HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORZEYFUL safely and effectively. See full prescribing information for ORZEYFUL.

ORZEYFUL™ (oveporexton) tablets, for oral use [controlled substance schedule pending]
Initial U.S. Approval: [initial U.S. approval pending controlled substance scheduling]

----------INDICATIONS AND USAGE----------
ORZEYFUL is an orexin receptor 2 (OX2R) agonist indicated for the treatment of narcolepsy type 1 (narcolepsy with cataplexy) in adult patients. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Administer ORZEYFUL tablets at approximately the same time each day. (2.1)
- ORZEYFUL may be taken with or without food. (2.1)
- Recommended dosage of ORZEYFUL is either (2.2):
  - Take 1 mg orally after awakening and then take 1 mg three to five hours later, OR
  - Take 2 mg orally after awakening and then take 2 mg three to five hours later.
- Maximum recommended total dosage of ORZEYFUL is 4 mg orally per day. (2.2)
- If a scheduled ORZEYFUL dose is missed, take the next dose at the next scheduled time. Do not take two doses at the same time. (2.4)
- See full prescribing information for ORZEYFUL dosage modifications due to drug interactions. (2.3, 7)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 0.5 mg, 1 mg, and 2 mg (3)

----------CONTRAINDICATIONS----------
ORZEYFUL is contraindicated in patients taking strong CYP3A inhibitors. (4, 7)

---------- WARNINGS AND PRECAUTIONS----------
- *Insomnia:* If insomnia persists beyond 7 days and significantly impacts daytime functioning or quality of life, consider ORZEYFUL dosage reduction or discontinuation. (5.1)
- *Urinary Frequency and Urgency:* Prior to initiation of ORZEYFUL treatment, inform patients about the risk of urinary frequency and urgency and screen patients for lower urinary tract symptoms. Monitor ORZEYFUL-treated patients with a history of overactive bladder for worsening urinary tract symptoms. (5.2)
- *Creatine Phosphokinase Elevations:* Advise patients to report unexplained muscle pain, weakness, or dark urine, particularly when engaging in vigorous physical activity or taking concomitant drugs associated with myotoxicity. (5.3)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥5%) are insomnia, pollakiuria, micturition urgency, and salivary hypersecretion. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *Strong CYP3A Inhibitors:* Concomitant use with ORZEYFUL is contraindicated. (7)
- *Moderate CYP3A Inhibitors:* Reduce ORZEYFUL dosage to 0.5 mg orally after awakening and then 0.5 mg three to five hours later (total dosage is 1 mg per day). (2.3, 7)
- *Strong and Moderate CYP3A Inducers:* Avoid concomitant use of ORZEYFUL with strong or moderate CYP3A inducers. (7)

---------- USE IN SPECIFIC POPULATIONS ----------
- *Severe Hepatic Impairment:* Avoid use of ORZEYFUL in patients with severe hepatic impairment (Child Pugh C) as it has not been studied in this population. (8.6)
- *Severe Renal Impairment on Dialysis:* Avoid use of ORZEYFUL in patients with severe renal impairment on dialysis (eGFR<15 mL/minute) as it has not been studied in this population. (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ORZEYFUL™ is indicated for the treatment of narcolepsy type 1 (narcolepsy with cataplexy) in adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Administer ORZEYFUL tablets at approximately the same time each day *[see Dosage and Administration (2.4)]*.

Swallow ORZEYFUL tablets whole with water. Do not split, crush or chew tablets. ORZEYFUL may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

2.2 Recommended Dosage and Administration

The recommended dosage of ORZEYFUL is either:

- Take 1 mg orally after awakening and then take 1 mg three to five hours later, OR
- Take 2 mg orally after awakening and then take 2 mg three to five hours later.

The maximum recommended total dosage of ORZEYFUL is 4 mg orally per day.

2.3 Dosage Modifications for CYP3A Inhibitors

ORZEYFUL is contraindicated in patients taking strong CYP3A inhibitors.

If ORZEYFUL is used concomitantly with moderate CYP3A inhibitors, reduce the ORZEYFUL dosage to 0.5 mg orally after awakening and then 0.5 mg three to five hours later (maximum recommended total dosage is 1 mg per day) *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

2.4 Recommendations Regarding Missed Doses

If a scheduled ORZEYFUL dose is missed, take the next dose at the next scheduled time. Do not take two doses at the same time.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 0.5 mg: light orange, round, debossed with “ ” and “0.5” on one side.
- 1 mg: orange, round, debossed with “ ” and “1” on one side.
- 2 mg: dark red, round, debossed with “ ” and “2” on one side.

4 CONTRAINDICATIONS

ORZEYFUL is contraindicated in patients taking strong CYP3A inhibitors *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Insomnia

In two pooled 12-week placebo-controlled phase 3 studies (Studies 1 and 2) *[see Clinical Studies (14)]* in patients with narcolepsy type 1, 60%, 55%, and 1% of patients in the ORZEYFUL 2 mg twice daily, ORZEYFUL 1 mg twice daily, and placebo groups, respectively, developed insomnia.

