WHAT HAPPENS TO PLASMA LEVELS WHEN A PATIENT MISSES THEIR DAILY DOSE OF FYCOMPA®?

Fycompa™ (perampanel) TABLETS 2 • 4 • 6 • 8 • 10 • 12 mg ORAL SUSPENSION 0.5 mg/mL CIII

Your treatment decision could make all the difference

RETHINK YOUR APPROACH TO CONVULSIVE SEIZURE FREEDOM

INDICATION

FYCOMPA (perampanel) is indicated in patients with epilepsy aged 4 years and older for partial-onset seizures (POS) with or without secondarily generalized seizures and adjunctive therapy for patients aged 12 years and older for primary generalized tonic-clonic (PGTC) seizures.

SELECTED SAFETY INFORMATION

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA**
- **Closely monitor patients particularly during the titration period and at higher doses**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening**

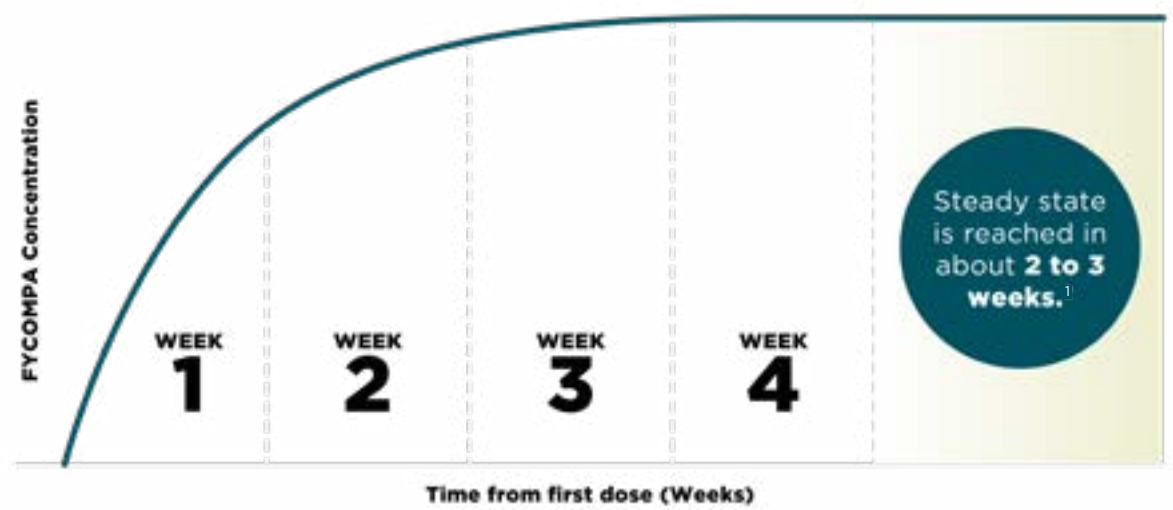
SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

In the partial-onset seizures clinical trials, hostility- and aggression-related adverse reactions occurred in 12% and 20% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. These effects in FYCOMPA-treated patients led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients. Homicidal ideation and/or threat have also been reported postmarketing in patients treated with FYCOMPA. The combination of alcohol and FYCOMPA significantly worsened mood and increased anger. Patients taking FYCOMPA should avoid the use of alcohol. Patients, their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least one month after the last dose of FYCOMPA, and especially when taking higher doses and during the initial few weeks of drug therapy (titration period) or at other times of dose increases. Similar serious psychiatric and behavioral events were observed in the primary generalized tonic-clonic (PGTC) seizure clinical trial.

Please see additional Important Safety Information throughout and accompanying Prescribing Information, including **Boxed WARNING**.

