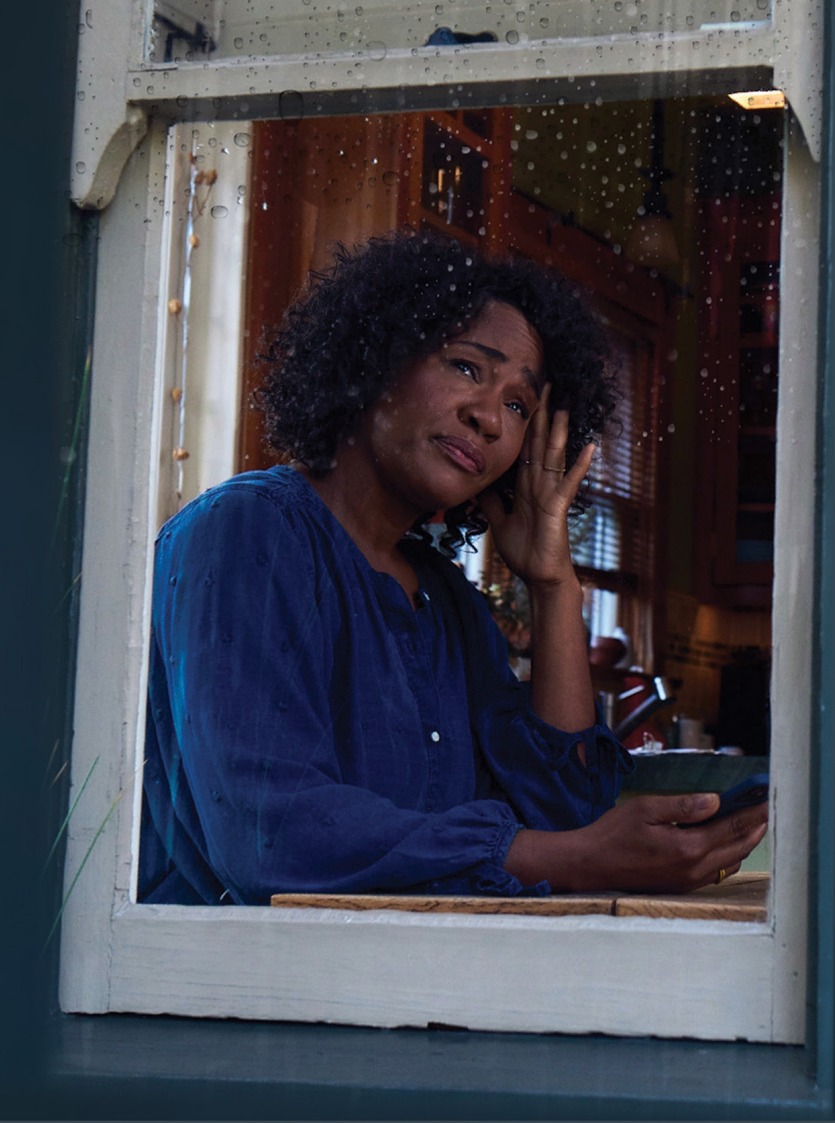

QULIPTA™ (atogepant) tablets CAN HELP PREVENT MIGRAINE ATTACKS

Migraine attacks? You can't always avoid triggers, like changes in the weather. QULIPTA™ gets right to work to prevent migraine attacks and keeps them away over time.

In a 3-month study, QULIPTA significantly reduced monthly migraine days.

Ask your healthcare provider about QULIPTA.

WHAT IS QULIPTA?

QULIPTA (atogepant) is a prescription medicine used for the preventive treatment of episodic migraine in adults.

IMPORTANT SAFETY INFORMATION

Before taking QULIPTA, tell your healthcare provider about all your medical conditions, including if you:

- Have kidney problems or are on dialysis
- Have liver problems
- Are pregnant or plan to become pregnant. It is not known if QULIPTA will harm your unborn baby
- Are breastfeeding or plan to breastfeed. It is not known if QULIPTA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking QULIPTA

Please see Brief Summary of the full Patient Information on the next page.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. QULIPTA may affect the way other medicines work, and other medicines may affect how QULIPTA works. Your healthcare provider may need to change the dose of QULIPTA when taken with certain other medicines.