Prior to ORZEYFUL treatment initiation, inform patients about the risk of insomnia at initiation of treatment. If insomnia persists beyond 7 days and significantly impacts daytime functioning or quality of life, consider ORZEYFUL dosage reduction or discontinuation *[see Adverse Reactions (6.1)]*.

5.2 Urinary Frequency and Urgency

ORZEYFUL may cause or worsen urinary frequency and urgency. In two pooled 12-week placebo-controlled phase 3 studies (Studies 1 and 2) *[see Clinical Studies (14)]* in patients with narcolepsy type 1:

- 58%, 53%, and 5% of patients in the ORZEYFUL 2 mg twice daily, ORZEYFUL 1 mg twice daily, and placebo groups, respectively, developed urinary frequency.
- 16%, 15%, and 1% of patients in the ORZEYFUL 2 mg twice daily, ORZEYFUL 1 mg twice daily, and placebo groups, respectively, developed urinary urgency.

These lower urinary tract symptoms are consistent with ORZEYFUL's mechanism of action through agonism of the orexin receptor 2 (OX2R) on central micturition pathways *[see Clinical Pharmacology (12.1)]*.

Prior to initiation of ORZEYFUL treatment, inform patients about the risk of urinary frequency and urgency and screen patients for lower urinary tract symptoms. Monitor ORZEYFUL-treated patients with a history of overactive bladder for worsening urinary tract symptom.

5.3 Creatine Phosphokinase Elevations

In two pooled 12-week placebo-controlled phase 3 studies (Studies 1 and 2) *[see Clinical Studies (14)]* in patients with narcolepsy type 1, asymptomatic creatine phosphokinase elevations >5x ULN were observed in 11% (21/196) of ORZEYFUL-treated patients and 5% (4/76) of placebo-treated patients. Two of these cases were characterized by markedly elevated CPK and transaminase levels; both patients discontinued treatment. None of the cases were associated with myoglobinuria or renal impairment.

Advise patients to report unexplained muscle pain, weakness, or dark urine, particularly when engaging in vigorous physical activity or taking concomitant drugs associated with myotoxicity.

6 ADVERSE REACTIONS

6.1 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 ORZEYFUL was evaluated in two 12-week placebo-controlled phase 3 studies (Studies 1 and 2) *[see Clinical Studies (14)]* in 196 ORZEYFUL-treated patients with narcolepsy type 1. Patients in the ORZEYFUL group received doses of 1 mg or 2 mg twice in the morning (the two doses were taken at least 3 hours apart with the second dose taken no later than 1 PM) for 12 weeks.

In these studies, the:

- Discontinuation rate due to an adverse reaction was 2.6% in ORZEYFUL-treated patients and 1.3% in placebo-treated patients.
- Most common adverse reactions (incidence ≥5% and greater than placebo) in ORZEYFUL-treated patients were insomnia, pollakiuria, micturition urgency, and salivary hypersecretion.

Table 1 describes the adverse reactions that occurred at a rate of ≥2% in ORZEYFUL-treated patients and more frequently than in placebo-treated patients in Studies 1 and 2.

Table 1: Adverse Reactions Reported in ≥2% of ORZEYFUL-Treated Patients and Greater than Rate of Placebo in Patients with Narcolepsy Type 1 (Studies 1 and 2)

Adverse Reaction	Placebo (N=76)	ORZEYFUL 1 mg twice daily (N=60)	ORZEYFUL 2 mg twice daily* (N=136)
Insomnia**	1%	55%	60%
Urinary frequency (pollakiuria)	5%	53%	58%
Urinary urgency (micturition urgency)	1%	15%	16%
Salivary hypersecretion	0%	8%	7%
Influenza	1%	5%	3%
Abdominal pain	0%	3%	1%
Oropharyngeal pain	0%	3%	1%
Paresthesia	0%	2%	2%
Rash	0%	0%	3%
Sinusitis	1%	5%	2%

* The two ORZEYFUL doses were taken at least 3 hours apart with the second dose taken no later than 1 PM
** Includes Insomnia, Middle Insomnia, and Initial Insomnia

Insomnia

In Studies 1 and 2, insomnia occurred in 58% of ORZEYFUL-treated patients and severe insomnia occurred in 1.5% of ORZEYFUL-treated patients. Regarding the insomnia events in ORZEYFUL-treated patients:

- Approximately 90% started within the first 2 days of therapy initiation, and 4% began between days 2 and 7 of therapy initiation.
- Approximately 63% resolved within 1 week of onset, and approximately 17% were ongoing at study completion.
- None led to study discontinuation or were classified as serious adverse reactions.