In patients starting FYCOMPA®

Model-Predicted FYCOMPA Concentration Following 4 mg/day for 4 weeks[1]



- The time to maximum serum concentration of FYCOMPA ranges between 0.5 to 2.5 hours under fasted conditions. Steady state is achieved in about 2 to 3 weeks[1]
- FYCOMPA is dosed once daily[1]
- Allow sufficient time to evaluate the effect of any dose changes

SELECTED SAFETY INFORMATION

SUICIDAL BEHAVIOR AND IDEATION

Antiepileptic drugs (AEDs), including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients. Anyone considering prescribing FYCOMPA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients, their caregivers, and families should be informed of the risk and advised to monitor and immediately report the emergence or worsening of depression, suicidal thoughts or behavior, thoughts about self-harm and/or any unusual changes in mood or behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

DIZZINESS AND GAIT DISTURBANCE

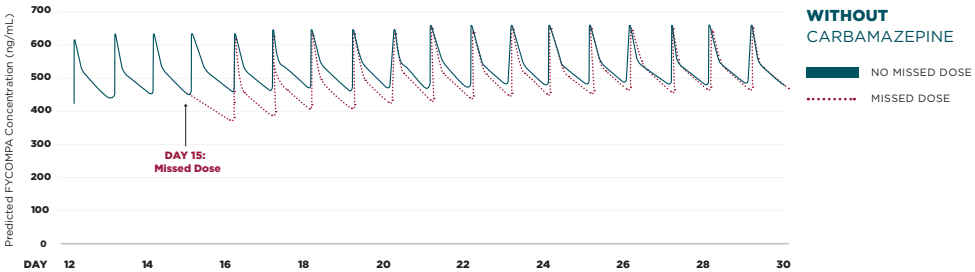
FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination. Dizziness and vertigo were reported in 35% and 47% of patients in the partial-onset seizure trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 10% of placebo-treated patients. Gait disturbance related events were reported in 12% and 16% of patients in the partial-onset seizure clinical trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 2% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase. These adverse reactions were also observed in the PGTC seizure clinical trial.

Please see additional Important Safety Information throughout and accompanying Prescribing Information, including **Boxed WARNING**.

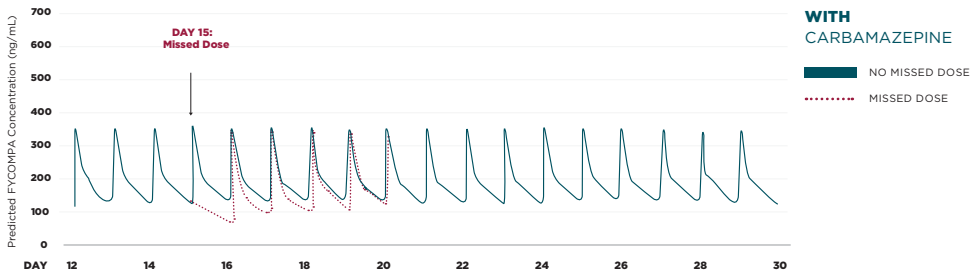
FYCOMPA has a long half-life of up to 105 hours[1,*]

In the event of a missed dose, PLASMA LEVELS REMAIN RELATIVELY STABLE[2]

FYCOMPA Concentration-Time Profiles From Day 12 Following 8 mg/day



FYCOMPA Concentration-Time Profiles From Day 12 Following 8 mg/day



STUDY OBJECTIVE

- To explore the effects of a missed dose on FYCOMPA steady-state plasma concentrations

STUDY DESIGN

- Pharmacokinetic model
- Used pharmacokinetic parameters from 19 Phase I studies conducted in adults (N=606)
- Simulations performed for patients receiving 8 mg/day of FYCOMPA
- Nonlinear mixed-effects modeling

STUDY LIMITATIONS

- Simulated pharmacokinetic model. Not prospectively carried out in patients; further studies needed to replicate findings

- FYCOMPA should be administered once daily at bedtime[1]
- **Patients who miss a dose should resume dosing the following day at their prescribed dose. Instruct patients to contact their physician if more than one day of dosing is missed**[1]