The most common side effects of QULIPTA are nausea, constipation, and fatigue. These are not all the possible side effects of QULIPTA.

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

If you are having difficulty paying for your medicine, AbbVie may be able to help. Visit AbbVie.com/myAbbVieAssist to learn more.

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QULIPTA™ (atogepant) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

QULIPTA is indicated for the preventive treatment of episodic migraine in adults.

CONTRAINDICATIONS

None.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of QULIPTA is 10 mg, 30 mg, or 60 mg taken orally once daily with or without food.

Dosage Modifications

Dosing modifications for concomitant use of specific drugs and for patients with renal impairment are provided in Table 1.

Table 1: Dosage Modifications for Drug Interactions and for Specific Populations

Dosage Modifications	Recommended Once Daily Dosage
Concomitant Drug *[see Drug Interactions]*	
Strong CYP3A4 Inhibitors	10 mg
Strong and Moderate CYP3A4 Inducers	30 mg or 60 mg
OATP Inhibitors	10 mg or 30 mg
Renal Impairment *[see Use in Specific Populations]*	
Severe Renal Impairment and End-Stage Renal Disease (CLcr <30 mL/min)	10 mg

ADVERSE REACTIONS

Clinical Trials Experience

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

The safety of QULIPTA was evaluated in 1958 patients with migraine who received at least one dose of QULIPTA. Of these, 839 patients were exposed to QULIPTA once daily for at least 6 months, and 487 patients were exposed for 12 months.

In the 12-week, placebo-controlled clinical studies (Study 1 and Study 2), 314 patients received at least one dose of QULIPTA 10 mg once daily, 411 patients received at least one dose of QULIPTA 30 mg once daily, 417 patients received at least one dose of QULIPTA 60 mg once daily, and 408 patients received placebo. Approximately 88% were female, 80% were White, 17% were Black, and 12% were of Hispanic or Latino ethnicity. The mean age at study entry was 41 years (range 18 to 74 years).

The most common adverse reactions (incidence at least 4% and greater than placebo) are nausea, constipation, and fatigue.

Table 2 summarizes the adverse reactions that occurred during Study 1 and Study 2.

Table 2: Adverse Reactions Occurring with an Incidence of At Least 2% for QULIPTA and Greater than Placebo in Studies 1 and 2

	Placebo (N= 408) %	QULIPTA 10 mg (N=314) %	QULIPTA 30 mg (N=411) %	QULIPTA 60 mg (N=417) %
Nausea	3	5	6	9
Constipation	1	6	6	6
Fatigue/Somnolence	3	4	4	6
Decreased Appetite	<1	2	1	2

The adverse reactions that most commonly led to discontinuation in Studies 1 and 2 were constipation (0.5%), nausea (0.5%), and fatigue/somnolence (0.5%).

Liver Enzyme Elevations

In Study 1 and Study 2, the rate of transaminase elevations over 3 times the upper limit of normal was similar between patients treated with QULIPTA (1.0%) and those treated with placebo (1.8%). However, there were cases with transaminase elevations over 3 times the upper limit of normal that were temporally associated with QULIPTA treatment; these were asymptomatic, and resolved within 8 weeks of discontinuation. There were no cases of severe liver injury or jaundice.

Decreases in Body Weight

In Studies 1 and 2, the proportion of patients with a weight decrease of at least 7% at any point was 2.8% for placebo, 3.8% for QULIPTA 10 mg, 3.2% for QULIPTA 30 mg, and 4.9% for QULIPTA 60 mg.

DRUG INTERACTIONS

CYP3A4 Inhibitors

Coadministration of QULIPTA with itraconazole, a strong CYP3A4 inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects. The recommended dosage of QULIPTA with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is 10 mg once daily. No dosage adjustment of QULIPTA is needed with concomitant use of moderate or weak CYP3A4 inhibitors.