Urinary Adverse Reactions

In Studies 1 and 2, urinary adverse reactions occurred in 63% of ORZEYFUL-treated patients and severe urinary adverse reactions occurred in 1% of ORZEYFUL-treated patients. Two

ORZEYFUL-treated patients discontinued treatment, one due to frequent urination and the other due to urinary incontinence.

Vital Sign Changes

In Studies 1 and 2, increases of in-clinic blood pressure (BP) and heart rate (HR) were noted on day 1 with higher frequency in ORZEYFUL-treated patients compared to placebo-treated patients. Increases in systolic and diastolic BP (>20 mm Hg) occurred in 22% and 9% of ORZEYFUL-treated patients and 13% and 7% of placebo-treated patients, respectively and increases in HR (>15 bpm) occurred in 30% of ORZEYFUL-treated patients and 22% of placebo-treated patients. The placebo adjusted mean changes in BP and HR from baseline in ORZEYFUL-treated patients were <5 mm Hg and <2 bpm by Week 12, respectively.

No significant differences in BP or HR were observed at Week 10 compared to baseline with 24-hour ambulatory blood pressure and heart rate monitoring.

Low-Density Lipoprotein Cholesterol Elevations

In Studies 1 and 2 *[see Clinical Studies (14)]*, LDL values >160 mg/dL were observed in 32% (62/196) of ORZEYFUL-treated patients and 20% (15/76) of placebo-treated patients. Mean (SD) LDL changes from baseline to Week 12 were +17.6 (21.9) mg/dL and +4.4 (17.5) mg/dL for the pooled ORZEYFUL treatment group (1 mg and 2 mg twice daily combined groups) and the placebo group, respectively.

7 DRUG INTERACTIONS

Table 2 describes drug interactions where concomitant use of another drug affects the use of ORZEYFUL.

Table 2: Concomitant Use of Other Drugs that Affect the Use of ORZEYFUL

Strong CYP3A Inhibitors	
Mechanism and Clinical Effect(s)	Concomitant use of ORZEYFUL with strong CYP3A inhibitors increases oveporexton exposure, which may increase the risk of ORZEYFUL-associated adverse reactions *[see Clinical Pharmacology (12.3)]*.
Prevention or Management	Concomitant use of ORZEYFUL with strong CYP3A inhibitors is contraindicated *[see Clinical Pharmacology (12.2)]*.
Moderate CYP3A Inhibitors	
Mechanism and Clinical Effect(s)	Concomitant use of ORZEYFUL with moderate CYP3A inhibitors increases oveporexton exposure, which may increase the risk of ORZEYFUL-associated adverse reactions *[see Clinical Pharmacology (12.3)]*.
Prevention or Management	Reduce the ORZEYFUL dosage to 0.5 mg two times daily with concomitant use of ORZEYFUL with moderate CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Strong and Moderate CYP3A Inducers	
Mechanism and Clinical Effect(s)	Concomitant use of ORZEYFUL with strong or moderate CYP3A inducers can increase oveporexton metabolism and decrease plasma levels of oveporexton, which may decrease the effectiveness of ORZEYFUL *[see Clinical Pharmacology (12.3)]*.
Prevention or Management	Avoid concomitant use with strong or moderate CYP3A inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to ORZEYFUL during pregnancy. Patients should be encouraged to enroll in the ORZEYFUL pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call 1-877-371-0309.

Risk Summary

Available data from clinical trials with ORZEYFUL use during pregnancy are insufficient to identify a drug associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Animal reproduction studies did not show evidence of embryofetal toxicity or effects on pre- and post-natal development *(see Data)*.

The background risk of major birth defects and miscarriage in adults with narcolepsy type 1 is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: Oveporexton was administered orally to pregnant rats during the period of organogenesis at 10, 100, and 750 mg/kg/day (approximately 118, 346, and 1166 times, respectively, the maximum recommended human dose (MRHD) based on AUC). No adverse embryofetal effects were observed up to 750 mg/kg/day.

Maternal toxicity of decreased body weight/gain, which correlated with decreased food consumption, was observed at 750 mg/kg/day (approximately 1166 times the MRHD based on AUC). Placental transfer of oveporexton was observed in pregnant rats.

Oveporexton was administered orally to pregnant rabbits during the period of organogenesis at 4, 20, and 100 mg/kg/day (approximately 11, 38, and 153 times, respectively the MRHD based on AUC). No adverse embryofetal effects were observed up to 100 mg/kg/day. Maternal toxicity of decreased body weight/gain, which correlated with decreased food consumption, was observed at 100 mg/kg/day (approximately 153 times the MRHD based on AUC).

In a pre- and postnatal development study, oveporexton was administered orally to pregnant rats from gestation day 7 through lactation day 20 at 1, 3, and 10 mg/kg/day (up to approximately 118 times the MRHD based on AUC). No adverse effects were observed up to 10 mg/kg/day.

8.2 Lactation

Risk Summary

There are no data available on the presence of oveporexton in human milk, the effects on the breastfed infant, or the effects on milk production. Animal studies indicate that oveporexton was present in the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORZEYFUL and any potential adverse effects on the breastfed infant from ORZEYFUL or from the underlying maternal condition.

