies, OASIS 1 and OASIS 2, to support the efficacy of elinzanetant for the treatment of moderate to severe VMS associated with menopause. The applicant also submitted a long-term study, OASIS 3, to provide additional supportive efficacy and safety data.

The study populations for all three studies consisted of postmenopausal women ages 40-65 who were seeking treatment for VMS and had completed a hot flash daily diary (HFDD) over a two week period. OASIS 1 and OASIS 2 required participants to have experienced at least 50 moderate to severe hot flashes over the last 7 days that the HFDD was completed, while OASIS 3 required patients to have experienced moderate to severe hot flashes, but with no minimum quantity.

OASIS 1 and OASIS 2 were identical in design; both were double-blind, randomized, placebo-controlled multicenter studies that included a 12-week initial period where participants were randomized 1:1 to receive elinzanetant 120 mg daily or placebo, followed by a 14-week period where all participants received elinzanetant 120 mg daily.

OASIS 1 included 396 participants from the United States, Europe, and Israel, while OASIS 2 included 400 participants from the United States, Europe, and Canada. The primary endpoint of both studies was the mean change in daily frequency of moderate to severe hot flashes at weeks 4 and 12 of the study.

In OASIS 1, the change from baseline in frequency of moderate to severe hot flashes at week 4 was -7.60 hot flashes per day on elinzanetant 120mg and -4.31 on placebo. At week 12, the change from baseline was -8.66 on elinzanetant and -5.44 on placebo. The difference in the change from baseline between groups was -3.29 [95% CI -4.47, -2.10] at week 4 and -3.22 [-4.81, -1.63] at week 12, resulting in a statistically significant difference in favor of elinzanetant 120mg ($p<0.0001$) at both timepoints.

In OASIS 2, the change from baseline in daily frequency of moderate to severe hot flashes at week 4 was -8.58 on elinzanetant and -5.54 on placebo. At week 12, the change from baseline was -9.72 on elinzanetant and -6.48 on placebo. The difference in the change from baseline between groups was -3.04 [-4.40, -1.68] at week 4 and -3.24 [-4.60, -1.88] at week 12, resulting in a statistically significant difference in favor of elinzanetant 120mg ($p<0.0001$) at both timepoints.

In addition to meeting the threshold of statistical significance, the results of OASIS 1 and OASIS 2 met the DUOG “14/2” criteria for a clinically meaningful reduction (i.e. a reduction of at least two moderate to severe hot flashes per day or 14 per week when compared to placebo).

A variety of secondary endpoints were utilized by the studies including mean severity of hot flashes, change in frequency of hot flashes at week 1, sleep disturbance (as measured by PROMIS SD-SF-8B total score), menopause-specific qualify of life (MENQOL) score, and depression (as measured by BDI-II score). All secondary endpoints showed statistically significant differences in favor of elinzanetant in both studies, with the exception of BDI-II score which was not significantly different between groups in either study. A continued effect of elinzanetant, as measured by frequency/severity of hot flashes in the HFDD as well as PROMIS and MENQOL scores, was observed at week 26 in both studies.

OASIS 3 was a randomized, multi-center, multi-country, double-blind, placebo-controlled, parallel-group trial in which participants were randomized to receive either elinzanetant 120 mg daily or placebo for the full 52-week treatment period.

The primary efficacy endpoint for OASIS 3 was the mean change in the frequency of moderate to severe VMS from baseline to week 12. The change from baseline in daily frequency of moderate to severe hot flashes at week 12 was -4.89 on elinzanetant and -2.45 on placebo. The difference in the change from baseline between groups was -1.69 [-2.19, -1.18] at week 12, and similar differences were observed at weeks 24, 36 and 50, indicating the treatment effect was sustained throughout the treatment period.

Based on the above results, the review team concluded that substantial evidence of efficacy had been established for elinzanetant in the treatment of moderate to severe VMS associated with menopause.[15e]

5. Risk Assessment & Safe-Use Conditions

A total of 1113 women received at least one dose of elinzanetant 120 mg in either OASIS 1, OASIS 2, OASIS 3, or the phase 2 SWITCH-1 dose-finding trial. Of these, 966 were treated for at least 12 weeks and 219 were treated for at least 50 weeks. There were no deaths in any of the four studies.