CYP3A4 Inducers

Coadministration of QULIPTA with steady state rifampin, a strong CYP3A4 inducer, resulted in a significant decrease in exposure of atogepant in healthy subjects. Concomitant administration of QULIPTA with moderate inducers of CYP3A4 can also result in decreased exposure of atogepant. The recommended dosage of QULIPTA with concomitant use of strong or moderate CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort, efavirenz, etravirine) is 30 mg or 60 mg once daily. No dosage adjustment of QULIPTA is needed with concomitant use of weak CYP3A4 inducers.

OATP Inhibitors

Coadministration of QULIPTA with single dose rifampin, an OATP inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects. The recommended dosage of QULIPTA with concomitant use of OATP inhibitors (e.g., cyclosporine) is 10 mg or 30 mg once daily.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of QULIPTA in pregnant women. In animal studies, oral administration of atogepant during the period of organogenesis (rats and rabbits) or throughout pregnancy and lactation (rats) resulted in adverse developmental effects (decreased fetal and offspring body weight in rats; increased incidence of fetal structural variations in rabbits) at exposures greater than those used clinically *[see* Data*]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The estimated rate of major birth defects (2.2%-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Animal Data

Oral administration of atogepant (0, 5, 15, 125, or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreases in fetal body weight and in skeletal ossification at the two highest doses tested (125 and 750 mg/kg), which were not associated with maternal toxicity. At the no-effect dose (15 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 4 times that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Oral administration of atogepant (0, 30, 90, or 130 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in an increase in fetal visceral and skeletal variations at the highest dose tested (130 mg/kg/day), which was associated with minimal maternal toxicity. At the no-effect dose (90 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 3 times that in humans at the MRHD.

Oral administration of atogepant (0, 15, 45, or 125 mg/kg/day) to rats throughout gestation and lactation resulted in decreased pup body weight at the highest dose tested (125 mg/kg/day), which persisted into adulthood. At the no-effect dose (45 mg/kg/day) for adverse effects on pre- and postnatal development, plasma exposure (AUC) was approximately 5 times that in humans at the MRHD.

Lactation

There are no data on the presence of atogepant in human milk, the effects of atogepant on the breastfed infant, or the effects of atogepant on milk production. In lactating rats, oral dosing with atogepant resulted in levels of atogepant in milk approximately 2-fold higher than that in maternal plasma. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for QULIPTA and any potential adverse effects on the breastfed infant from QULIPTA or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Population pharmacokinetic modeling suggests no clinically significant pharmacokinetic differences between elderly and younger subjects. Clinical studies of QULIPTA did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

The renal route of elimination plays a minor role in the clearance of atogepant. In patients with severe renal impairment (CLcr 15-29 mL/min), and in patients with end-stage renal disease (ESRD) (CLcr <15 mL/min), the recommended dosage of QULIPTA is 10 mg once daily. For patients with ESRD undergoing intermittent dialysis, QULIPTA should preferably be taken after dialysis. No dose adjustment is recommended for patients with mild or moderate renal impairment.

Hepatic Impairment

No dose adjustment of QULIPTA is recommended for patients with mild or moderate hepatic impairment. Avoid use of QULIPTA in patients with severe hepatic impairment *[see Adverse Reactions]*.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Atogepant was administered orally to mice (0, 5, 20, or 75 mg/kg/day in males; 0, 5, 30, 160 mg/kg/day in females) and rats (0, 10, 20, or 100 mg/kg in males; 0, 25, 65, or 200 mg/kg in females) for up to 2 years. There was no evidence of drug-related tumors in either species. Plasma exposures at the highest doses tested in mice and rats were approximately 8 and 20-35 times, respectively, that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Mutagenicity

Atogepant was negative in in vitro (Ames, chromosomal aberration test in Chinese Hamster Ovary cells) and in vivo (rat bone marrow micronucleus) assays.

Impairment of Fertility

Oral administration of atogepant (0, 5, 20, or 125 mg/kg/day) to male and female rats prior to and during mating and continuing in females to Gestation Day 7 resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) at the highest dose tested are approximately 15 times that in humans at the MRHD.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions

Inform patients that QULIPTA may interact with certain other drugs, and that dosage modifications of QULIPTA may be recommended when used with some other drugs. Advise patients to report to their healthcare provider the use of any other prescription medications, over-the-counter medications, herbal products, or grapefruit juice *[see Drug Interactions]*.

