Perampanel is a non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal over excitation.

The precise mechanism by which FYCOMPA exerts its antiepileptic effects in humans is unknown.

**12.2 Pharmacodynamics**

Psychomotor Performance

In a healthy volunteer study to assess the effects of FYCOMPA tablets on psychomotor performance using a standard battery of assessments including simulated driving, single and multiple daily doses of FYCOMPA 4 mg did not impair simple psychomotor tasks, driving performance, or sensorimotor coordination. Single and multiple doses of 8 mg and 12 mg impaired psychomotor performance in a dose-related manner. Car handling ability was impaired after dosing of FYCOMPA 12 mg, but postural stability was not significantly impaired. Performance testing returned to baseline within 2 weeks of cessation of FYCOMPA dosing.

Interactions with Alcohol

In the above study (*see Psychomotor Performance*), when administered to healthy subjects receiving alcohol to achieve a blood concentration of 80-100 mg/100 mL, FYCOMPA consistently impaired simple psychomotor performance after single doses of 4 to 12 mg, and after 21 days of multiple 12 mg/day doses. The effects of FYCOMPA on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol. FYCOMPA enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion, and depression.

Potential to Prolong QT Interval

In a placebo-controlled thorough QT study of perampanel in healthy subjects, there was no evidence that perampanel caused QT interval prolongation of clinical significance at doses of 6 or 12 mg (i.e., the upper bound of the 95% confidence interval for the largest placebo-adjusted baseline-corrected QTc was below 10 msec). The exposures observed with the 12 mg dose in this study will not cover the exposures expected in patients with hepatic impairment taking doses over 6 mg/day. At the highest recommended dose (12 mg), perampanel did not prolong the QTc interval to any clinically relevant extent.

**12.3 Pharmacokinetics**

Pharmacokinetics of perampanel are similar in healthy subjects, patients with partial-onset seizures, and patients with primary generalized tonic-clonic seizures. The half-life of perampanel is about 105 hours, so that steady state is reached in about 2-3 weeks. AUC of perampanel increased in a dose-proportional manner after single-dose administration of 0.2-12 mg tablets and after multiple-dose administration of 1-12 mg tablets once daily.

FYCOMPA oral suspension has comparable bioavailability to FYCOMPA tablets under steady state. Both formulations may be used interchangeably.

The pharmacokinetics of perampanel are similar when used as monotherapy or as adjunctive therapy for the treatment of partial-onset seizures (in the absence of concomitant moderate or strong CYP3A4 inducers).

Absorption

Perampanel is rapidly and completely absorbed after oral administration with negligible first-pass metabolism. Median time to reach peak concentration ($t_{max}$) ranged from 0.5 to 2.5 hours under fasted condition. Co-administration of FYCOMPA tablet with a high fat meal had no impact on the total exposure ($AUC_{0\text{-}inf}$) of perampanel and reduced the peak plasma concentration ($C_{max}$) of perampanel by 11%-40%. The $t_{max}$ was delayed by approximately 1-3 hours in fed state compared to that under fasted conditions.

Distribution

Data from *in vitro* studies indicate that, in the concentration range of 20 to 2000 ng/mL, perampanel is approximately 95-96% bound to plasma proteins, mainly bound to albumin and α1-acid glycoprotein. Blood to plasma ratio of perampanel is 0.55-0.59.

Metabolism

Perampanel is extensively metabolized via primary oxidation and sequential glucuronidation. Oxidative metabolism is primarily mediated by CYP3A4/5 and to a lesser extent by CYP1A2 and CYP2B6, based on results of *in vitro* studies using recombinant human CYPs and human liver microsomes. Other CYP enzymes may also be involved.

Following administration of radiolabeled perampanel, unchanged perampanel accounted for 74-80% of total radioactivity in systemic circulation, whereas only trace amounts of individual perampanel metabolites were detected in plasma.

Elimination

Following administration of a radiolabeled perampanel tablet dose to 8 healthy elderly subjects, 22% of administered radioactivity was recovered in the urine and 48% in the feces. In urine and feces, recovered radioactivity was primarily composed of a mixture of oxidative and conjugated metabolites. Population pharmacokinetic analysis of pooled data from 19 Phase 1 studies reported that $t_{1/2}$ of perampanel was 105 hours on average. Apparent clearance of perampanel in healthy subjects and patients was approximately 12 mL/min.

Specific Populations

*Hepatic Impairment*

The pharmacokinetics of perampanel following a single 1 mg tablet dose were evaluated in 12 subjects with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 demographically matched healthy subjects. The total (free and protein bound) exposure ($AUC_{0\text{-}inf}$) of perampanel was 50% greater in subjects with mild hepatic impairment and more than doubled (2.55-fold) in subjects with moderate hepatic impairment compared to their healthy controls. The $AUC_{0\text{-}inf}$ of free perampanel in subjects with mild and moderate hepatic impairment was 1.8-fold and 3.3-fold, respectively, of those in matched healthy controls. The $t_{1/2}$ was prolonged in subjects with mild impairment (306 vs. 125 hours) and moderate impairment (295 vs. 139 hours). Perampanel has not been studied in subjects with severe hepatic impairment *[see Dosage and Administration (2.4), Use in Specific Populations (8.6)]*.