For the safety analysis by the review team, the data from the shorter-term OASIS 1 and OASIS 2 studies were pooled due to their identical structure, and the data from the long-term OASIS 3 study was reviewed separately. The rates of serious adverse events (SAE) among the OASIS 1 and 2 populations was 1.2% (5/400) in the elinzanetant group and 0.8% (3/393) in the placebo group. For OASIS 3, the rate of SAE was 4.2% in the elinzanetant group and 1.9% in the placebo group. In OASIS 3, SAE rates were similar during the early period but began to separate after ~120 days, and reached their maximum separation at approximately 200 days, suggesting there could be a cumulative or delayed effect and that the full safety profile may not be captured by the shorter-term studies.

The majority of SAEs were assessed by the review team as likely unrelated to elinzanetant. Most represented typical medical events expected in postmenopausal women, including infections (pneumonia, UTIs, meningitis), cardiovascular events (MI, PE, DVT), planned surgeries, trauma/accidents, progression of pre-existing conditions (MS, diabetes), and cancers that occurred after treatment discontinuation.

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

During the course of the review, hypotension/orthostatic hypotension, risk of pregnancy loss, central nervous system effects, and liver toxicity were a focus of the safety review.

- Hypotension/orthostatic hypotension: The review team identified cases of hypotension and orthostatic hypotension in the clinical program and requested case narratives, as well as an overall breakdown of subjects' blood pressure readings, in the July 11 information request. The applicant's response provided the requested information and clarified that many subjects had low blood pressure at baseline or were on concomitant medications that could affect blood pressure. Out of 78 subjects with low blood pressure measurements, only 3 were symptomatic and none required medical intervention. While hypotension was more common with elinzanetant compared to placebo in the clinical trials, the difference was small and the review team ultimately did not recommend adding a warning to the product labeling for this risk.

- Pregnancy loss: A warning will be added to the Warnings and Precautions section of labeling based primarily on non-clinical findings. Warning 5.3 addresses the risk of pregnancy loss, based on evidence from animal studies that elinzanetant can cause pregnancy loss or stillbirth. Pregnancy is listed as a contraindication in the proposed labeling for elinzanetant and given the nature of the patient population for VMS (post-menopausal women) it would be unlikely for the drug to be prescribed in patients with the potential to become pregnant.

Central nervous system effects, and liver toxicity will be discussed in more detail in the following sections as they were deemed serious and possibly related to elinzanetant.

5.1. Central Nervous System Effects

A total of five patients experienced syncope during treatment with the study drug. The agency sent an information request (IR) on July 11, 2025 requesting additional information and case narratives on the five patients who experienced syncope, as well as several patients who experienced events that had the potential to be CNS-related such as motor vehicle accidents or falls. The applicant submitted a response on July 22, 2025.

One participant in OASIS 1, a 52-year-old woman (subject (b) (6)), experienced syncope 5 days after starting treatment, which resulted in discontinuation of the study drug. Another participant in OASIS 3, a 56-year-old woman (subject (b) (6)), experienced syncope 55 days after starting treatment. In both cases, extensive workups and imaging were performed that did not reveal any clear alternative etiology, leading the review team to classify the two events as possibly related to elinzanetant.

The other three patients with syncope were unlikely to be elinzanetant-induced according to the review team, due to the fact that there were alternate potential etiologies and the patients were able to continue the study drug without further incident. Additionally, with regard to the patients experiencing events such as falls and accidents, the review team determined those events were not caused by syncope or other CNS effects. Therefore, the agency determined that a warning for syncope will not be included in labeling at this time given the small number of events and lack of clear attribution to the study drug.