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Dublin, Ireland

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Migraine and Sexuality

Are Migraine and Libido Linked?

When it comes to sexual desire and performance, migraineurs - specifically female migraineurs - have long been getting a bad rap. For whatever reason, the "not tonight, honey.... I have a headache" cliché has transmogrified into a widely held assumption that females with migraine are hyposexual. Low on libido. Frigid "ice queens" who prefer to avoid sexual activity.

Taking this assumption at face value, one immediately is confronted by the obvious question: why? Why exactly should the 28 million American females with migraine have a lower level of sexual desire and performance than their migraine-free counterparts? As no plausible answer immediately springs to mind, it must be that in support of this sweeping assumption there exists a solid foundation of supportive scientific evidence from well-conducted research and a clear consensus from "the experts". True?

Well...not really. While the peer-reviewed medical literature contains many articles indicating that migraine negatively impacts quality of life, and while some investigators have reported that this negative impact extends to sexual desire and performance, there is accumulating evidence to refute the notion that female migraineurs are "hyposexual".

In 2006, researchers at Wake Forest University found higher levels of sexual desire in their research subjects with migraine than in those with tension-type headache. They hypothesized that this difference could be biologic in origin and specifically related to a protein, serotonin, that serves as one of the brain's major neurotransmitters. Higher levels of serotonin correlate with low sexual desire. The selective serotonin reuptake inhibitors (SSRIs), medications that elevate serotonin levels and are commonly used to treat anxiety and depression, are well known to decrease libido and inhibit orgasm. In migraine low levels of serotonin are the rule.

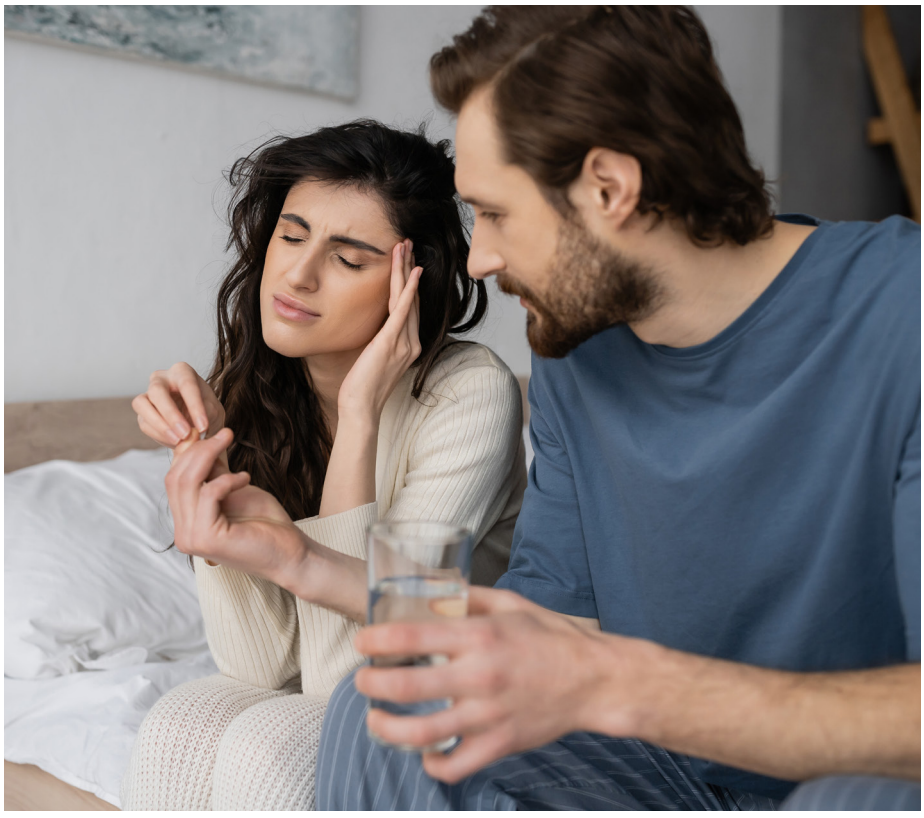
In a separate study published in the journal ***Cephalalgia*** in 2013, well over half of the female migraineurs surveyed reported that sexual activity relieved or terminated their episodes of acute migraine. A third of the migraine group reported specifically using sex to treat their acute migraine headaches. The investigators hypothesized that this positive therapeutic effect of sexual activity and orgasm resulted from the consequent release of endorphins. In addition, noting that orgasm produces an increase in brain serotonin, they took the Wake Forest group's hypothesis a step further by suggesting that an increased "sex drive" in those with migraine, a disorder commonly associated with low levels of serotonin in the brain, might reflect the brain's quest to rectify that deficiency through sexual activity.