Data

Animal Data: Following administration of a single dose of radiolabeled oveporexton (100 mg/kg) in lactating rats, oveporexton was detected in milk.

8.4 Pediatric Use

The safety and effectiveness of ORZEYFUL in pediatric patients have not been established.

8.5 Geriatric Use

In Studies 1 and 2 *[see Clinical Studies (14)]*, 1 (<1%) ORZEYFUL-treated patient was 65 years of age or older. Clinical studies of ORZEYFUL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger adult patients *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Avoid use of ORZEYFUL in patients with severe hepatic impairment (HI) (Child-Pugh C) as it has not been studied in this population *[see Clinical Pharmacology (12.3)]*.

The recommended ORZEYFUL dosage in patients with mild HI or moderate HI (Child-Pugh A or B, respectively) is the same in those with normal hepatic function *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Avoid use of ORZEYFUL in patients with severe renal impairment (RI) on dialysis (eGFR<15 mL/minute) as it has not been studied in this population *[see Clinical Pharmacology (12.3)]*.

The recommended ORZEYFUL dosage in patients with mild RI (estimated glomerular filtration rate (eGFR) ≥60 to <90 mL/minute), moderate RI (eGFR 30 to <60 mL/minute), or severe RI not requiring dialysis (eGFR ≥15 to <30 mL/minute) is the same in those with normal kidney function *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ORZEYFUL contains oveporexton. (Controlled substance schedule to be determined after review by the Drug Enforcement Administration.)

9.2 Abuse

ORZEYFUL has potential for abuse. Abuse of ORZEYFUL may lead to substance use disorder, including addiction. Drug abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

ORZEYFUL can also be misused. Drug misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Misuse, like abuse, is often associated with higher doses and/or more frequent use of the drug, which may lead to adverse reactions similar to those seen in the context of abuse and addiction.

Human Abuse Potential Study

The abuse potential of ORZEYFUL 6 mg, 18 mg, and 30 mg (1.5, 4.5 and 7.5 times the maximum recommended daily dose, respectively) was assessed relative to phentermine 75 mg, (a Schedule IV controlled substance) in a human abuse potential study in individuals experienced with the

recreational use of CNS stimulants. Results from this clinical study demonstrated that ORZEYFUL produced Drug Liking scores greater than that of placebo and similar to or lower than phentermine.

In this crossover study, euphoria was not reported in placebo-treated patients, and was reported in 0 to 4.2% of ORZEYFUL-treated patients and 4.1% of phentermine treated patients. “Feeling jittery” was reported in 0% of placebo-treated patients, 0 to 2% of ORZEYFUL-treated patients and 0% of phentermine-treated patients.

Recommendations to Reduce the Risk of Abuse and Monitor for Abuse
Health care providers should carefully evaluate patients for a recent history of drug abuse, especially those with a history of CNS stimulant (e.g., methylphenidate, amphetamine, or cocaine) and follow such patients closely, observing them for signs of misuse or abuse of ORZEYFUL (e.g., incrementation of doses, drug-seeking behavior).

9.3 Dependence

Physical dependence of ORZEYFUL was evaluated in clinical studies. The 277 patients that completed or discontinued treatment in repeat-dose studies were monitored for post-treatment adverse reactions and there was limited evidence of withdrawal-related adverse events upon ORZEYFUL discontinuation to indicate physical dependence.

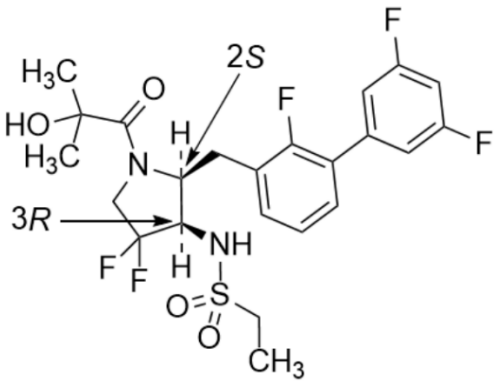
10 OVERDOSAGE

There is no specific antidote for an overdose of ORZEYFUL. Treatment should be symptomatic and supportive. If an overdose of ORZEYFUL occurs, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

ORZEYFUL contains oveporexton, an orexin receptor 2 (OX2R) agonist.

Oveporexton is described chemically as: N-{(2S,3R)-4,4-Difluoro-1-(2-hydroxy-2-methylpropanoyl)-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl}ethanesulfonamide.The molecular formula is: $C_{23}H_{25}F_5N_2O_4S$ and the molecular weight is 520.51. Oveporexton’s structural formula is:



Oveporexton is a white to nearly white powder.