The risk of seizure was also evaluated. Subject (b) (6), a 58-year-old woman in OASIS 2, was hospitalized after experiencing three seizures in one day, 46 days after starting treatment. This patient

had a history of generalized tonic-clonic seizures over 30 years prior and was treated with two anticonvulsants that were discontinued in (b) (6) after which the patient remained seizure-free until this incident. The patient discontinued the study drug after these seizures and the adverse event was deemed related to elinzanetant by both the investigator and the agency review team. In addition, it was also noted that subject (b) (6) (mentioned above) experienced syncope accompanied with other symptoms such as blurred vision and slurred speech that suggested a seizure could have occurred, but this was never confirmed nor ruled out.

The agency's determination that these CNS SAEs are possibly drug-related is supported by nonclinical data and the pharmacology of elinzanetant. In rat toxicology studies, convulsions and tremors were observed at multiple dose levels. Additionally, one metabolite of elinzanetant (BAY 3462933) inhibits the GABAA receptor, and multiple metabolites inhibit progesterone receptors; antagonists of both receptors are known to have proconvulsant effects.

Participants taking elinzanetant in clinical trials also experienced non-serious CNS depressive effects such as dizziness, somnolence, and fatigue at higher rates when compared to placebo. The Applicant conducted a driving ability study which was reviewed by the Division of Pharmacometrics (DPM).[16] Some patients taking elinzanetant 120 mg or 240 mg exhibited a difference in driving ability compared to placebo. The average difference between the elinzanetant and placebo groups was statistically significant but did not meet the predefined threshold for driving impairment.

In summary, the review team recommended adding two CNS-related warnings to the Warnings and Precautions section of labeling. Warning 5.2 states that some patients who take Lynkuet may experience somnolence and should refrain from driving or engaging in hazardous occupations or activities until somnolence has resolved. Warning 5.4 states that Lynkuet should be used in caution in patients with a history of seizures or with conditions that lower the seizure threshold.

5.2. Liver Toxicity

Drug-induced liver toxicity was an adverse event of concern throughout the review of elinzanetant, due to its similarity to fezolinetant. Fezolinetant was approved in 2023 with a warning for hepatic transaminase elevations seen in clinical trials, and a Boxed Warning was later added in late 2024 after multiple cases of severe liver injury were seen in the post-market setting.

Nonclinical data suggested that liver toxicity may be a concern for elinzanetant. Rats and monkeys exposed to elinzanetant in short-term animal toxicity studies experienced hepatocellular necrosis. Elinzanetant and its metabolites also act as inducers of certain CYP enzymes, which can contribute to drug-induced liver injury (DILI).

In the phase 3 clinical trials (OASIS 1, 2, and 3) there were 8 patients in the elinzanetant groups who experienced either an AST/ALT elevation above 3 times the upper limit of normal (>3X ULN) or alkaline phosphatase >2X ULN, compared to two patients in the placebo groups. These cases were referred to the Agency's DILI team for further evaluation.[17]

One case was considered possible DILI by the DILI team, a 60-year old female with an ALT >8X ULN. The independent Liver Safety Monitoring Board (LSMB) did not concur with the DILI team's assessment of this case and concluded it was unlikely to be drug-related due to the long latency (day 399) and timing (5 weeks after discontinuation of the drug).

There were two other cases in phase 1/2 trials that the DILI team categorized as probable DILI, both of which had shorter latency (7 and 85 days) and resolution of the liver injury after discontinuation of the drug. Of the three possible DILI cases, none met the Hy's Law criteria of AST/ALT >3X ULN and total bilirubin >2X ULN.

CDER Computational Toxicology was consulted to perform a quantitative structure-activity relationship (QSAR) analysis,[18] which indicated that there is a key structural difference between elinzanetant and fezolinetant. Fezolinetant contains a thiadiazole ring that can readily undergo decarboxylation to reactive carbene metabolites that are believed to be the source of the drug's hepatotoxicity. Elinzanetant's benzene ring is much less likely to undergo this reaction, thus, elinzanetant is unlikely to have a hepatotoxic potential comparable to that of fezolinetant.