*Renal Impairment*

A dedicated study has not been conducted to evaluate the pharmacokinetics of perampanel in patients with renal impairment. Population pharmacokinetic analysis was performed on pooled data from patients with partial-onset seizures and receiving FYCOMPA tablets up to 12 mg/day in placebo-controlled clinical trials. Results showed that perampanel apparent clearance was decreased by 27% in patients with mild renal impairment (creatinine clearance 50-80 mL/min) compared to patients with normal renal function (creatinine clearance >80 mL/min), with a corresponding 37% increase in AUC. Considering the substantial overlap in the exposure between normal and mildly impaired patients, no dosage adjustment is necessary for patients with mild renal impairment. Perampanel has not been studied in patients with severe renal impairment and patients undergoing hemodialysis *[see Dosage and Administration (2.5), Use in Specific Populations (8.7)]*.

*Sex*

In a population pharmacokinetic analysis of patients with partial-onset and primary generalized tonic-clonic seizures receiving FYCOMPA tablets in placebo-controlled clinical trials, perampanel apparent clearance in females (0.54 L/hr) was 18% lower than in males (0.66 L/hr). No dosage adjustment is necessary based on sex.

*Pediatrics*

In a population pharmacokinetic analysis of healthy subjects and pediatric and adult patients with partial onset seizures, including 123 children 4 years to less than 12 years of age, 226 adolescents 12 years to less than 18 years of age, and 1912 adults 18 years of age and older, no significant effect of age or body weight on perampanel clearance was found.

*Geriatrics*

In a population pharmacokinetic analysis of patients with partial-onset seizures and primary generalized tonic-clonic seizures ranging in age from 12 to 74 years receiving FYCOMPA tablets in placebo-controlled trials, no significant effect of age on perampanel apparent clearance was found *[see Dosage and Administration (2.6), Use in Specific Populations (8.5)]*.

*Race*

In a population pharmacokinetic analysis of patients with partial-onset seizures and primary generalized tonic-clonic seizures, which included 614 Caucasians, 15 Blacks, 4 Japanese, 4 American Indians/Alaska Natives, 79 Chinese and 108

other Asians receiving FYCOMPA tablets in placebo-controlled trials, no significant effect of race on perampanel apparent clearance was found. No dosage adjustment is necessary.

**Drug Interaction Studies**

***In Vitro* Assessment of Drug Interactions**

*Drug Metabolizing Enzymes*

In human liver microsomes, perampanel at a concentration of 30 µmol/L, about 10 fold the steady state $C_{max}$ at a 12 mg dose, had a weak inhibitory effect on CYP2C8, CYP3A4, UGT1A9, and UGT2B7. Perampanel did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, UGT1A1, UGT1A4, and UGT1A6 up to a concentration of 30 µmol/L.

Compared with positive controls (including phenobarbital and rifampin), perampanel was found to weakly induce CYP2B6 (30 µmol/L) and CYP3A4/5 (≥3 µmol/L) in cultured human hepatocytes. Perampanel also induced UGT1A1 (≥3 µmol/L) and UGT1A4 (30 µmol/L). Perampanel did not induce CYP1A2 at concentrations up to 30 µmol/L.

*Transporters*

*In vitro* studies showed that perampanel is not a substrate or significant inhibitor of the following: organic anion transporting polypeptides 1B1 and 1B3; organic anion transporters 1, 2, 3, and 4; organic cation transporters 1, 2, and 3; efflux transporters P-glycoprotein and Breast Cancer Resistance Protein.

***In Vivo* Assessment of Drug Interactions**

Drug Interactions with AEDs

*Effect of Concomitant AEDs on FYCOMPA:*

Carbamazepine. As an inducer of CYP enzymes, carbamazepine increases perampanel clearance. Steady state administration of carbamazepine at 300 mg BID in healthy subjects reduced the $C_{max}$ and $AUC_{0\text{-}inf}$ of a single 2 mg tablet dose of perampanel by 26% and 67%, respectively. The $t_{1/2}$ of perampanel was shortened from 56.8 hours to 25 hours. In clinical studies examining partial-onset and primary generalized tonic-clonic seizures, a population pharmacokinetic analysis showed that perampanel AUC was reduced by 64% in patients on carbamazepine compared to the AUC in patients not on enzyme-inducing AEDs *[see Dosage and Administration (2.3), Drug Interactions (7.2)]*.

Oxcarbazepine. In clinical studies examining partial-onset and primary generalized tonic-clonic seizures, a population pharmacokinetic analysis showed that perampanel AUC was reduced by 48% in patients on oxcarbazepine compared to patients not on enzyme-inducing AEDs *[see Dosage and Administration (2.3), Drug Interactions (7.2)]*.

Eslicarbazepine. Eslicarbazepine is structurally similar to oxcarbazepine and thus may also reduce perampanel plasma concentrations when used concomitantly.

Phenytoin. In clinical studies examining partial-onset and primary generalized tonic-clonic seizures, a population pharmacokinetic analysis showed that perampanel AUC was reduced by 43% in patients on phenytoin compared to patients not on enzyme-inducing AEDs *[see Dosage and Administration (2.3), Drug Interactions (7.2)]*.

Phenobarbital and Primidone: In a population pharmacokinetic analysis of patients with partial-onset and primary generalized tonic-clonic seizures in clinical trials (40 patients co-administered phenobarbital and 9 patients co-administered primidone), no significant effect on perampanel AUC was found. A modest effect of phenobarbital and primidone on perampanel concentrations cannot be excluded.

Topiramate: Population pharmacokinetic analysis of patients with partial-onset and primary generalized tonic-clonic seizures in clinical trials showed that perampanel AUC was reduced by approximately 19% in patients on topiramate compared to patients not on enzyme-inducing AEDs.

Other AEDs: Population pharmacokinetic analysis of patients with partial-onset and primary generalized tonic-clonic seizures in clinical trials showed that clobazam, clonazepam, lamotrigine, levetiracetam, valproate, and zonisamide did not have an effect on perampanel clearance.