splay, and decreased hindlimb grip strength were observed at all doses. Effects on pup body weight, pup growth, hindlimb splay, impairment in the water maze performance, and auditory startle persisted after dosing was stopped. A no-effect dose for postnatal developmental toxicity was not identified in this study.

Oral administration of perampanel (1, 5, 5/10 mg/kg/day; high dose increased on PND 56) to juvenile dogs for 33 weeks, starting on PND 42, resulted in CNS signs (incoordination, excessive grooming/licking/scratching, spatial disorientation, and/or ataxic gait) at all doses tested.

8.5 Geriatric Use
Clinical studies of FYCOMPA did not include sufficient numbers of patients aged 65 and over to determine the safety and efficacy of FYCOMPA in the elderly population. Because of increased likelihood for adverse reactions in the elderly, dosing titration should proceed slowly in patients aged 65 years and older *[see Dosage and Administration (2.5)]*.

8.6 Hepatic Impairment
Use of FYCOMPA in patients with severe hepatic impairment is not recommended, and dosage adjustments are recommended in patients with mild or moderate hepatic impairment *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment
Dose adjustment is not required in patients with mild renal impairment. FYCOMPA should be used with caution in patients with moderate renal impairment, and slower titration may be considered. Use in patients with severe renal impairment or patients undergoing hemodialysis is not recommended *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
FYCOMPA contains perampanel and is listed as a Schedule III controlled substance.

9.2 Abuse
Prescription drug abuse is the intentional non-therapeutic use of a drug, even once, for its rewarding psychological or physiological effects. Drug addiction, which develops after repeated drug abuse, is characterized by a strong desire to take a drug despite harmful consequences, difficulty in controlling its use, giving a higher priority to drug use than to obligations, increased tolerance, and sometimes physical withdrawal. Drug abuse and drug addiction are separate and distinct from physical dependence (for example, abuse may not be accompanied by physical dependence) *[see Drug Abuse and Dependence (9.3)]*.

Studies of human abuse potential were performed to evaluate the abuse potential of FYCOMPA (8 mg, 24 mg, and 36 mg) as compared to alprazolam C-IV (1.5 mg and 3 mg), and oral ketamine C-III (100 mg) in recreational polydrug users. Supra-therapeutic doses of FYCOMPA 24 and 36 mg produced responses for “Euphoria” that were similar to ketamine 100 mg and alprazolam 3 mg. For “High,” FYCOMPA 24 mg and 36 mg produced responses comparable to ketamine 100 mg and significantly higher than both doses of alprazolam on a visual analog scale (VAS). “Drug Liking,” “Overall Drug Liking,” and “Take Drug Again” for FYCOMPA were each statistically lower than ketamine 100 mg. In addition, for “Bad Drug Effects,” FYCOMPA 24 mg and 36 mg produced responses significantly higher than ketamine 100 mg.
For “Sedation,” FYCOMPA 24 and 36 mg produced responses similar to alprazolam 3 mg and higher than ketamine 100 mg.

Additionally, on VAS measures related to dissociative phenomena such as “Floating,” “Spaced Out,” and “Detached,” FYCOMPA at supratherapeutic doses produced responses similar to ketamine 100 mg and greater than both doses of alprazolam tested. Of note, due to somnolence a number of subjects had missing data around T_{max} of FYCOMPA. The above described data might represent an underestimate of FYCOMPA’s effects. The duration of effects of higher doses of FYCOMPA on the majority of measures was much greater than alprazolam 3 mg and ketamine 100 mg.

In this study, the incidence of euphoria following FYCOMPA administration 8 mg, 24 mg, and 36 mg was 37%, 46%, 46%, respectively, which was higher than alprazolam 3 mg (13%) but lower than ketamine 100 mg (89%).

9.3 Dependence
Physical dependence is characterized by withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug.

A nonclinical dependence study in rats demonstrated withdrawal symptoms, including hyperreactivity to handling, muscle rigidity, and decreases in food consumption and body weights.

FYCOMPA may cause dependence and withdrawal symptoms that may include anxiety, nervousness, irritability, fatigue, lethargy, asthenia, mood swings, and insomnia.

10 OVERDOSAGE

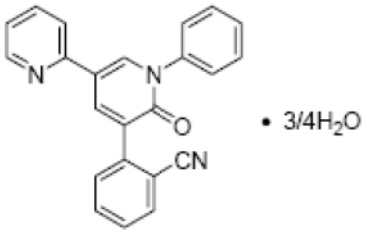
The highest reported overdose of FYCOMPA was 300 mg. Events reported after FYCOMPA overdose include somnolence, stupor, coma, psychiatric or behavioral reactions, altered mental status, and dizziness or gait disturbances.

There is no available specific antidote to the overdose reactions of FYCOMPA. In the event of overdose, standard medical practice for the management of any overdose should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital sign measurement is recommended. A certified poison control center should be contacted for updated information on the management of overdose with FYCOMPA. Due to its long half-life, the reactions caused by FYCOMPA could be prolonged.

11 DESCRIPTION
FYCOMPA tablets and oral suspension contain perampanel, a non-competitive AMPA receptor antagonist, as a 4:3 hydrate.

The chemical name of the active ingredient is 2-(1′,6′-dihydro-6′-oxo-1′-phenyl[2,3′-bipyridin]-5′-yl)-benzonitrile, hydrate (4:3).

The molecular formula is $C_{23}H_{15}N_3O \cdot ¾H_2O$ and the molecular weight is 362.90 (349.39 for anhydrous perampanel). It is a white to yellowish white powder. It is freely soluble in 1-methyl-2-pyrrolidinone, sparingly soluble in acetonitrile and acetone, slightly soluble in methanol, ethanol and ethyl acetate, very slightly soluble in 1-octanol and diethyl ether, and practically insoluble in heptane and water. The chemical structure is:



Tablets
FYCOMPA tablets are round, bi-convex, film-coated tablets containing 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg of perampanel. Tablets contain the following inactive ingredients: lactose monohydrate, low substituted hydroxypropyl cellulose, povidone, microcrystalline cellulose, magnesium stearate, hypromellose, polyethylene glycol, talc, and titanium dioxide. Tablets of different strengths may contain yellow ferric oxide (10 mg and 2 mg), red ferric oxide (2 mg, 4 mg, 6 mg, 8 mg), black ferric oxide (8 mg), and FD&C Blue No. 2 (indigo carmine) aluminum lake (10 mg and 12 mg).

Oral Suspension
FYCOMPA oral suspension is a white to off-white opaque liquid providing perampanel in a concentration of 0.5 mg/mL. The oral suspension contains the following inactive ingredients: sorbitol, microcrystalline cellulose, carboxymethyl-cellulose sodium, poloxamer, simethicone, citric acid, sodium benzoate and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

Other strong CYP3A inducers (e.g., rifampin, St. John's wort) may also greatly increase clearance of perampanel and reduce perampanel plasma concentrations *[see Drug Interactions (7.2)]*.

Effect of FYCOMPA on Concomitant AEDs:
FYCOMPA tablets up to 12 mg/day did not significantly affect the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide based on a population pharmacokinetic analysis of patients with partial-onset seizures in clinical trials. FYCOMPA had a statistically significant effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid, but the increases in clearance of these drugs were each less than 10% at the highest perampanel dose evaluated (12 mg/day). FYCOMPA co-administration resulted in a 26% decrease in oxcarbazepine clearance and increased its concentrations. The concentrations of 10-monohydroxy metabolite (MHD), the active metabolite of oxcarbazepine, were not measured.

Drug-drug Interaction Studies with Other Drugs

Effect of Other Drugs on FYCOMPA

Ketoconazole. Co-administration of single 1-mg dose of perampanel tablet with 400 mg once daily doses of ketoconazole, a strong CYP3A4 inhibitor, for 8 days in healthy subjects prolonged perampanel $t_{1/2}$ by 15% (67.8 vs. 58.4 hours) and increased $AUC_{0\text{-}inf}$ by 20%.

Contraceptives. Perampanel C_{max} and $AUC_{0\text{-}72h}$ were not altered when a single 6-mg dose of perampanel tablet was administered to healthy female subjects following a 21-day course of oral contraceptives containing ethinylestradiol 30 µg and levonorgestrel 150 µg.

Effect of FYCOMPA on Other Drugs
Midazolam. Perampanel administered as 6 mg tablet once daily doses for 20 days decreased $AUC_{0\text{-}inf}$ and C_{max} of midazolam (a CYP3A4 substrate) by 13% and 15%, respectively, in healthy subjects.

Contraceptives. Co-administration of perampanel 4 mg tablet once daily with an oral contraceptive containing ethinylestradiol 30 µg and levonorgestrel 150 µg for 21 days did not alter C_{max} or $AUC_{0\text{-}24h}$ of either ethinylestradiol or levonorgestrel in healthy female subjects. In another study, a single dose of the oral contraceptive was administered following 21-day once daily dosing of FYCOMPA 12 mg or 8 mg tablets in healthy females. FYCOMPA at 12 mg did not alter $AUC_{0\text{-}24h}$ of ethinylestradiol but decreased its C_{max} by 18%, and also decreased C_{max} and $AUC_{0\text{-}24h}$ of levonorgestrel by 42% and 40%, respectively. FYCOMPA at 8 mg did not have significant effect on C_{max} or $AUC_{0\text{-}24h}$ of either ethinylestradiol or levonorgestrel, with a decrease in $AUC_{0\text{-}24h}$ of levonorgestrel (9% on average) *[see Drug Interactions (7.1), Use in Specific Populations (8.3)]*.

Levodopa. Perampanel tablets administered as 4 mg once daily doses for 19 days had no effect on C_{max} and $AUC_{0\text{-}inf}$ of levodopa in healthy subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis
Perampanel was administered orally to mice (1, 3, 10, or 30 mg/kg/day) and rats (10, 30, or 100 mg/kg/day in males; 3, 10, or 30 mg/kg/day in females) for up to 104 weeks. There was no evidence of drug-related tumors in either species. Plasma perampanel exposures (AUC) at the highest doses tested were less than that in humans dosed at 8 mg/day.

Mutagenesis
Perampanel was negative in the *in vitro* Ames and mouse lymphoma *tk* assays, and in the *in vivo* rat micronucleus assay.

Impairment of Fertility
In male and female rats administered perampanel (oral doses of 1, 10, or 30 mg/kg/day) prior to and throughout mating and continuing in females to gestation day 6, there were no clear effects on fertility. Prolonged and/or irregular estrus cycles were observed at all doses but particularly at the highest dose tested. Plasma perampanel exposures (AUC) at all doses were lower than that in humans dosed at 8 mg/day.