The review team concluded that the cases of possible DILI in the clinical trials, in combination with non-clinical findings, can be mitigated via labeling addressing the risk of elevated hepatic transaminases. The currently proposed Warnings and Precautions section includes a warning (5.1) to discontinue Lynkuet in case of signs or symptoms of liver injury, accompanied by instructions to check liver enzymes at baseline and again after 3 months. Due to the lack of clinically significant liver injuries or cases meeting the Hy's Law criteria, and a structural analysis of elinzanetant's potential to cause liver injury as compared to fezolinetant, the review team concluded this risk does not warrant a Boxed Warning at this time.

6. Expected Postmarket Use

Vasomotor symptoms of menopause (VMS) affect a large population of women, and the symptoms can have a significant impact on quality of life including sleep, energy, mental health, sexual function, and the ability to perform activities of daily life. Gynecologists and primary care providers typically diagnose and manage symptoms related to menopause on an out-patient basis. Drug utilization data gathered from fezolinetant indicates over 200,000 women treated since approval in 2023 with use increasing over time.[19] Given the similarities to fezolinetant, we expect elinzanetant to be prescribed primarily in the outpatient setting, by gynecologists and primary care providers who are already familiar with managing vasomotor symptoms of menopause with currently available therapies. These providers are likely familiar with monitoring pharmacologic therapies that require regular bloodwork, including signs, symptoms and managing liver injury.

There is unlikely to be significant off-label use of elinzanetant for coniditions other than VMS. No neurokinin 3 antagonists have been approved for conditions other than VMS. Unlike fezolinetant, elinzanetant is also an antagonist of NK1, and other NK1 antagonists have been approved for indications such as chemotherapy-induced or post-operative nausea and vomiting. Elinzanetant could theoretically be prescribed off-label for this indication, but there would be little reason for prescribers to do so when other NK1 inhibitors developed and approved for this purpose are available.

Thus, we expect prescribing of elinzanetant to be limited to the treatment of VMS associated with menopause. The proposed indication for elinzanetant is treatment of moderate to severe VMS, so there will likely be some off-label use in patients with mild VMS (defined as sensations of heat without sweating or the inability to complete an activity)[20]. We expect the safety profile in these patients to be similar to that of the target population.

No adverse events will be addressed through a Boxed Warning in labeling and no concerning care gaps (knowledge or behavior-related) have been identified with the intended scope of use and practice. Therefore, labeling is sufficient to communicate the safe-use recommendations with managing patients treated with elinzanetant.

7. Discussion of the Need for a REMS

Based on the efficacy and safety information currently available, FDA determined that a REMS is not necessary to ensure the benefits of elinzanetant outweigh the risks. Specifically, DRM and DUOG considered the risks of CNS effects and drug-induced liver toxicity.

The CNS-related risks, including the potential for seizures, can be adequately addressed through labeling. While nonclinical studies showed convulsions in rats and there was one clinical case of generalized tonic-clonic seizure in a patient with a prior seizure history, the overall incidence was low. The labeling will also include warnings about CNS depressant effects, potential next-day impairment, and advice regarding driving ability. These CNS effects such as fatigue, somnolence, and dizziness, while more common, were generally mild to moderate in severity and manageable through appropriate patient counseling and dosing recommendations (taking medication at bedtime).

With respect to hepatoxicity, while a small number of clinical trial participants experienced drug-induced liver injury (DILI) or elevations in liver enzymes, these cases were infrequent and modest in severity. The labeling will include appropriate warnings and precautions with recommendations for baseline liver function testing, follow-up monitoring at 3 months, and guidance to discontinue elinzanetant if symptoms suggestive of liver injury occur.

Many common medications include a risk of liver injury and/or hepatic enzyme elevations, and the prescribing population should be familiar with management of these risks, including monitoring liver function periodically. Similarly, CNS depression is a common side effect for a variety of medications, and prescribers should be familiar with how to counsel patients on these effects. Further, provider and patient education through labeling is expected to provide sufficient risk mitigation for the identified safety concerns without necessitating the more restrictive measures of a REMS program, which could add undue burden to the health care system with minimal additional benefit in absence of data indicating a particularly concerning signal of a serious adverse event.

8. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Lynkuet beyond routine pharmacovigilance and labeling.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore, a REMS is not necessary for Lynkuet (elinzanetant) to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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