ORZEYFUL (oveporexton) tablets for oral administration contains 0.5 mg, 1 mg, or 2 mg of oveporexton. The inactive ingredients are hydroxypropyl cellulose, magnesium stearate, mannitol,

microcrystalline cellulose, and sodium starch glycolate (type A). The tablet coating consists of calcium carbonate, ferric oxide red, ferric oxide yellow, hypromellose 2910, and polyethylene glycol 8000.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of oveporexton in the treatment of narcolepsy type 1 (NT1) is through agonism of the orexin receptor 2 (OX2R). NT1 is associated with the loss of orexin neuropeptide signaling.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Based on a comprehensive concentration-QTc analysis, there was no clinically relevant effect of ORZEYFUL (i.e., ≥10 ms) on the QTc interval up to 11 times the mean steady state C_{max} at the maximum recommended dose.

12.3 Pharmacokinetics

Oveporexton showed dose proportional increase in exposures (C_{max} and AUC_{0-t}) at steady state over the dosage range of 1 mg twice daily to 2 mg twice daily. With two times daily administration, steady state was reached within 5 days, with an accumulation ratio of approximately 1.6 after a ORZEYFUL dosage of 1 mg twice daily to 2 mg twice daily.

Absorption

Oveporexton median (min, max) time to maximum plasma concentration (T_{max}) is 1.5 hours (1 to 4 hours) at steady state.

Effect of Food: No clinically significant differences in the pharmacokinetics of oveporexton were observed following administration with a high-fat high-calorie meal *[see Dosage and Administration (2.1)]*.

Distribution

The apparent steady state volume of distribution of oveporexton is approximately 325 L. Protein binding is high (>96%) and concentration-independent in human plasma. The whole blood to plasma concentration ratio ranged from 0.61 to 0.90.

Elimination

The mean terminal elimination half-life of oveporexton is approximately 23.2 hours.

Metabolism: Oveporexton is primarily eliminated by hepatic metabolism. CYP3A4 is the predominant CYP enzyme involved in oveporexton metabolism with no major metabolites identified in circulation.

Excretion: After a single 25 mg radiolabeled oral dose of oveporexton, 80.5% of the total dose was recovered in feces and 11.0% was recovered in urine. Renal elimination of unchanged drug accounts for <1% of the total clearance of oveporexton.

Specific Populations

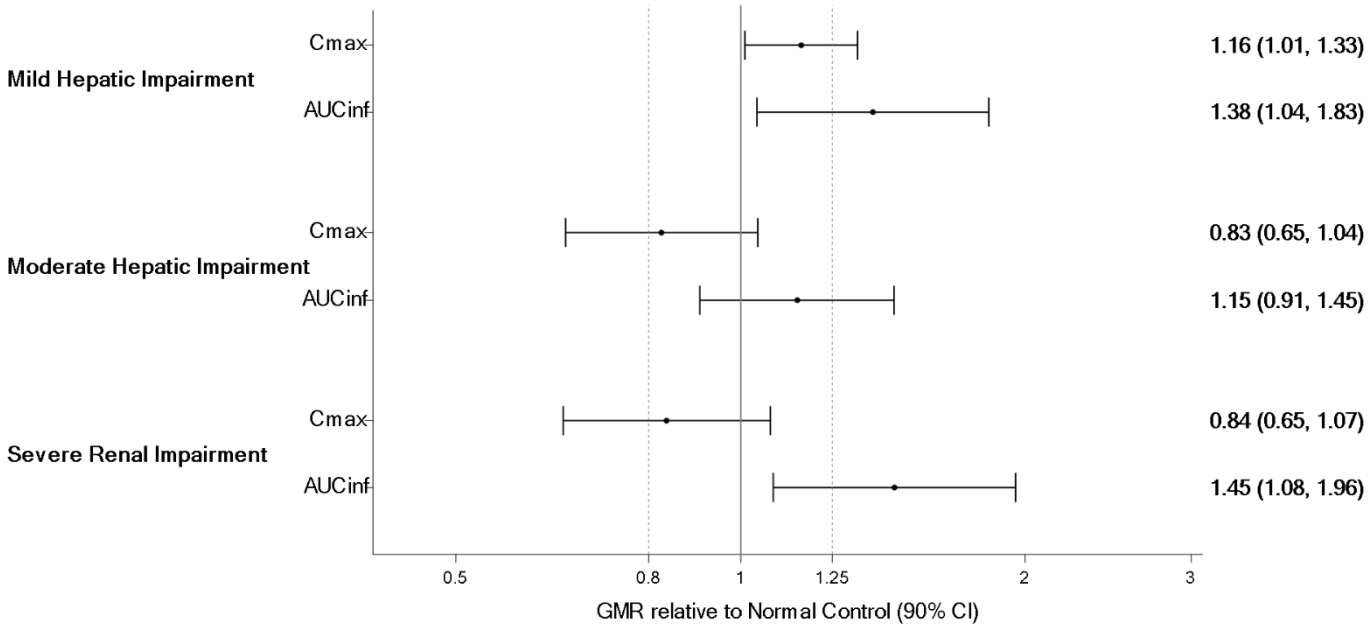
Patients with Hepatic Impairment: Exposure of oveporexton in patients with mild hepatic impairment (HI) (Child-Pugh A) or moderate HI (Child-Pugh B) compared to patients with normal hepatic function is summarized in Figure 1. Changes in oveporexton exposures (AUC_{inf}) due to HI did not exceed 2-fold compared to patients with normal hepatic function *[see Use in Specific Populations (8.6)]*.