14 CLINICAL STUDIES

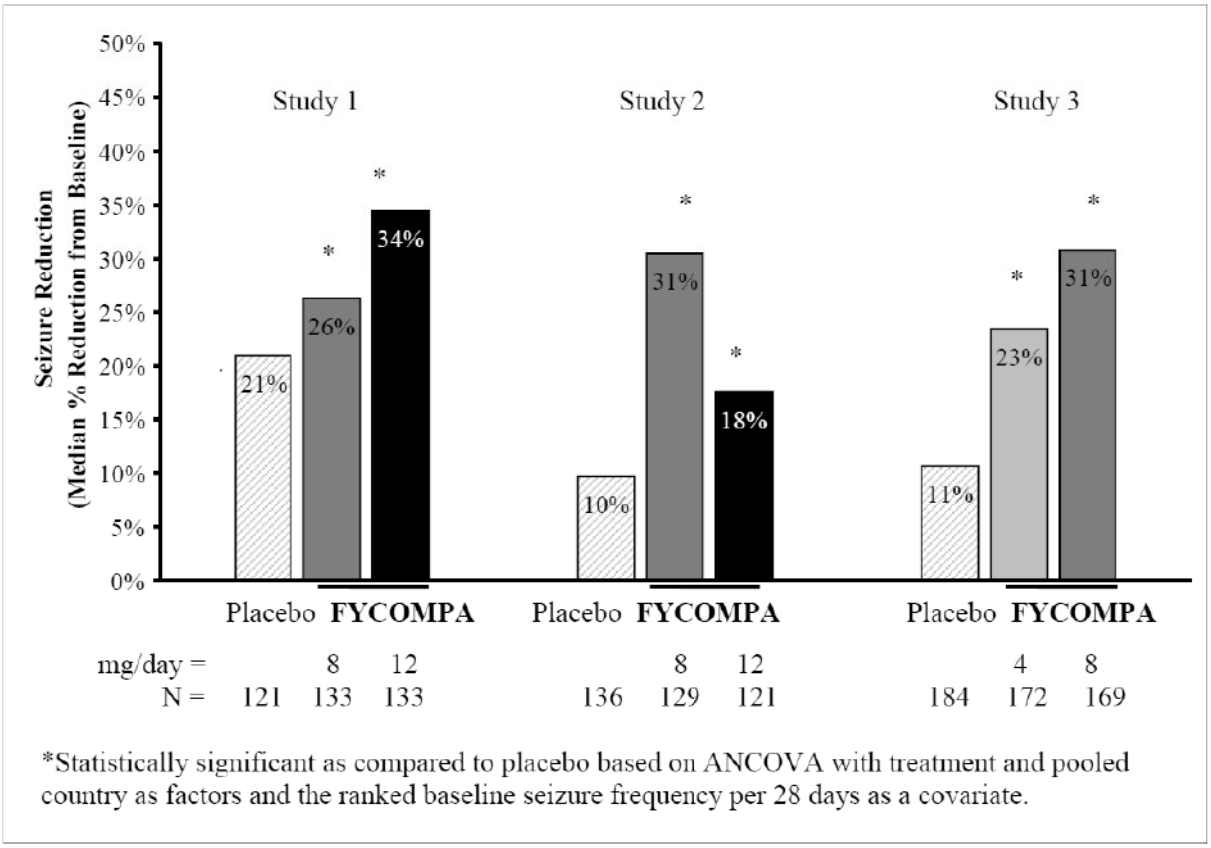
14.1 Partial-Onset Seizures

The efficacy of FYCOMPA in partial-onset seizures, with or without secondary generalization, was studied in patients who were not adequately controlled with 1 to 3 concomitant AEDs in 3 randomized, double-blind, placebo-controlled, multicenter trials (Studies 1, 2, and 3) in adult and pediatric patients (12 years of age and older). All trials had an initial 6-week Baseline Period, during which patients were required to have more than five seizures in order to be randomized. The Baseline Period was followed by a 19-week Treatment Period consisting of a 6-week Titration Phase and a 13-week Maintenance Phase. Patients in these 3 trials had a mean duration of epilepsy of approximately 21 years and a median baseline seizure frequency ranging from 9 to 14 seizures per 28 days. During the trials, more than 85% of patients were taking 2 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation, and approximately 50% were on at least one AED known to induce CYP3A4, an enzyme critical to the metabolism of FYCOMPA (i.e., carbamazepine, oxcarbazepine, or phenytoin), resulting in a significant reduction in FYCOMPA's serum concentration *[see Drug Interactions (7.2), Clinical Pharmacology (12.3)]*.

Each study evaluated placebo and multiple FYCOMPA dosages (see Figure 1). During the Titration period in all 3 trials, patients on FYCOMPA received an initial 2 mg once daily dose, which was subsequently increased in weekly increments of 2 mg per day to the final dose. Patients experiencing intolerable adverse reactions were permitted to have their dose reduced to the previously tolerated dose.

The primary endpoint in Studies 1, 2, and 3 was the percent change in seizure frequency per 28 days during the Treatment Period as compared to the Baseline Period. The criterion for statistical significance was $p<0.05$. A statistically significant decrease in seizure rate was observed at doses of 4 to 12 mg per day. Dose response was apparent at 4 to 8 mg with little additional reduction in frequency at 12 mg per day.

Figure 1. Median Percent Reduction in Seizure Frequency per 28 Days from Baseline to Treatment Period



*Statistically significant as compared to placebo based on ANCOVA with treatment and pooled country as factors and the ranked baseline seizure frequency per 28 days as a covariate.

Tables 4 and 5 present an analysis combining data from all 3 studies, grouping patients based upon whether or not concomitant enzyme-inducing AEDs (carbamazepine, oxcarbazepine, or phenytoin) were used. The analysis revealed a substantially reduced effect in the presence of inducers.

Table 4. Median Percent Reduction for Combined Studies (Study 1, 2 and 3) Based on the Presence or Absence of Concomitant Enzyme-Inducing AEDs (carbamazepine, oxcarbazepine, phenytoin)[a]

	Without Enzyme-Inducing AEDs		With Enzyme-Inducing AEDs	
	Placebo %	FYCOMPA %	Placebo %	FYCOMPA %
2 mg/day	16	23	14	16
4 mg/day	16	22	14	33
8 mg/day	19	45	12	24
12 mg/day	19	54	9	22

[a] Patients from Latin American region are excluded because of a significant treatment-by-region interaction due to high placebo response

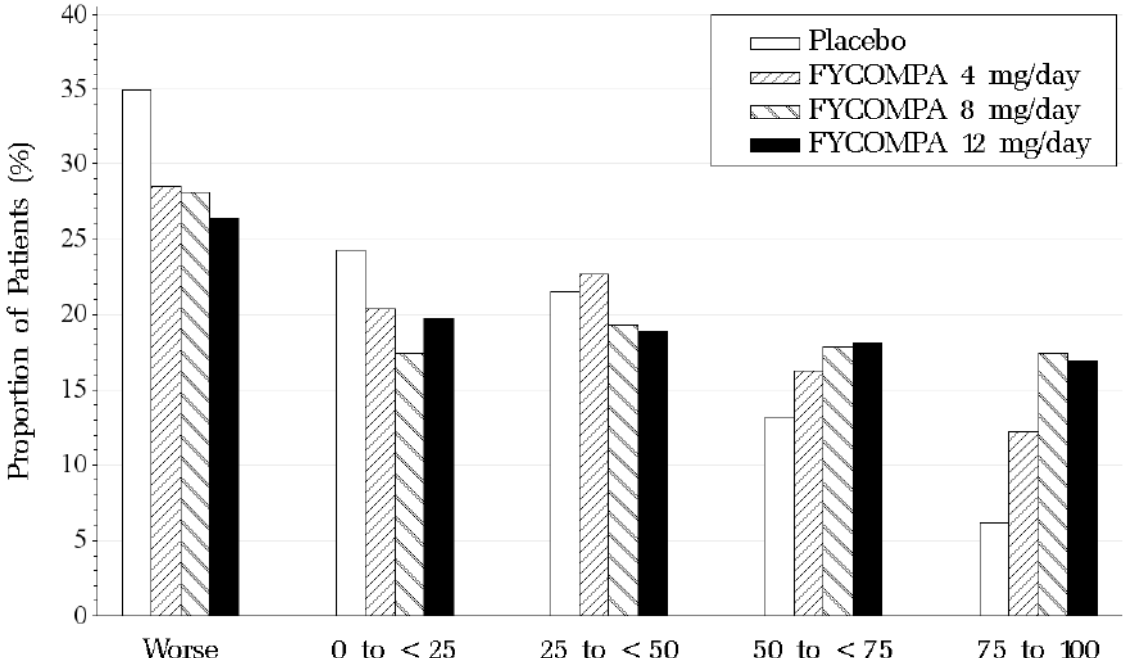
Table 5. Responder Rate for Combined Studies (Study 1, 2 and 3) Based on the Presence or Absence of Concomitant Enzyme-Inducing AEDs (carbamazepine, oxcarbazepine, phenytoin)[a,b]

	Without Enzyme-Inducing AEDs		With Enzyme-Inducing AEDs	
	Placebo %	FYCOMPA %	Placebo %	FYCOMPA %
2 mg/day	19	26	18	20
4 mg/day	19	35	18	26
8 mg/day	17	45	19	32
12 mg/day	15	54	21	33

[a] Patients from Latin American region are excluded because of a significant treatment-by-region interaction due to high placebo response
[b] The proportion of patients with at least a 50% decrease in seizure frequency

Figure 2 shows the proportion of patients with different percent reductions during the maintenance phase over baseline across all three trials. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in the remaining four categories.

Figure 2. Proportion of Patients Exhibiting Different Percent Reductions During the Maintenance Phase Over Baseline Across All Three Trials.



The percentages of patients with a 50% or greater reduction in seizure frequency were 19%, 29%, 35%, 35% for placebo, 4, 8, and 12 mg, respectively.

14.2 Primary Generalized Tonic-Clonic (PGTC) Seizures

The efficacy of FYCOMPA as adjunctive therapy in patients 12 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic seizures was established in one multicenter, randomized, double-blind, placebo-controlled study (Study 4), conducted at 78 sites in 16 countries. Eligible patients on a stable dose of 1 to 3 AEDs experiencing at least 3 primary generalized tonic-clonic seizures during the 8-week baseline period were randomized to either FYCOMPA or placebo. Efficacy was analyzed in 162 patients (FYCOMPA N=81, placebo N=81) who received medication and at least one post-treatment seizure assessment. Patients were titrated over 4 weeks up to a dose of 8 mg per day or the highest tolerated dose and treated for an additional 13 weeks on the last dose level achieved at the end of the titration period. The total treatment period was 17 weeks. Study drug was given once per day.

The primary endpoint was the percent change from baseline in primary generalized tonic-clonic seizure frequency per 28 days during the treatment period as compared to the baseline period. The criterion for statistical significance was $p<0.05$. Table 6 shows the results of this study. A statistically significant decrease in seizure rate was observed with FYCOMPA compared to placebo.