In a 2018 clinic-based study involving 200 heterosexual and sexually active females with migraine presenting to a university-based headache clinic and 200 migraine-free females matched for age, race/ethnicity, body mass index (BMI) and educational, social, economic and marital status, my colleagues and I found that the headache clinic patients with episodic migraine reported a higher libido, a higher monthly frequency of sexual intercourse and a higher likelihood of intercourse resulting in orgasm. All participants completed the Female Sexual Function Index (FSFI), a 6-aspect measure of sexual desire, arousal, lubrication, orgasm, satisfaction and pain. The mean score for the episodic migraine clinic patients was significantly higher than that recorded from the migraine-free control group. Similar to results from the 2013 ***Cephalalgia*** study, 25% of the migraine patients reported successfully using intercourse resulting in orgasm to terminate a migraine attack.

In a subsequent study whose results will be presented at the 2023 annual scientific meeting of the American Headache Society, we sought to confirm the results of our 2018 study and to eliminate any selection bias introduced by our having assessed only migraine patients actively under care in our headache clinic. We evaluated 150 female migraine patients from our clinic, 100 migraine-free but otherwise matched controls and 67 individuals with migraine selected randomly from the general population. As with the 2018 study, all participants completed the FSFI. Bot the clinic-based migraine group and the general population migraine group recorded mean FSFI scores significantly higher than that of the migraine-free control group. In this study as well as our 2018 study, mean FSFI scores in the subgroup of patients with chronic migraine were significantly lower than what was recorded from the episodic migraine subgroup.

Summing up…

1. While the results from published research are conflicting, there does not exist convincing evidence that females with episodic migraine have a lower libido or lower levels of sexual performance than females free of migraine. If anything, at least for many females with *episodic* migraine, it is precisely the opposite.
2. As with quality of life generally, those females with a greater migraine burden – and specifically those with *chronic* migraine – appear to have lower libido and lower levels of sexual performance than either females with episodic migraine, or females who are migraine-free.
3. For many female (and male) migraineurs, intercourse and orgasm may serve as a means of reducing or terminating acute migraine headache, and many within this fortunate group specifically use sex as a treatment for acute migraine.



Related to the last point, is the opposite also true? Can sexual activity and orgasm trigger migraine? Any strenuous physical activity can serve as a migraine trigger for some individuals, but only a very small percentage of migraineurs specifically identify sex as a trigger. Of note, recurrent episodes of sudden, severe and brief duration headache occurring just prior to or during orgasm is highly suggestive of so-called "primary headache associated with sexual activity", a primary headache disorder that is the topic of this issue's "Doctor on Call" (page 22).

In conclusion, as with most matters sexual the association between migraine and sexual desire/activity/performance is complex and multifaceted. In terms of *libido* (and no matter how one chooses to define or measure that elusive noun), being female and having migraine neither guarantees one will be a voracious sexual superstar nor condemns one to Arctic sexual frigidity . For many, an acute migraine episode will remove all appetite for sexual intercourse quite effectively, whereas for others intercourse and orgasm may act as a reliable alternative to use of medication for treating the episode. Suffice it to say that if you have migraine, if your headache disorder is adversely impacting your quality of life, and if at least a portion of that reduction involves your sex life, it is clearly time to seek advice and treatment from a healthcare provider experienced in the management of migraine.

John F Rothrock, MD