***Established in Phase I clinical trials with healthy adults. In pediatric patients ages 4-11, the half-life of FYCOMPA is long but is reduced by approximately half.[3] In the presence of concomitant moderate or strong CYP3A4 inducers, FYCOMPA continues to have a long half-life but it is reduced by approximately half in both adults and pediatrics.[3]**

Please see additional Important Safety Information throughout and accompanying Prescribing Information, including **Boxed WARNING.**

Fycompa™ (perampanel) TABLETS 2•4•6•8•10•12 mg ORAL SUSPENSION 0.5 mg/mL

Visit FYCOMPA.com/hcp to learn more about the steady-state plasma concentration in the first few weeks of FYCOMPA® administration

SELECTED SAFETY INFORMATION

SOMNOLENCE AND FATIGUE

FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events. Somnolence was reported in 16% and 18% of patients in the partial-onset seizure trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 7% of placebo-treated patients. Fatigue-related events were reported in 12% and 15% of patients in the partial-onset seizure trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 5% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase. These adverse reactions were also observed in the PGTC seizure clinical trial. Patients should be advised against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known. Patients should be carefully observed for signs of central nervous system (CNS) depression when FYCOMPA is used with other drugs with sedative properties because of potential additive effects.

FALLS

Falls were reported in 5% and 10% of patients in the partial-onset seizure clinical trials randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 3% of placebo-treated patients.

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

DRESS, also known as **multiorgan hypersensitivity**, has been reported in patients taking AEDs, including FYCOMPA. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement. If signs or symptoms are present, immediately evaluate the patient and discontinue FYCOMPA if an alternative etiology for signs or symptoms cannot be established.

WITHDRAWAL OF AEDs

A gradual withdrawal is generally recommended with AEDs to minimize the potential of increased seizure frequency, but if withdrawal is a response to adverse events, prompt withdrawal can be considered.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in patients aged 12 years and older receiving FYCOMPA (≥5% and ≥1% higher than placebo) include dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, headache, vomiting, contusion, abdominal pain, and anxiety. Adverse reactions in patients aged 4 to <12 years were generally similar to patients aged 12 years and older.

DRUG INTERACTIONS

FYCOMPA may decrease the efficacy of contraceptives containing levonorgestrel. Plasma levels of perampanel were decreased when administered with known moderate and strong CYP3A4 inducers, including, carbamazepine, phenytoin, or oxcarbazepine. Multiple dosing of FYCOMPA 12 mg per day enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when FYCOMPA is used in combination with other CNS depressants.

PREGNANCY AND LACTATION

Physicians are advised to recommend that pregnant patients taking FYCOMPA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Caution should be exercised when FYCOMPA is administered to pregnant or nursing women as there are no adequate data on the developmental risk associated with use in pregnant women, and no data on the presence of perampanel in human milk, the effects on the breastfed child, or the effects of the drug on milk production.

HEPATIC AND RENAL IMPAIRMENT

Use in patients with severe hepatic or severe renal impairment is not recommended. Dosage adjustments are recommended in patients with mild or moderate hepatic impairment. Use with caution in patients with moderate renal impairment.

DRUG ABUSE AND DEPENDENCE

FYCOMPA is a Schedule III controlled substance and has the potential to be abused and lead to drug dependence and withdrawal symptoms including anxiety, nervousness, irritability, fatigue, asthenia, mood swings, and insomnia.

References: 1. FYCOMPA US Prescribing Information. Coral Gables, FL: Catalyst Pharmaceuticals, Inc. **2.** Gidal BE, Majid O, Ferry J, et al. The practical impact of altered dosing on perampanel plasma concentrations: pharmacokinetic modeling from clinical studies. *Epilepsy Behav.* 2014;35:6-12. **3.** Data on file. Catalyst Pharmaceuticals, Inc., Coral Gables, FL.

Please see additional Important Safety Information throughout and accompanying Prescribing Information, including **Boxed WARNING**.

Fycompa™ (perampanel) TABLETS 2 • 4 • 6 • 8 • 10 • 12 mg ORAL SUSPENSION 0.5 mg/mL