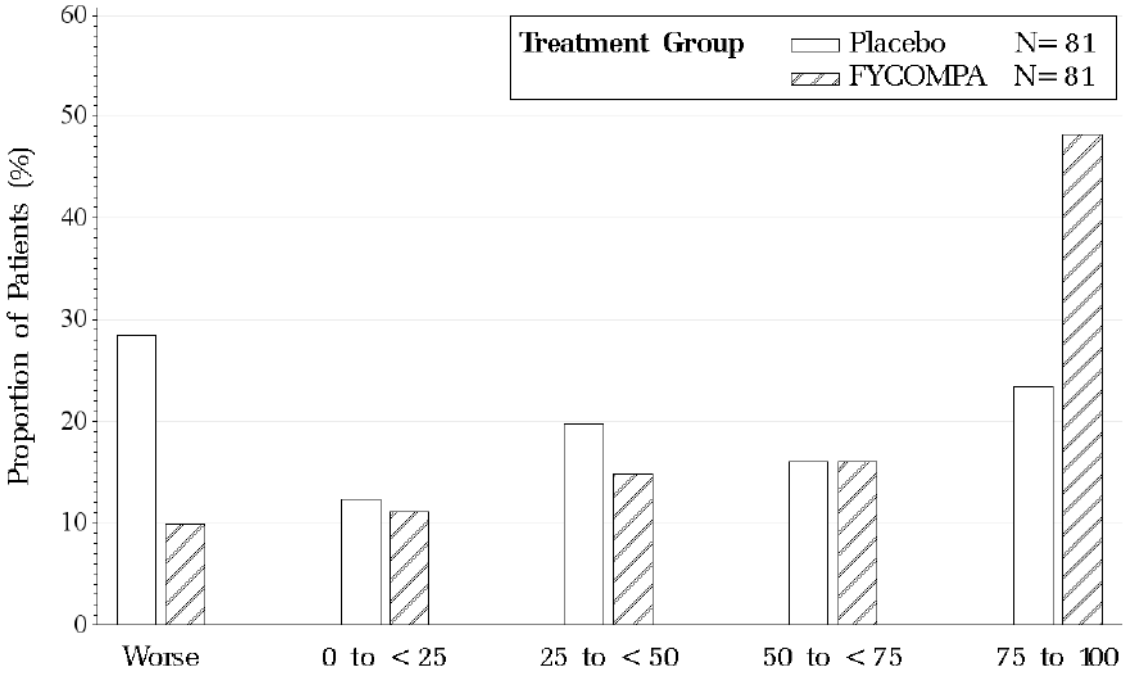
Table 6. Median Percent Reduction from Baseline in Primary Generalized Tonic-Clonic Seizure Frequency in Study 4

	Placebo (N=81)	FYCOMPA 8 mg (N=81)
Percent Reduction During Treatment	38	76[a]

[a] P-value compared to placebo: <0.0001. Statistically significant as compared to placebo based on ANCOVA with treatment and pooled country as factors and the ranked baseline seizure frequency per 28 days as a covariate.

Figure 3 shows the proportion of patients with different percent reductions during the maintenance phase over baseline in primary generalized tonic-clonic seizure frequency. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in the remaining four categories.

Figure 3. Proportion of Patients Exhibiting Different Percent Reductions During the Maintenance Phase Over Baseline in Primary Generalized Tonic-Clonic Seizure Frequency.



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FYCOMPA Tablets

- 2 mg are orange, round, biconvex, film-coated tablets debossed with "2" on one side and "Є 275" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-272-30
  Bottles of 90 NDC 62856-272-90

- 4 mg are red, round, biconvex, film-coated tablets debossed with "4" on one side and "Є 277" on the other. They are supplied as follows:

Bottles of 30 NDC 62856-274-30
Bottles of 90 NDC 62856-274-90

- 6 mg are pink, round, biconvex, film-coated tablets debossed with "6" on one side and "Є 294" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-276-30
  Bottles of 90 NDC 62856-276-90

- 8 mg are purple, round, biconvex, film-coated tablets debossed with "8" on one side and "Є 295" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-278-30
  Bottles of 90 NDC 62856-278-90

- 10 mg are green, round, biconvex, film-coated tablets debossed with "10" on one side and "Є 296" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-280-30
  Bottles of 90 NDC 62856-280-90

- 12 mg are blue, round, biconvex, film-coated tablets debossed with "12" on one side and "Є 297" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-282-30
  Bottles of 90 NDC 62856-282-90

FYCOMPA Oral Suspension
- 0.5 mg/mL is a white to off-white opaque liquid. It is supplied in a round amber PET bottle with a child-resistant closure. It is packaged with a dispenser set that provides two 20-mL graduated oral dosing syringes and a push-in bottle adapter.
- Bottle containing 340 mL NDC 62856-290-38

16.2 Storage
Tablets: store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]

Oral Suspension: Do not store above 30°C (86°F). Do not freeze. Use within 90 days after the first opening of the bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration of Oral Suspension
Advise patients who are prescribed the oral suspension to shake the bottle well before every administration and to use the adaptor and oral dosing syringe provided. Advise patients that a household teaspoon or tablespoon is not an adequate measuring device. Instruct patients to discard any unused FYCOMPA oral suspension remaining 90 days after first opening the bottle *[see Dosage and Administration (2.7)]*.

Serious Psychiatric and Behavioral Reactions
Counsel patients, families, and caregivers of patients of the need to monitor for the emergence of anger, aggression, hostility, hallucinations, delusions, confusion, unusual changes in mood, personality, or behavior, and other behavioral symptoms. Advise them to report any such symptoms immediately to their healthcare providers *[see Warnings and Precautions (5.1)]*.

Suicidal Thinking and Behavior
Counsel patients, their caregivers, and families that AEDs, including FYCOMPA, may increase the risk of suicidal thinking and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Instruct patients, caregivers, and families to report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.2)]*.

Neurologic Effects: Dizziness, Gait Disturbance, Somnolence, and Fatigue
Counsel patients that FYCOMPA may cause dizziness, gait disturbance, somnolence, and fatigue. Advise patients taking FYCOMPA not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with FYCOMPA *[see Warnings and Precautions (5.3)]*.

Falls
Counsel patients that FYCOMPA may cause falls and injuries *[see Warnings and Precautions (5.4)]*.

DRESS/Multi-organ Hypersensitivity
Instruct patients that a fever associated with signs of other organ system involvement (e.g., rash, lymphadenopathy, hepatic dysfunction) may be drug-related and should be reported to their healthcare provider immediately *[see Warnings and Precautions (5.5)]*.

Withdrawal of Antiepileptic Drugs
Counsel patients that abrupt discontinuation of FYCOMPA may increase seizure frequency *[see Warnings and Precautions (5.6)]*.

Contraceptives
Counsel females of reproductive potential that FYCOMPA may decrease efficacy of contraceptives containing levonorgestrel, and advise them to use an additional non-hormonal form of contraception while using FYCOMPA and for a month after discontinuation *[see Drug Interactions (7.1), Use in Specific Populations (8.3)]*.

Alcohol and Other CNS Depressants
Counsel patients that FYCOMPA may enhance the impairment effects of alcohol. These effects may also be seen if FYCOMPA is taken with other CNS depressants *[see Drug Interactions (7.3)]*.

Missed Doses
Counsel patients that if they miss a dose, they should resume dosing the following day at their prescribed daily dose. Instruct patients to contact their physician if more than one day of dosing is missed.

Controlled Substance
Counsel patients that FYCOMPA is a controlled substance that can be misused and abused *[see Drug Abuse and Dependence (9.1)]*.

Pregnancy Registry
Advise women who are exposed to FYCOMPA during pregnancy that there is a pregnancy exposure registry that monitors pregnancy outcomes. Encourage these patients to enroll in the NAAED Pregnancy Registry *[see Use in Specific Populations (8.1)]*.

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Marketed by Eisai Inc., Nutley, NJ 07110

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MEDICATION GUIDE

FYCOMPA® (fī-COM-puh) (perampanel) tablets, for oral use, CIII

FYCOMPA® (fī-COM-puh) (perampanel) oral suspension, CIII

What is the most important information I should know about FYCOMPA?

1. **FYCOMPA may cause mental (psychiatric) problems, including:**
   - new or worse aggressive behavior (including homicidal behavior), hostility, anger, anxiety, or irritability
   - being suspicious or distrustful (believing things that are not true)
   - seeing objects or hearing things that are not there
   - confusion
   - difficulty with memory
   - other unusual or extreme changes in behavior or mood

   Tell your healthcare provider right away if you have any new or worsening mental problems while taking FYCOMPA.
2. **Like other antiepileptic drugs, FYCOMPA may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**
   Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
   - thoughts about suicide or dying
   - new or worse depression
   - feeling agitated or restless
   - trouble sleeping (insomnia)
   - acting aggressive, being angry, or violent
   - an extreme increase in activity and talking (mania)
   - attempt to commit suicide
   - new or worse anxiety
   - panic attacks
   - new or worse irritability
   - acting on dangerous impulses
   - other unusual changes in behavior or mood

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop FYCOMPA without first talking with a healthcare provider. Stopping FYCOMPA suddenly can cause serious problems. Stopping FYCOMPA suddenly can cause you to have seizures more often.

What is FYCOMPA?

FYCOMPA is a prescription medicine used:

- to treat partial-onset seizures with or without secondarily generalized seizures in people with epilepsy who are 4 years of age and older
- with other medicines to treat primary generalized tonic-clonic seizures in people with epilepsy who are 12 years of age and older

FYCOMPA is a controlled substance (CIII) because it can be abused or lead to drug dependence. Keep your FYCOMPA in a safe place to protect it from theft. Never give your FYCOMPA to anyone else because it may harm them. Selling or giving away this medicine is against the law.

It is not known if FYCOMPA is safe and effective for partial onset seizures in children under 4 years of age or for primary generalized tonic clonic seizures in patients under 12 years of age.

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

- have or have had depression, mood problems, aggressive or hostile behavior (for example, homicidal behavior), suicidal thoughts or behavior, or other psychiatric problems.
- have liver or kidney problems
- drink alcohol
- have abused prescription medicines, street drugs, or alcohol in the past
- are pregnant or plan to become pregnant. It is not known if FYCOMPA will harm your unborn baby.
  - If you become pregnant while taking FYCOMPA, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334 or go to http://www.aedpregnancyregistry.org. The purpose of this registry is to collect information about the safety of FYCOMPA and other antiepileptic medicine during pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if FYCOMPA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take FYCOMPA. You and your healthcare provider should decide if you will take FYCOMPA or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Taking FYCOMPA with certain other medicines can cause side effects or reduce the benefit of either drug. **Especially tell your healthcare provider if you take:**

- contraceptives (birth control). FYCOMPA may lower your contraceptive's ability to prevent pregnancy if your contraceptive contains levonorgestrel. Use an additional non-hormonal form of contraception (like condoms or a diaphragm and spermicide) while using FYCOMPA and for 1 month after you have stopped taking FYCOMPA.
- carbamazepine (CARBATROL, TEGRETOL, TEGRETOL-XR, EQUETRO, EPITOL)
- phenytoin (DILANTIN, PHENYTEK)
- oxcarbazepine (TRILEPTAL)
- rifampin (RIFADIN, RIMACTANE)
- St. John's Wort

How should I take FYCOMPA?