Patients with severe HI (Child-Pugh C) were not evaluated in clinical trials *[see Use in Specific Populations (8.6)]*.

Patients with Renal Impairment: Exposures of oveporexton in patients with severe renal impairment (RI) (eGFR<15 mL/min; not on dialysis) compared to patients with normal renal function is summarized in Figure 1. Changes in oveporexton exposures (AUC_{inf}) due to RI did not exceed 2-fold compared to patients with normal renal function.

Patients with ESRD (eGFR <15 mL/minute or dialysis patients) were not evaluated in clinical trials.

Figure 1: Effects of Hepatic and Renal Impairment on Oveporexton Pharmacokinetics



Other Specific Populations: Based on population pharmacokinetic analysis, age, sex, race/ethnicity, and body weight did not have clinically meaningful effects on the pharmacokinetics of oveporexton.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effects of Other Drugs on ORZEYFUL

- *Strong and Moderate CYP3A Inhibitors:* Concomitant use of ORZEYFUL with itraconazole (a strong CYP3A inhibitor) resulted in increases in oveporexton AUC_{inf} (7.4-fold increase) and C_{max} (1.7-fold increase), compared to the use of ORZEYFUL alone. The half-life of oveporexton was approximately 5-fold longer in the presence of itraconazole *[see Drug Interactions (7)]*. Concomitant use of ORZEYFUL with fluconazole (a moderate CYP3A inhibitor) resulted in increases in oveporexton AUC_{inf} (2.9-fold increase) and C_{max} (1.5-fold increase), compared to the use of ORZEYFUL alone. The half-life of oveporexton was approximately 2-fold longer in the presence of fluconazole *[see Drug Interactions (7)]*.
- *Weak CYP3A Inhibitors:* Based on physiologically-based pharmacokinetic (PBPK) modeling, no clinically meaningful interaction is expected during concomitant use of ORZEYFUL with weak CYP3A inhibitors.
- *Strong and Moderate CYP3A Inducers:* Concomitant use of ORZEYFUL with phenytoin (a strong CYP3A inducer) resulted in decreases in oveporexton AUC_{inf} and C_{max} by 81% and 56%, respectively, compared to use of ORZEYFUL alone *[see Drug Interactions (7)]*. Based on PBPK modeling, concomitant use of ORZEYFUL with a moderate CYP3A inducer is predicted to decrease AUC_{inf} and C_{max} by 73% and 55%, respectively, compared to use of ORZEYFUL alone *[see Drug Interactions (7)]*.

- *Weak CYP3A Inducers:* Based on PBPK modeling, no clinically meaningful interaction is expected during concomitant use of ORZEYFUL with weak CYP3A inducers.

Effects of ORZEYFUL on Other Drugs
Based on a clinical evaluation of the effect of oveporexton on CYP3A activity assessed by 4β-hydroxycholesterol to cholesterol ratios and PBPK modeling, oveporexton is not expected to affect CYP3A activity or alter systemic exposure of CYP3A substrates at the maximum recommended ORZEYFUL dose.

Based on a clinical evaluation of the effects of oveporexton on OATP1B1/B3 activity assessed by Coproporphyrin I (CPI) and Coproporphyrin III (CPIII), there was no apparent risk of inhibition of these transporters at the maximum recommended ORZEYFUL dose.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes
In vitro, oveporexton exposures at the maximum recommended ORZEYFUL dose is not expected to directly inhibit or induce CYP enzymes (CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6).

Drug Transporter Systems

- *Transporter Inhibition: In vitro*, oveporexton did not inhibit P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2K, or MRP2.
- *In vitro*, oveporexton was an inhibitor of efflux transporters BSEP, MRP3, MRP4, and MDR3. However, inhibition of these transporters by oveporexton is not expected at the maximum recommended ORZEYFUL dose.
- *Transporter Substrate: In vitro*, oveporexton was not a substrate of P-gp, BCRP, OATP1B1, or OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Oveporexton did not increase the incidence of tumors in rats treated for 2 years at oral doses up to 100 mg/kg/day (>335 times the MRHD based on AUC). Oveporexton did not increase the incidence of tumors in transgenic (TG) ras H2 mice treated for 26 weeks at oral doses up to 600 mg/kg/day (males) and 300 mg/kg/day (females).