- See the Instructions for Use below for complete information on how to use the dosing syringes and how to measure the dose of FYCOMPA Oral Suspension.
- Take FYCOMPA exactly as your healthcare provider tells you. Your healthcare provider will tell you how much FYCOMPA to take and when to take it. FYCOMPA is usually taken 1 time a day at bedtime.
- Your healthcare provider may change the dose. Do not change the dose without talking to your healthcare provider.
- If you take FYCOMPA Oral Suspension, shake the bottle well before you take each dose.
- Measure the dose of FYCOMPA Oral Suspension using the bottle adapter and dosing syringes provided. **Do not** use a household teaspoon.
- Talk to your healthcare provider about what to do if you miss more than 1 dose of FYCOMPA.
- If you take too much FYCOMPA, call your local Poison Control Center or go to the nearest hospital emergency room right away.

What should I avoid while taking FYCOMPA?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how FYCOMPA affects you. FYCOMPA may make you dizzy, sleepy, or tired.
- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking FYCOMPA until you talk to your healthcare provider. FYCOMPA taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse. FYCOMPA when taken with alcohol may also make your mood worse, increase anger, confusion, and depression.

What are the possible side effects of FYCOMPA?
See **"What is the most important information I should know about FYCOMPA?"**
FYCOMPA may cause other serious side effects, including:

- **Dizziness, vertigo (sense of spinning), and problems walking normally.** You may have problems walking normally if you are unsteady because you feel dizzy. These symptoms can increase when the dose of FYCOMPA is increased. Your risk of feeling dizzy and having problems walking normally may be higher if you are elderly.
- **Sleepiness and tiredness.** See **"What should I avoid while taking FYCOMPA?"**
- **Increased risk of falls.** Taking FYCOMPA can increase your chance of falling. These falls can cause serious injuries. Your risk of falling may be higher if you are elderly.
- **A serious allergic reaction that may affect your skin or other parts of your body such as your liver, kidneys, heart, or blood cells.** This allergic reaction can be life-threatening and can cause death. Call your healthcare provider right away if you have:
  - a skin rash, hives
  - fever or swollen glands that do not go away
  - swelling of your face
  - shortness of breath, swelling of the legs, yellowing of the skin or whites of the eyes, or dark urine.

The most common side effects of FYCOMPA include:

- dizziness
- sleepiness
- tiredness
- irritability
- falls
- nausea and vomiting
- weight gain
- vertigo (sense of spinning)
- problems walking normally
- problems with muscle coordination
- headache
- bruising
- abdominal pain
- anxiety

These are not all of the possible side effects of FYCOMPA. For more information ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FYCOMPA?

- Store FYCOMPA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Store FYCOMPA oral suspension below 86°F (30°C). **Do not** freeze.
- Replace the cap tightly after opening.
- Use FYCOMPA oral suspension within 90 days after the bottle is first opened.

Keep FYCOMPA and all medicines out of the reach of children.

General information about the safe and effective use of FYCOMPA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FYCOMPA for a condition for which it was not prescribed. Do not give FYCOMPA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about FYCOMPA that is written for health professionals.

What are the ingredients in FYCOMPA?

Active ingredient: perampanel

Inactive ingredients (tablets): lactose monohydrate, low substituted hydroxypropyl cellulose, povidone, microcrystalline cellulose, magnesium stearate, hypromellose, polyethylene glycol, talc, and titanium dioxide. Tablets of different strengths also may contain yellow ferric oxide (10 mg and 2 mg), red ferric oxide (2 mg, 4 mg, 6 mg, 8 mg), black ferric oxide (8 mg), and FD&C blue # 2 (indigo carmine) aluminum lake (10 mg and 12 mg).

Inactive ingredients (oral suspension): sorbitol, microcrystalline cellulose, carboxymethylcellulose sodium, poloxamer, simethicone, citric acid, sodium benzoate, and purified water.

Marketed by Eisai Inc., Nutley, NJ 07110

FYCOMPA® is a trademark owned by Eisai R&D Management Co. Ltd. For more information, go to www.FYCOMPA.com or 1-888-274-2378.

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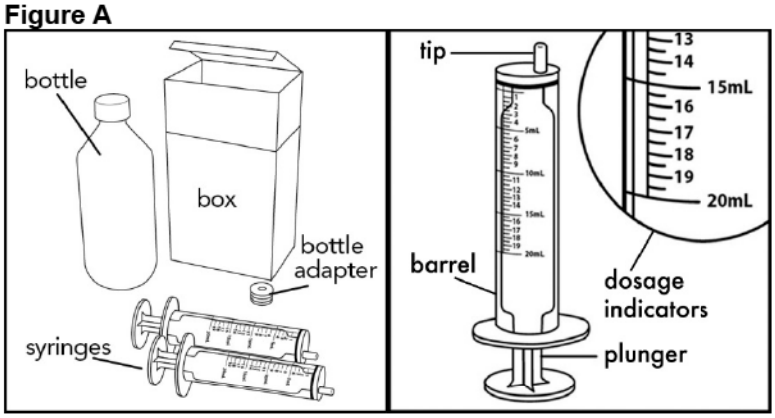
This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 12/2021

Instructions for Use
FYCOMPA® (fī-COM-puh)
(perampanel)
Oral Suspension

Read this Instructions for Use before you start using FYCOMPA Oral Suspension and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

Prepare the FYCOMPA Oral Suspension dose
You will need the following supplies: **See Figure A**
• FYCOMPA Oral Suspension bottle
• Bottle adapter
• Dosing syringe (2 dosing syringes are included in the FYCOMPA Oral Suspension box)

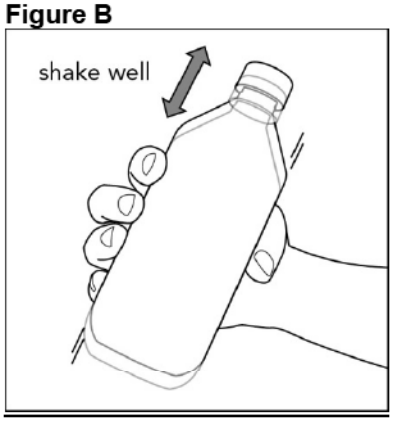
Figure A



Step 1. Remove the FYCOMPA Oral Suspension bottle, bottle adapter, and 2 syringes from the box. **See Figure A**

Step 2. Shake the bottle well before each use. **See Figure B**

Figure B



Step 3. Uncap the bottle and insert the bottle adapter into the bottle by pressing downward. **See Figure C and Figure D**

Figure C

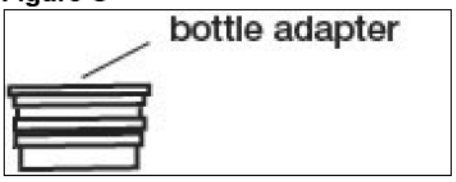
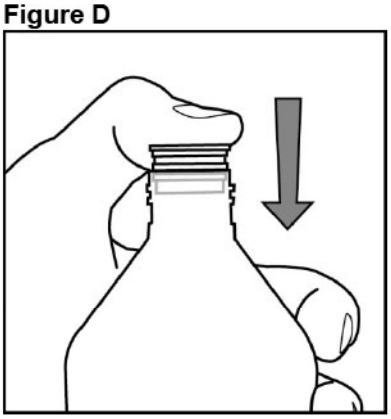


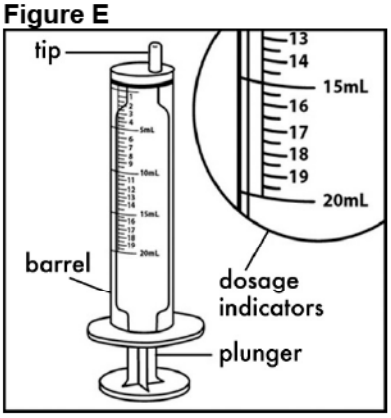
Figure D



After the bottle adapter is in place, it cannot be removed.

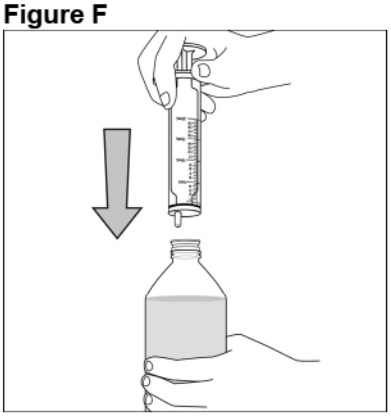
Step 4. Check the dose in milliliters (mL) as prescribed by your healthcare provider. Find this number on the syringe. **See Figure E**

Figure E



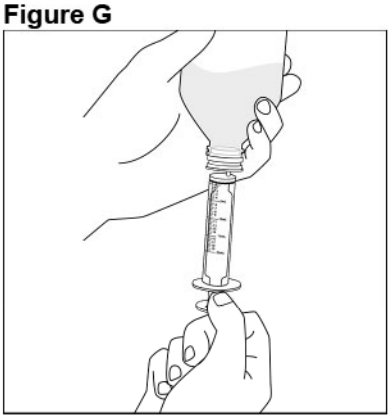
Step 5. Push the plunger of the syringe all the way down then insert the syringe into the upright bottle through the opening in the bottle adapter. **See Figure F**

Figure F



Step 6. With the syringe in place, turn the bottle upside down. Pull the plunger to withdraw the dose prescribed by your healthcare provider (the amount of liquid medicine in Step 4). If you see air bubbles in the oral syringe, fully push in the plunger so that the oral solution flows back into the bottle. Then, withdraw the prescribed dose of oral suspension. **See Figure G**

Figure G



Measure the mLs of medicine from the **white** layer at the end of the plunger, not the black layer.

Step 7. If the dose is more than 20 mL, you can use:
• 2 syringes

or

• 1 syringe, taking 2 steps to draw up the medicine in that same syringe

For example:
If the dose is 24 mL, draw up 20 mL in the first syringe and the remaining 4 mL in the second syringe.

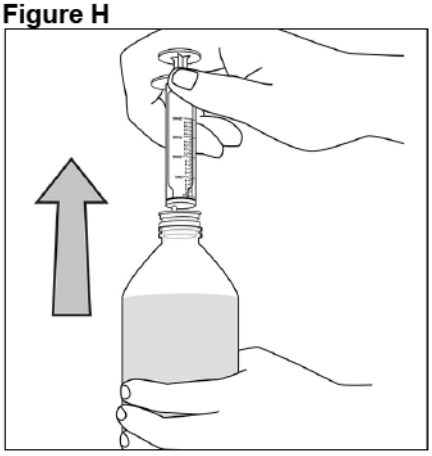
or

If the dose is 24 mL, draw up 20 mL in the single syringe and squirt the medicine into the mouth, then draw up the remaining 4 mL in that same syringe.

If the dose is more than 20 mL, repeat Steps 4 through 6 when drawing up the remaining dose of medicine.

Step 8. Turn the bottle right-side up and remove the syringe from the bottle adapter. **See Figure H**

Figure H



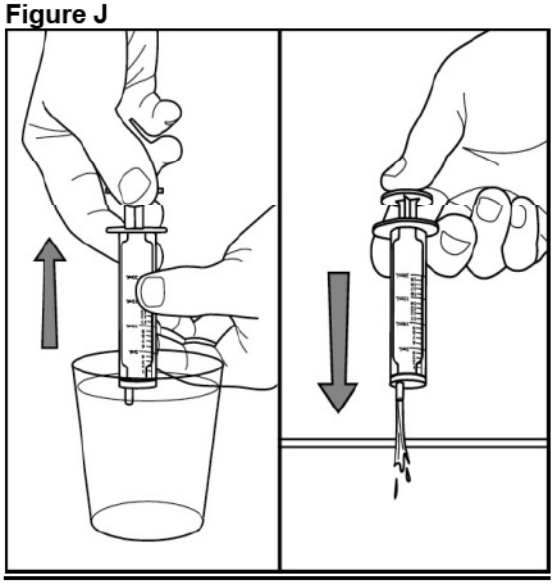
Step 9. Slowly squirt the FYCOMPA oral suspension directly into the corner of the mouth until all of the liquid medicine is given. If you need 2 syringes for the dose, slowly squirt the medicine from the first syringe into the mouth, then slowly squirt the medicine from the second syringe into the mouth. **See Figure I**

Figure I



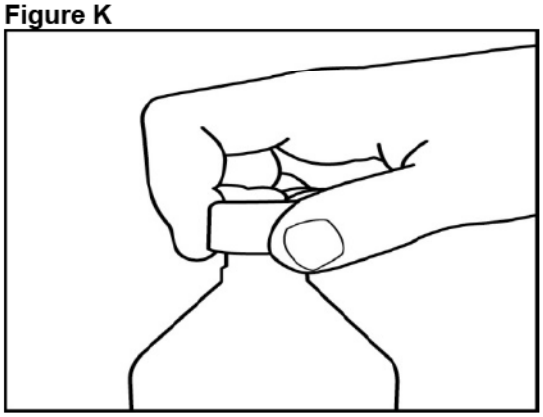
Step 10. Rinse the syringe (or syringes) with tap water after each use. **See Figure J**
• Fill a cup with water
• Pull back on the plunger and draw the water from the cup into the syringe
• Push down on the plunger to release the water into the sink

Figure J



Step 11. Cap the bottle tightly. The cap will fit over the bottle adapter. **See Figure K**

Figure K



How should I store FYCOMPA Oral Suspension?

- Store FYCOMPA oral suspension below 86°F (30°C). **Do not** freeze.
- Replace the cap tightly after opening.

FYCO-US4519

- Use FYCOMPA oral suspension within 90 days after the bottle is first opened.
- After 90 days safely throw away any FYCOMPA Oral Suspension that has not been used.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Revised: 12/2021

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 2 mg film-coated tablets
Fycompa 4 mg film-coated tablets
Fycompa 6 mg film-coated tablets
Fycompa 8 mg film-coated tablets
Fycompa 10 mg film-coated tablets
Fycompa 12 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fycompa 2 mg film-coated tablets

Each film-coated tablet contains 2 mg perampanel.

Excipient with known effect: Each 2 mg tablet contains 78.5 mg of lactose (as monohydrate).
For the full list of excipients, see section 6.1.

Fycompa 4 mg film-coated tablets

Each film-coated tablet contains 4 mg perampanel.

Excipient with known effect: Each 4 mg tablet contains 157.0 mg of lactose (as monohydrate).
For the full list of excipients, see section 6.1.

Fycompa 6 mg film-coated tablets

Each film-coated tablet contains 6 mg perampanel.

Excipient with known effect: Each 6 mg tablet contains 151.0 mg of lactose (as monohydrate).
For the full list of excipients, see section 6.1.

Fycompa 8 mg film-coated tablets

Each film-coated tablet contains 8 mg perampanel.

Excipient with known effect: Each 8 mg tablet contains 149.0 mg of lactose (as monohydrate).
For the full list of excipients, see section 6.1.

Fycompa 10 mg film-coated tablets

Each film-coated tablet contains 10 mg perampanel.

Excipient with known effect: Each 10 mg tablet contains 147.0 mg of lactose (as monohydrate).
For the full list of excipients, see section 6.1.

Fycompa 12 mg film-coated tablets

Each film-coated tablet contains 12 mg perampanel.

Excipient with known effect: Each 12 mg tablet contains 145.0 mg of lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Fycompa 2 mg film-coated tablets

Orange, round, biconvex tablet, engraved with E275 on one side and '2' on other side

Fycompa 4 mg film-coated tablets

Red, round, biconvex tablet, engraved with E277 on one side and '4' on other side

Fycompa 6 mg film-coated tablets

Pink, round, biconvex tablet, engraved with E294 on one side and '6' on other side

Fycompa 8 mg film-coated tablets

Purple, round, biconvex tablet, engraved with E295 on one side and '8' on other side

Fycompa 10 mg film-coated tablets

Green, round, biconvex tablet, engraved with E296 on one side and '10' on other side

Fycompa 12 mg film-coated tablets

Blue, round, biconvex tablet, engraved with E297 on one side and '12' on other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fycompa (perampanel) is indicated for the adjunctive treatment of
- partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age and older.
- primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalised epilepsy (IGE).

4.2 Posology and method of administration

Posology

Fycompa must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability.
Perampanel should be taken orally once daily at bedtime.
The physician should prescribe the most appropriate formulation and strength according to weight and dose. Alternate formulations of perampanel are available, including oral suspension

Partial-Onset Seizures
Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective therapy in partial-onset seizures.

The following table summarises the recommended posology for adults, adolescents and children from 4 years of age. More details are provided below the table.

	Adult/adolescent (12 years and older)	Children (4 – 11 years); weighing:		
		≥ 30 kg	20 - < 30 kg	< 20 kg
Recommended starting dose	2 mg/day	2 mg/day	1 mg/day	1 mg/day
Titration (incremental steps)	2 mg/day (no more frequently than weekly intervals)	2 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)
Recommended maintenance dose	4 – 8 mg/day	4 – 8 mg/day	4 – 6 mg/day	2 – 4 mg/day
Titration (incremental steps)	2 mg/day (no more frequently than weekly intervals)	2 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)	0.5 mg/day (no more frequently than weekly intervals)
Recommended maximum dose	12 mg/day	12 mg/day	8 mg/day	6 mg/day

Adults, adolescents age ≥ 12 years
Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 4 to 11 years) weighing ≥ 30 kg
Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 4 to 11 years of age) weighing 20 kg and < 30 kg
Treatment with Fycompa should be initiated with a dose of 1 mg/day. The dose may be increased based on clinical response and tolerability by increments of 1 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 6 mg/day. Depending upon individual clinical response and tolerability at a dose of 6 mg/day, the dose may be increased by increments of 1 mg/day to 8 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 4 to 11 years of age) weighing < 20 kg
Treatment with Fycompa should be initiated with a dose of 1 mg/day. The dose may be increased based on clinical response and tolerability by increments of 1 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 2 mg/day to 4 mg/day. Depending upon individual clinical response and tolerability at a dose of 4 mg/day, the dose may be

increased by increments of 0.5 mg/day to 6 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Primary Generalised Tonic-Clonic Seizures
Perampanel at a dose up to 8 mg/day has been shown to be effective in primary generalised tonic-clonic seizures.

The following table summarises the recommended posology for adults, adolescents and children from 7 years of age. More details are provided below the table.

	Adult/adolescent (12 years and older)	Children (7 – 11 years); weighing:		
		≥ 30 kg	20 - < 30 kg	< 20 kg
Recommended starting dose	2 mg/day	2 mg/day	1 mg/day	1 mg/day
Titration (incremental steps)	2 mg/day (no more frequently than weekly intervals)	2 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)
Recommended maintenance dose	Up to 8 mg/day	4 – 8 mg/day	4 – 6 mg/day	2 – 4 mg/day
Titration (incremental steps)	2 mg/day (no more frequently than weekly intervals)	2 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)	0.5 mg/day (no more frequently than weekly intervals)
Recommended maximum dose	12 mg/day	12 mg/day	8 mg/day	6 mg/day

Adults, adolescents age ≥ 12 years
Treatment with Fycompa should be initiated at a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks, as per half-life considerations described below) to a maintenance dose of up to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased up to 12 mg/day, which may be effective in some patients (see section 4.4). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 7 to 11 years) weighing ≥ 30 kg
Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 7 to 11 years of age) weighing 20 kg and < 30 kg
Treatment with Fycompa should be initiated with a dose of 1 mg/day. The dose may be increased based on clinical response and tolerability by increments of 1 mg (either weekly or every 2 weeks as

per half-life considerations described below) to a maintenance dose of 4 mg/day to 6 mg/day. Depending upon individual clinical response and tolerability at a dose of 6 mg/day, the dose may be increased by increments of 1 mg/day to 8 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 7 to 11 years of age) weighing < 20 kg
Treatment with Fycompa should be initiated with a dose of 1 mg/day. The dose may be increased based on clinical response and tolerability by increments of 1 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 2 mg/day to 4 mg/day. Depending upon individual clinical response and tolerability at a dose of 4 mg/day, the dose may be increased by increments of 0.5 mg/day to 6 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Withdrawal
It is recommended that discontinuation be undertaken gradually to minimise the potential for rebound seizures. However, due to its long half-life and subsequent slow decline in plasma concentrations, perampanel can be discontinued abruptly if absolutely needed.

Missed doses
Single missed dose: As perampanel has a long half-life, the patient should wait and take their next dose as scheduled.

If more than 1 dose has been missed, for a continuous period of less than 5 half-lives (3 weeks for patients not taking perampanel metabolism-inducing anti-epileptic drugs (AED), 1 week for patients taking perampanel metabolism-inducing AEDs (see section 4.5)), consideration should be given to re-start treatment from the last dose level.