Mutagenesis
Oveporexton was not mutagenic in an *in vitro* bacterial reverse mutation assay (Ames assay). Oveporexton was positive for genotoxic potential in an *in vitro* micronucleus assay; however, no genotoxic effects were observed in an *in vivo* bone marrow micronucleus assay or a liver comet assay in rats.

Impairment of Fertility
In a male and female fertility study, rats were treated orally with oveporexton at 10, 100, and 750 mg/kg/day (approximately 68, 311, 747 and 120, 455, 1499 times the MRHD based on AUC in males and females, respectively). Males were treated for 9 weeks prior to mating and 28 days through mating. Females were treated 2 weeks prior to mating, through mating, and through Gestation Day 6. In males, there were no effects on fertility or reproductive performance at any dose. In females, decreases in the number of corpora lutea followed by decreased numbers of implantations and live embryos were observed at 750 mg/kg/day.

14 CLINICAL STUDIES

The efficacy of ORZEYFUL for the treatment of narcolepsy type 1 (NT1) was evaluated in two randomized, multicenter, double-blind placebo controlled 12-week parallel group studies (Study 1 [NCT06470828] and Study 2 [NCT06505031]). Patients enrolled in both studies had a diagnosis of NT1 according to the International Classification of Sleep Disorders (ICSD-3) or International Classification of Sleep Disorders-Text Revision (ICSD-3-TR) criteria.

- In Study 1, 168 patients were randomized 2:3:3 to receive oral placebo (N=41) twice in the morning, ORZEYFUL 1 mg (N=61) twice in the morning, or ORZEYFUL 2 mg (N=66) twice in the morning. In all dosing groups, the two doses were taken at least 3 hours apart with the second dose taken no later than 1 PM.
- In Study 2, 105 patients were randomized 1:2 to receive oral placebo (N=35) or ORZEYFUL 2 mg (N=70) twice, in the morning. The two doses were taken at least 3 hours apart with the second dose taken no later than 1 PM.

Key Efficacy Endpoints

The primary efficacy endpoint in Studies 1 and 2 was the change from baseline to Week 12 in the mean sleep latency from the Maintenance of Wakefulness Test (MWT). MWT measures a patient's ability to remain awake during the daytime in a darkened, quiet environment. Patients were instructed to remain awake for as long as possible during 40-minute test sessions, and sleep latency was determined as the mean number of minutes patients could remain awake across the four test sessions. A normative mean sleep latency is defined as ≥20 minutes, with a clinically significant improvement defined to be an increase from baseline of more than 2 minutes.

Pre-specified secondary endpoints in Studies 1 and 2 included the:

- Epworth Sleepiness Scale (ESS) total score. ESS is an 8-item questionnaire by which patients rate their perceived likelihood of falling asleep during daily activities. A score of ≤10 is considered within the normative range, and a reduction of 2 points from baseline is defined as a clinically significant improvement.
- Weekly Cataplexy Rate (WCR). WCR is calculated from patients' self-reported cataplexy events in a daily diary. A reduction of at least 25% in the frequency of daily or weekly episodes, based on diary entries, is defined as a clinically significant improvement.
- Narcolepsy Severity Scale for Clinical Trials (NSS-CT) total score. NSS-CT is a 15-item self-administered questionnaire that assesses the overall severity of narcolepsy symptoms: daytime sleepiness, cataplexy, sleep paralysis, hallucinations, and disrupted nighttime sleep (DNS).
- Patient Global Impression of Change (PGI-C) score. The PGI-C is a self-administered questionnaire that assesses the overall global impression of the narcolepsy symptoms by the patient as the change due to treatment relative to baseline. The PGI-C was evaluated on a 7-point scale, centered at no change, and ranging from "very much worse" to "very much improved".

Important Baseline Disease Characteristics and Demographics

In Study 1, the mean age was 31 years (range 16 to 65 years of age), 58% were female; 35% were White, 16% were Asian, 4% were Black or African American, <1% were multiple races, and 44% were not known or reported; 45% were not of Hispanic or Latino ethnicity, 8% were of Hispanic or Latino ethnicity, and 47% the ethnicity was not known or reported.

In Study 2, the mean age was 31 years (range 18 to 62 years), 48% were Female, 45% were White, and 20% were Asian, and 35% had an unknown race; 65% were not of Hispanic or Latino ethnicity and 35% the ethnicity was not known or reported.

Efficacy Results

In Studies 1 and 2, ORZEYFUL 1 mg and 2 mg two times daily treatment groups, compared to the placebo treatment groups, demonstrated statistically significant improvements in the:

- Change from baseline to Week 12 in the:
  - Mean sleep latency from the MWT (primary efficacy endpoint).
  - ESS total score and the NSS CT total score.
- WCR and the PGI-C score at Week 12.

Efficacy results MWT, ESS, and WCR for Studies 1 and 2 are summarized in Table 3 below. In Studies 1 and 2:

- Examination of efficacy in males and females did not reveal clear evidence of differences in efficacy due to sex.
- There was insufficient data to examine if there were differences in efficacy by race/ethnicity.