If a patient has discontinued perampanel for a continuous period of more than 5 half-lives, it is recommended that initial dosing recommendations given above should be followed.

Elderly (65 years of age and above)
Clinical studies of Fycompa in epilepsy did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Analysis of safety information in 905 perampanel-treated elderly patients (in double-blind studies conducted in non-epilepsy indications) revealed no age-related differences in the safety profile. In combination with the lack of age-related difference in perampanel exposure, the results indicate that dose-adjustment in the elderly is not required. Perampanel should be used with caution in elderly taking into account the drug interaction potential in polymedicated patients (see section 4.4).

Renal impairment
Dose adjustment is not required in patients with mild renal impairment. Use in patients with moderate or severe renal impairment or patients undergoing haemodialysis is not recommended.

Hepatic impairment
Dose increases in patients with mild and moderate hepatic impairment should be based on clinical response and tolerability. For patients with mild or moderate hepatic impairment, dosing can be initiated at 2 mg. Patients should be up-titrated using 2 mg doses no faster than every 2 weeks based on tolerability and effectiveness.
Perampanel dosing for patients with mild and moderate impairment should not exceed 8 mg.
Use in patients with severe hepatic impairment is not recommended.

Paediatric population
The safety and efficacy of perampanel have not yet been established in children below 4 years of age in the POS indication or in children below 7 years of age in the PGTCS indication.

Method of administration

Fycompa should be taken as single oral dose at bedtime. It may be taken with or without food (see section 5.2). The tablet should be swallowed whole with a glass of water. It should not be chewed, crushed or split. The tablets cannot be split accurately as there is no break line.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicinal products in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for perampanel.
Therefore, patients (children, adolescents, and adults) should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens - Johnson Syndrome (SJS), which can be life-threatening or fatal, have been reported (frequency unknown; see section 4.8) in association with perampanel treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

Symptoms of DRESS include typically, although not exclusively, fever, rash associated with other organ system involvement, lymphadenopathy, liver function tests abnormalities and eosinophilia. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

Symptoms of SJS include typically although not exclusively, skin detachment (epidermal necrosis/blister) < 10%, erythematous skin (confluent), rapid progression, painful atypical target-like lesions and/or purpuric macules in wide dissemination or large erythema (confluent), bullous/erosive involvement of more than 2 mucous membranes.

If signs and symptoms suggestive of these reactions appear, perampanel should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS or DRESS with the use of perampanel, treatment with perampanel must not be restarted in this patient at any time.

Absence and myoclonic seizures

Absence and myoclonic seizures are two common generalised seizure types that frequently occur in IGE patients. Other AEDs are known to induce or aggravate these seizure types. Patients with myoclonic seizures and absence seizures should be monitored while on Fycompa.

Nervous system disorders

Perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines (see section 4.7).

Hormonal contraceptives

At doses of 12 mg/day Fycompa may decrease the effectiveness of progestative-containing hormonal contraceptives; in this circumstance additional non-hormonal forms of contraception are recommended when using Fycompa (see sections 4.5 and 4.6).

Falls

There appears to be an increased risk of falls, particularly in the elderly; the underlying reason is unclear.

Aggression,psychotic disorder

Aggressive, hostile, and abnormal behaviours have been reported in patients receiving perampanel therapy. In perampanel-treated patients in clinical trials, aggression, anger, irritability, and psychotic disorder were reported more frequently at higher doses. Most of the reported events were either mild or moderate, and patients recovered either spontaneously or with dose adjustment. However, thoughts of harming others, physical assault, or threatening behaviour were observed in some patients (<1% in perampanel clinical trials). Homicidal ideation has been reported in patients. Patients and caregivers should be counselled to alert a healthcare professional immediately if significant changes in mood or patterns of behaviour are noted. The dosage of perampanel should be reduced if such symptoms occur and discontinuation should be considered if symptoms are severe (see section 4.2).

Abuse potential

Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of perampanel abuse.

Concomitant CYP 3A inducing anti-epileptic medicinal products

Response rates after addition of perampanel at fixed doses were less when patients received concomitant CYP3A enzyme-inducing anti-epileptic medicinal products (carbamazepine, phenytoin, oxcarbazepine) as compared to response rates in patient who received concomitant non-enzyme-inducing anti-epileptic medicinal products. Patients' response should be monitored when they are switching from concomitant non-inducer anti-epileptic medicinal products to enzyme inducing medicinal products and vice versa. Depending upon individual clinical response and tolerability, the dose may be increased or decreased 2 mg at a time (see section 4.2).

Other concomitant (non- anti-epileptic) cytochrome P450 inducing or inhibiting medicinal products

Patients should be closely monitored for tolerability and clinical response when adding or removing cytochrome P450 inducers or inhibitors, since perampanel plasma levels can be decreased or increased; the dose of perampanel may need to be adjusted accordingly.

Hepatotoxicity

Cases of hepatotoxicity (mainly hepatic enzyme increased) with perampanel in combination with other antiepileptic drugs have been reported. If hepatic enzymes elevation is observed, monitoring of liver function should be considered.

Excipients

Lactose intolerance
Fycompa tablets contains lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Fycompa is not considered a strong inducer or inhibitor of cytochrome P450 or UGT enzymes (see section 5.2).

Hormonal contraceptives

In healthy women receiving 12 mg (but not 4 or 8 mg/day) for 21 days concomitantly with a combined oral contraceptive, Fycompa was shown to decrease the levonorgestrel exposure (mean C_{max} and AUC values were each decreased by 40%). Ethinylestradiol AUC was not affected by Fycompa 12 mg whereas C_{max} was decreased by 18%. Therefore, the possibility of decreased efficacy of hormonal progestative-containing contraceptives should be considered for women needing Fycompa 12 mg/day and an additional reliable method (intra-uterine device (IUD), condom) is to be used (see section 4.4).

Interactions between Fycompa and other anti-epileptic medicinal products

Potential interactions between Fycompa and other anti-epileptic drugs (AEDs) were assessed in clinical studies. A population PK analysis of three pooled Phase 3 studies in adolescent and adult patients with partial-onset seizures evaluated the effect of Fycompa (up to 12 mg once daily) on the PK of other AEDs. In another population PK analysis of pooled data from twenty Phase 1 studies in healthy subjects, with Fycompa up to 36 mg, and one Phase 2 and six Phase 3 studies in paediatric, adolescent, and adult patients with partial-onset seizures or primary generalised tonic-clonic seizures, with Fycompa up to 16 mg once daily, evaluated the effect of concomitant AEDs of perampanel clearance. The effect of these interactions on average steady state concentration is summarised in the following table.

AED coadministered	**Influence of AED on Fycompa concentration**	**Influence of Fycompa on AED concentration**
Carbamazepine	3 fold decrease	<10% decrease
Clobazam	No influence	<10% decrease
Clonazepam	No influence	No influence
Lamotrigine	No influence	<10% decrease
Levetiracetam	No influence	No influence
Oxcarbazepine	2 fold decrease	35% increase [1)]
Phenobarbital	20% decrease	No influence
Phenytoin	2 fold decrease	No influence
Topiramate	20% decrease	No influence
Valproic Acid	No influence	<10% decrease
Zonisamide	No influence	No influence

1) Active metabolite monohydroxycarbazepine was not assessed.

Based on the results from the population pharmacokinetic analysis of patients with partial-onset seizures and patients with primary generalised tonic-clonic seizures the total clearance of Fycompa was increased when co-administered with carbamazepine (3-fold), and phenytoin or oxcarbazepine

(2-fold), which are known inducers of enzymes of metabolism (see section 5.2). This effect should be taken into account and managed when adding or withdrawing these anti-epileptic drugs from a patient's treatment regimen. Clonazepam, levetiracetam, phenobarbital, topiramate, zonisamide, clobazam, lamotrigine and valproic acid did not affect to a clinically relevant manner the clearance of Fycompa.

In a population pharmacokinetic analysis of patients with partial-onset seizures, Fycompa did not affect to a clinically relevant manner the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, zonisamide, carbamazepine, clobazam, lamotrigine and valproic acid, at the highest perampanel dose evaluated (12 mg/day).

Perampanel was found to decrease the clearance of oxcarbazepine by 26%. Oxcarbazepine is rapidly metabolised by cytosolic reductase enzyme to the active metabolite, monohydroxycarbazepine. The effect of perampanel on monohydroxycarbazepine concentrations is not known.

Perampanel is dosed to clinical effect regardless of other AEDs.

Effect of perampanel on CYP3A substrates

In healthy subjects, Fycompa (6 mg once daily for 20 days) decreased midazolam AUC by 13%. A larger decrease in exposure of midazolam (or other sensitive CYP3A substrates) at higher Fycompa doses cannot be excluded.

Effect of cytochrome P450 inducers on perampanel pharmacokinetics

Strong inducers of cytochrome P450, such as rifampicin and hypericum, are expected to decrease perampanel concentrations and the potential for higher plasma concentrations of reactive metabolites in their presence has not been excluded. Felbamate has been shown to decrease the concentrations of some medicinal products and may also reduce perampanel concentrations.

Effect of cytochrome P450 inhibitors on perampanel pharmacokinetics

In healthy subjects, the CYP3A4 inhibitor ketoconazole (400 mg once daily for 10 days) increased perampanel AUC by 20% and prolonged perampanel half--life by 15% (67.8 h vs 58.4 h). Larger effects cannot be excluded when perampanel is combined with a CYP3A inhibitor with longer half-life than ketoconazole or when the inhibitor is given for a longer treatment duration.

Levodopa
In healthy subjects, Fycompa (4 mg once daily for 19 days) had no effect on C_{max} or AUC of levodopa.

Alcohol

The effects of perampanel on tasks involving alertness and vigilance such as driving ability were additive or supra-additive to the effects of alcohol itself, as found in a pharmacodynamic interaction study in healthy subjects. Multiple dosing of perampanel 12 mg/day increased levels of anger, confusion, and depression as assessed using the Profile of Mood State 5-point rating scale (see section 5.1). These effects may also be seen when Fycompa is used in combination with other central nervous system (CNS) depressants.

Paediatric population

Interaction studies have only been performed in adults.
In a population pharmacokinetic analysis of adolescent patients age ≥ 12 years and children age 4 to 11 years, there were no notable differences compared to the adult population.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and contraception in males and females

Fycompa is not recommended in women of childbearing potential not using contraception unless clearly necessary. Fycompa may decrease the effectiveness of progestative-containing hormonal contraceptives. An additional non-hormonal form of contraception is, therefore recommended (see sections 4.4 and 4.5).

Pregnancy

There are limited amounts of data (less than 300 pregnancy outcomes) from the use of perampanel in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats at maternally toxic doses (see section 5.3). Fycompa is not recommended during pregnancy.

Breast-feeding

Studies in lactating rats have shown excretion of perampanel and/or its metabolites in milk (for details see section 5.3). It is not known whether perampanel is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fycompa therapy taking into account the benefit of breast--feeding for the child and the benefit of therapy for the woman.

Fertility

In the fertility study in rats, prolonged and irregular oestrous cycles were observed at high-dose (30 mg/kg) in females; however, these changes did not affect the fertility and early embryonic development. There were no effects on male fertility (see section 5.3). The effect of perampanel on human fertility has not been established.

4.7 Effects on ability to drive and use machines

Fycompa has moderate influence on the ability to drive and use machines.
Perampanel may cause dizziness and somnolence and, therefore, may influence the ability to drive or use machines. Patients are advised not to drive a vehicle, operate complex machinery or engage in other potentially hazardous activities until it is known whether perampanel affects their ability to perform these tasks (see sections 4.4 and 4.5).

4.8 Undesirable effects

Summary of the safety profile

In all controlled and uncontrolled trials in patients with partial-onset seizures, 1,639 patients have received perampanel of whom 1,147 have been treated for 6 months and 703 for longer than 12 months.

In the controlled and uncontrolled study in patients with primary generalised tonic-clonic seizures, 114 patients have received perampanel of whom 68 have been treated for 6 months and 36 for longer than 12 months.

Adverse reactions leading to discontinuation:
In the controlled Phase 3 partial-onset seizures clinical trials, the rate of discontinuation as a result of an adverse reaction was 1.7% (3/172), 4.2% (18/431) and 13.7% (35/255) in patients randomised to receive perampanel at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 1.4% (6/442) in patients randomised to receive placebo. The adverse reactions most commonly (≥ 1%

in the total perampanel group and greater than placebo) leading to discontinuation were dizziness and somnolence.

In the controlled Phase 3 primary generalised tonic-clonic seizures clinical trial, the rate of discontinuation as a result of an adverse reaction was 4.9% (4/81) in patients randomised to receive perampanel 8 mg, and 1.2% (1/82) in patients randomised to receive placebo. The adverse reaction most commonly leading to discontinuation (≥ 2% in the perampanel group and greater than placebo) was dizziness.

Post-marketing use

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with perampanel treatment (see section 4.4).

Tabulated list of adverse reactions

In the table below, adverse reactions, which were identified based on review of the full Fycompa clinical studies safety database, are listed by System Organ Class and frequency. The following convention has been used for the classification of adverse reactions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), not known (cannot be estimated from the available data).

Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Very common	Common	Uncommon	Not known
Metabolism and nutrition disorders		Decreased appetite Increased appetite		
Psychiatric disorders		Aggression Anger Anxiety Confusional state	Suicidal ideation Suicide attempt Hallucinations Psychotic disorder	
Nervous system disorders	Dizziness Somnolence	Ataxia Dysarthria Balance disorder Irritability		
Eye disorders		Diplopia Vision blurred		
Ear and labyrinth disorders		Vertigo		
Gastrointestinal disorders		Nausea		
Skin and subcutaneous tissue disorders				Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)* Stevens - Johnson Syndrome (SJS)*

System Organ Class	Very common	Common	Uncommon	Not known
Musculoskeletal and connective tissue disorders		Back pain		
General disorders		Gait disturbance Fatigue		
Investigations		Weight increased		
Injury, poisoning and procedural complications		Fall		

* See section 4.4

Paediatric population

Based on the clinical trial database of 196 adolescents exposed to perampanel from double-blind studies for partial-onset seizures and primary generalised tonic-clonic seizures, the overall safety profile in adolescents was similar to that of adults, except for aggression, which was observed more frequently in adolescents than in adults.

Based on the clinical trial database of 180 paediatric patients exposed to perampanel from a multicentre, open label study, the overall safety profile in children was similar to that established for adolescents and adults, except for somnolence, irritability, aggression, and agitation which were observed more frequently in the paediatric study compared to studies in adolescents and adults.

Available data in children did not suggest any clinically significant effects of perampanel on growth and development parameters including body weight, height, thyroid function, insulin-like growth factor-1 (IGF-1) level, cognition (as assessed by Aldenkamp-Baker neuropsychological assessment schedule [ABNAS]), behaviour (as assessed by Child Behavior Checklist [CBCL]), and dexterity (as assessed by Lafayette Grooved Pegboard Test [LGPT]). However, long term effects [greater than 1 year] on learning, intelligence, growth, endocrine function, and puberty in children remain unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There have been post-marketing cases of intentional and accidental overdose in paediatric patients with doses of perampanel up to 36 mg and in adult patients with doses up to 300 mg. The adverse reactions observed included altered mental status, agitation, aggressive behaviour, coma and depressed level of consciousness. The patients recovered without sequelae.

There is no available specific antidote to the effects of perampanel.

General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. In view of its long half-life, the effects caused by perampanel could be prolonged. Because of low renal clearance special interventions such as forced diuresis, dialysis or haemoperfusion are unlikely to be of value.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX22

Mechanism of action

Perampanel is a first-in-class selective, 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 overexcitation. Activation of AMPA receptors by glutamate is thought to be responsible for most fast excitatory synaptic transmission in the brain. In *in vitro* studies, perampanel did not compete with AMPA for binding to the AMPA receptor, but perampanel binding was displaced by noncompetitive AMPA receptor antagonists, indicating that perampanel is a noncompetitive AMPA receptor antagonist. *In vitro*, perampanel inhibited AMPA-induced (but not NMDA-induced) increase in intracellular calcium. *In vivo*, perampanel significantly prolonged seizure latency in an AMPA-induced seizure model.

The precise mechanism by which perampanel exerts its antiepileptic effects in humans remains to be fully elucidated.

Pharmacodynamic effects

A pharmacokinetic-pharmacodynamic (efficacy) analysis was performed based on the pooled data from the 3 efficacy trials for partial-onset seizures. In addition, a pharmacokinetic-pharmacodynamic (efficacy) analysis was performed in one efficacy trial for primary generalised tonic-clonic seizures. In both analyses, perampanel exposure is correlated with reduction in seizure frequency.

Psychomotor performance
Single and multiple doses of 8 mg and 12 mg impaired psychomotor performance in healthy volunteers in a dose-related manner. The effects of perampanel on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol. Psychomotor performance testing returned to baseline within 2 weeks of cessation of perampanel dosing.

Cognitive function
In a healthy volunteer study to assess the effects of perampanel on alertness, and memory using a standard battery of assessments, no effects of perampanel were found following single and multiple doses of perampanel up to 12 mg/day.

In a placebo-controlled study conducted in adolescent patients, no significant changes in cognition relative to placebo as measured by Cognitive Drug Research (CDR) System Global Cognition Score were observed for perampanel. In the open label extension, no significant changes were observed in global CDR system score after 52 weeks of perampanel treatment (see section 5.1 Paediatric population).

In an open-label uncontrolled study conducted in paediatric patients, no clinically important changes in cognition relative to baseline as measured by ABNAS were observed following adjunctive perampanel therapy (see section 5.1 Paediatric population).

Alertness and mood
Levels of alertness (arousal) decreased in a dose-related manner in healthy subjects dosed with perampanel from 4 to 12 mg/day. Mood deteriorated following dosing of 12 mg/day only; the changes in mood were small and reflected a general lowering of alertness. Multiple dosing of perampanel 12 mg/day also enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion and depression as assessed using the Profile of Mood State 5-point rating scale.

Cardiac electrophysiology
Perampanel did not prolong the QTc interval when administered in daily doses up to 12 mg/day, and did not have a dose-related or clinically important effect on QRS duration.

Clinical efficacy and safety

Partial-Onset Seizures
The efficacy of perampanel in partial-onset seizures was established in three adjunctive therapy 19 week, randomised, double-blind, placebo-controlled, multicentre trials in adult and adolescent patients. Patients had partial-onset seizures with or without secondary generalisation and were not adequately controlled with one to three concomitant AEDs. During a 6-week baseline period, patients were required to have more than five seizures with no seizure-free period exceeding 25 days. In these three trials, patients had a mean duration of epilepsy of approximately 21.06 years. Between 85.3% and 89.1% of patients were taking two to three concomitant AEDs with or without concurrent vagal nerve stimulation.

Two studies (studies 304 and 305) compared doses of perampanel 8 and 12 mg/day with placebo and the third study (study 306) compared doses of perampanel 2, 4 and 8 mg/day with placebo. In all three trials, following a 6-week Baseline Phase to establish baseline seizure frequency prior to randomisation, patients were randomised and titrated to the randomised dose. During the Titration Phase in all three trials, treatment was initiated at 2 mg/day and increased in weekly increments of 2 mg/day to the target dose. Patients experiencing intolerable adverse events could remain on the same dose or have their dose decreased to the previously tolerated dose. In all three trials, the Titration Phase was followed by a Maintenance Phase that lasted 13 weeks, during which patients were to remain on a stable dose of perampanel.

The pooled 50% responder rates were placebo 19%, 4 mg 29%, 8 mg 35% and 12 mg 35%. A statistically significant effect on the reduction in 28-day seizure frequency (Baseline to Treatment Phase) as compared to the placebo group was observed with perampanel treatment at doses of 4 mg/day (Study 306), 8 mg/day (Studies 304, 305 and 306), and 12 mg/day (Studies 304 and 305). The 50% responder rates in the 4 mg, 8 mg and 12 mg groups were respectively 23.0%, 31.5%, and 30.0% in combination with enzyme-inducing anti-epileptic medicinal products and were 33.3%, 46.5% and 50.0% when perampanel was given in combination with non-enzyme-inducing anti-epileptic medicinal products. These studies show that once-daily administration of perampanel at doses of 4 mg to 12 mg was significantly more efficacious than placebo as adjunctive treatment in this population.

Data from placebo-controlled studies demonstrate that improvement in seizure control is observed with a once-daily perampanel dose of 4 mg and this benefit is enhanced as the dose is increased to 8 mg/day. No efficacy benefit was observed at the dose of 12 mg as compared to the dose of 8 mg in the overall population. Benefit at the dose of 12 mg was observed in some patients who tolerate the dose of 8 mg and when the clinical response to that dose was insufficient. A clinically meaningful reduction in seizure frequency relative to placebo was achieved as early as the second week of dosing when patients reached a daily dose of 4 mg.

1.7 to 5.8% of the patients on perampanel in the clinical studies became seizure free during the 3 month maintenance period compared with 0%-1.0% on placebo

Open label extension study
Ninety-seven percent of the patients who completed the randomised trials in patients with partial-onset seizures were enrolled in the open label extension study (n = 1186). Patients from the randomised trial were converted to perampanel over 16 weeks followed by a long-term maintenance period (≥ 1 year). The mean average daily dose was 10.05 mg.