Table 3: Efficacy Results for Maintenance of Wakefulness Test, Epworth Sleepiness Scale, and Weekly Cataplexy Rate in Patients with Narcolepsy Type 1 at 12 Weeks (Studies 1 and 2)

Study	Treatment Group (N)	Baseline Mean (SD)	LS Mean Change from Baseline (SE)	LS Mean Difference from Placebo (95% CI)
Mean Sleep Latency from the Maintenance of Wakefulness Test (minutes)				
Study 1	Placebo twice daily* (41)	5.1 (6.8)	-1.3 (1.5)	--
	ORZEYFUL 1 mg† twice daily* (61)	5.5 (7.7)	12.5 (1.3)	13.8 (10.2, 17.4)
	ORZEYFUL 2 mg† twice daily* (66)	4.4 (5.5)	15.9 (1.2)	17.2 (13.7, 20.7)
Study 2	Placebo twice daily* (35)	4.1 (4.9)	-1.0 (1.5)	--
	ORZEYFUL 2 mg† twice daily* (70)	4.8 (4.9)	19.1 (1.3)	20.1 (16.6, 23.6)
Epworth Sleepiness Scale Total Score				
Study 1	Placebo twice daily* (41)	18.2 (3.6)	-1.4 (0.8)	--
	ORZEYFUL 1 mg† twice daily* (61)	18.2 (2.6)	-9.4 (0.7)	-8.0 (-9.9, -6.1)
	ORZEYFUL 2 mg† twice daily* (66)	19.0 (3.2)	-11.2 (0.6)	-9.8 (-11.6, -7.9)
Study 2	Placebo twice daily* (35)	17.9 (3.0)	-1.6 (0.7)	--
	ORZEYFUL 2 mg† twice daily* (70)	17.3 (3.4)	-11.1 (0.6)	-9.5 (-11.1, -8.0)

	Treatment Group (N)	Baseline Mean (SD)	Week 12 Mean (SD)	Incidence Rate Ratio vs. Placebo (95% CI)
Weekly Cataplexy Rate				
Study 1	Placebo twice daily* (41)	48.9 (56.6)	28.3 (36.4)	--
	ORZEYFUL 1 mg† twice daily* (61)	38.3 (45.9)	9.0 (12.2)	0.34 (0.20, 0.57)
	ORZEYFUL 2 mg† twice daily* (66)	41.6 (39.2)	12.6 (18.6)	0.38 (0.23, 0.61)
Study 2	Placebo twice daily* (35)	45.8 (40.1)	29.2 (32.4)	--
	ORZEYFUL 2 mg† twice daily* (70)	33.2 (39.6)	7.1 (12.9)	0.25 (0.15, 0.42)

SD = standard deviation; SE = standard error; LS Mean = least square mean; CI = confidence interval

***** Two times daily, at least 3-5 hours apart

† Statistically significantly superior to the placebo group after adjusting for multiplicity

16 HOW SUPPLIED/STORAGE AND HANDLING

Table 4 displays the strengths and identifying characteristics of ORZEYFUL (oveporexton) tablets.

Table 4: Strengths and Identifying Characteristics of ORZEYFUL (oveporexton) Tablets

Strength	Color / Shape	Marking	Quantity in Bottle	NDC Number
0.5 mg	Light orange, round tablet	debossed with "⌓" and "0.5" on one side	60	64764-205-60
1 mg	Orange, round tablet	debossed with "⌓" and "1" on one side	60	64764-210-60
2 mg	Dark red, round tablet	debossed with "⌓" and "2" on one side	60	64764-220-60

Store ORZEYFUL at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Insomnia

Prior to ORZEYFUL treatment initiation, inform patients about the risk of insomnia at initiation of treatment *[see Warnings and Precautions (5.1)]*.

Urinary Frequency and Urgency

Prior to ORZEYFUL treatment initiation, inform patients about the risk of urinary frequency and urgency *[see Warnings and Precautions (5.2)]*.

Creatine Phosphokinase Elevations

Advise patients to report unexplained muscle pain, weakness, or dark urine, particularly when engaging in vigorous physical activity or taking concomitant drugs associated with myotoxicity *[see Warnings and Precautions (5.3)]*.

Drug Interactions

Inform patients that ORZEYFUL may interact with some drugs. Advise patients to inform their healthcare provider about all drugs they are taking, including prescription and nonprescription drugs, vitamins, and herbal products. Advise patients to consult their healthcare provider before starting or stopping any prescription drug, nonprescription drug, or supplement *[see Drug Interactions (7)]*.

Pregnancy

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ORZEYFUL during pregnancy *[see Use in Specific Populations (8.1)]*.

Missed Dose

Inform patients to take ORZEYFUL tablets at approximately the same time each day. If they miss a dose, they should skip the missed dose and take the next dose at the regular time. They should not take two doses at the same time *[see Dosage and Administration (2.4)]*.

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