Primary Generalised Tonic-Clonic Seizures
Perampanel as adjunctive therapy in patients 12 years of age and older with idiopathic generalised epilepsy experiencing primary generalised tonic-clonic seizures was established in a multicentre,

randomised, double-blind, placebo-controlled study (Study 332). Eligible patients on a stable dose of 1 to 3 AEDs experiencing at least 3 primary generalised tonic-clonic seizures during the 8-week baseline period were randomised to either perampanel or placebo. The population included 164 patients (perampanel N = 82, placebo N = 82). Patients were titrated over four weeks to a target dose of 8 mg per day or the highest tolerated dose and treated for an additional 13 weeks on the last dose level achieved at the end of the titration period. The total treatment period was 17 weeks. Study drug was given once per day.

The 50% primary generalised tonic-clonic seizures responder rate during the Maintenance Period was significantly higher in the perampanel group (58.0%) than in the placebo group (35.8%), P = 0.0059. The 50% responder rate was 22.2% in combination with enzyme-inducing anti-epileptic medicinal products and was 69.4% when perampanel was given in combination with non-enzyme-inducing anti-epileptic medicinal products. The number of perampanel patients taking enzyme-inducing anti-epileptic medicinal products was small (n = 9). The median percent change in primary generalised tonic-clonic seizure frequency per 28 days during the Titration and Maintenance Periods (combined) relative to Prerandomisation was greater with perampanel (-76.5%) than with placebo (-38.4%), P < 0.0001. During the 3 months maintenance period, 30.9% (25/81) of the patients on perampanel in the clinical studies became free of PGTC seizures compared with 12.3% (10/81) on placebo.

Other subtypes of idiopathic generalised seizure
The efficacy and safety of perampanel in patients with myoclonic seizures have not been established. The available data are insufficient to reach any conclusions.
The efficacy of perampanel in the treatment of absence seizures has not been demonstrated.
In Study 332, in patients with PGTC seizures who also had concomitant myoclonic seizures, freedom from seizures was achieved in 16.7% (4/24) on perampanel compared to 13.0% (3/23) in those on placebo. In patients with concomitant absence seizures, freedom from seizures was achieved in 22.2% (6/27) on perampanel compared to 12.1% (4/33) on placebo. Freedom from all seizures was achieved in 23.5% (19/81) of patients on perampanel compared to 4.9% (4/81) of patients on placebo.

Open label extension phase
Of the 140 patients who completed the Study 332, 114 patients (81.4%) had entered the Extension phase. Patients from the randomised trial were converted to perampanel over 6 weeks followed by a long-term maintenance period (≥ 1 year). In the Extension Phase, 73.7% (84/114) of patients have a modal daily perampanel dose of greater than 4 to 8 mg/day and 16.7% (19/114) had a modal daily dose of greater than 8 to 12 mg/day. A decrease in PGTC seizure frequency of at least 50% was seen in 65.9% (29/44) of patients after 1 year of treatment during the Extension Phase (relative to their pre-perampanel baseline seizure frequency). These data were consistent with those for percent change in seizure frequency and showed that the PGTC 50% responder rate was generally stable across time from about week 26 through the end of year 2. Similar results were seen when all seizures and absence vs. myoclonic seizures were evaluated over time.

Conversion to monotherapy
In a retrospective study of clinical practice, 51 patients with epilepsy who received perampanel as adjunctive treatment converted to perampanel monotherapy. The majority of these patients had a history of partial onset seizures. Of these, 14 patients (27%) reverted to adjunctive therapy in the following months. Thirty four (34) patients were followed up for at least 6 months and, of these, 24 patients (71%) remained on perampanel monotherapy for at least 6 months. Ten (10) patients were followed up for at least 18 months and, of these, 3 patients (30%) remained on perampanel monotherapy for at least 18 months.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Fycompa in one or more subsets of the paediatric population in treatment-resistant epilepsies (localisation-related and age-related epilepsy syndromes) (see section 4.2 for information on adolescent and paediatric use).

The three pivotal double-blind placebo-controlled phase 3 studies included 143 adolescents between the ages of 12 and 18. The results in these adolescents were similar to those seen in the adult population.

Study 332 included 22 adolescents between the ages of 12 and 18. The results in these adolescents were similar to those seen in the adult population.

A 19-week, randomised, double-blind, placebo-controlled study with an open-label extension phase (Study 235) was performed to assess the short-term effects on cognition of Fycompa (target dose range of 8 to 12 mg once daily) as adjunctive therapy in 133 (Fycompa n = 85, placebo n = 48) adolescent patients, aged 12 to less than 18 years old, with inadequately controlled partial-onset seizures. Cognitive function was assessed by the Cognitive Drug Research (CDR) System Global Cognition t-Score, which is a composite score derived from 5 domains testing Power of Attention, Continuity of Attention, Quality of Episodic Secondary Memory, Quality of Working Memory, and Speed of Memory. The mean change (SD) from baseline to end of double-blind treatment (19 weeks) in CDR System Global Cognition t-Score was 1.1 (7.14) in the placebo group and (minus) –1.0 (8.86) in the perampanel group, with the difference between the treatment groups in LS means (95% CI) = (minus) -2.2 (-5.2, 0.8). There was no statistically significant difference between the treatment groups (p = 0.145). CDR System Global Cognition t-Scores for placebo and perampanel were 41.2 (10.7) and 40.8 (13.0), respectively at the baseline. For patients with perampanel in the open label extension (n = 112), the mean change (SD) from baseline to end of open-label treatment (52 weeks) in CDR System Global Cognition t-Score was (minus) -1.0 (9.91). This was not statistically significant (p = 0.96). After up to 52 weeks of treatment with perampanel (n = 114), no effect on bone growth was observed. No effects on weight, height and sexual development were seen following up to 104 weeks of treatment (n = 114).

An open-label, uncontrolled study (Study 311) was performed to assess the exposure-efficacy relationship of perampanel as adjunctive therapy in 180 paediatric patients (aged 4 to 11 years old) with inadequately controlled partial-onset seizures or primary generalised tonic-clonic seizures. Patients were titrated over 11 weeks to a target dose of 8 mg/day or the maximum tolerated dose (not to exceed 12 mg/day) for patients not taking concomitant CYP3A-inducing antiepileptic drugs (carbamazepine, oxcarbazepine, eslicarbazepine and phenytoin) or 12 mg/day or the maximum tolerated dose (not to exceed 16 mg/day) for patients taking a concomitant CYP3A-inducing antiepileptic drug. Perampanel dose achieved at the end of titration was maintained for 12 weeks (for a total of 23 weeks of exposure) at the completion of the core study. Patients who entered into Extension Phase were treated for an additional 29 weeks for a total exposure duration of 52 weeks.

In patients with partial-onset seizures (n = 148 patients), the median change in seizure frequency per 28 days, the 50% or greater responder rate, and seizure-free rate following 23 weeks of perampanel treatment were -40.1%, 46.6% (n = 69/148), and 11.5% (n = 17/148), respectively, for total partial-onset seizures. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 108 patients, -69.4%), 50% responder rate (Weeks 40-52: 62.0%, n = 67/108), and seizure-free rate (Weeks 40-52: 13.0%, n = 14/108) were sustained following 52 weeks of perampanel treatment.

In a subset of partial-onset seizure patients with secondarily generalised seizures (n = 54 patients), the corresponding values were -58.7%, 64.8% (n = 35/54), and 18.5% (n = 10/54), respectively, for secondarily generalised tonic-clonic seizures. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 41 patients, -73.8%), 50% responder rate (Weeks 40-52: 80.5%, n = 33/41), and seizure-free rate (Weeks 40-52: 24.4%, n = 10/41) were sustained following 52 weeks of perampanel treatment.

In patients with primary generalised tonic-clonic seizures (n = 22 patients, with 19 patients aged 7-<12 years and 3 patients aged 4-<7 years), the median change in seizure frequency per 28 days, the 50% or greater responder rate, and seizure-free rate were -69.2%, 63.6% (n = 14/22), and 54.5% (n = 12/22), respectively. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 13 patients, -100.0%), 50% responder rate (Weeks 40-52: 61.5%, n = 8/13), and

seizure-free rate (Weeks 40-52: 38.5%, n = 5/13) were sustained following 52 weeks of perampanel treatment. These results should be considered cautiously as the number of patients is very small.

Similar results were obtained in a subset of patients with primary generalised tonic-clonic seizures of idiopathic generalised epilepsy (IGE) (n = 19 patients, with 17 patients aged 7-<12 years and 2 patients aged 4-<7 years; the corresponding values were -56.5%, 63.2% (n = 12/19), and 52.6% (n = 10/19), respectively. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 11 patients, -100.0%), 50% responder rate (Weeks 40-52: 54.5%, n = 6/11), and seizure-free rate (Weeks 40-52: 36.4%, n = 4/11) were sustained following 52 weeks of perampanel treatment. These results should be considered cautiously as the number of patients is very small.

5.2 Pharmacokinetic properties

The pharmacokinetics of perampanel have been studied in healthy adult subjects (age range 18 to 79), adults, adolescents, and paediatric patients with partial-onset seizures and primary generalised tonic-clonic seizures, adults with Parkinson's disease, adults with diabetic neuropathy, adults with multiple sclerosis, and patients with hepatic impairment.

Absorption

Perampanel is readily absorbed after oral administration with no evidence of marked first--pass metabolism. Co-administration of perampanel tablets with a high fat meal had no impact on the peak plasma exposure (C_{max}) or total exposure ($AUC_{0\text{-}inf}$) of perampanel. The t_{max} was delayed by approximately 1 hour compared to that under fasted conditions.

Distribution

Data from *in vitro* studies indicate that perampanel is approximately 95% bound to plasma proteins.

In vitro studies show that perampanel is not a substrate or significant inhibitor of organic anion transporting polypeptides (OATP) 1B1 and 1B3, organic anion transporters (OAT) 1, 2, 3, and 4, organic cation transporters (OCT) 1, 2, and 3, and the efflux transporters P-glycoprotein and Breast Cancer Resistance Protein (BCRP).

Biotransformation

Perampanel is extensively metabolised via primary oxidation and sequential glucuronidation. The metabolism of perampanel is mediated primarily by CYP3A based on clinical study results in healthy subjects administered radiolabelled perampanel and supported by *in vitro* studies using recombinant human CYPs and human liver microsomes.

Following administration of radiolabelled perampanel, only trace amounts of perampanel metabolites were observed in plasma.

Elimination

Following administration of a radiolabelled perampanel dose to either 8 healthy adults or elderly subjects, approximately 30% of recovered radioactivity was found in the urine and 70% in the faeces. In urine and faeces, recovered radioactivity was primarily composed of a mixture of oxidative and conjugated metabolites. In a population pharmacokinetic analysis of pooled data from 19 Phase 1 studies, the average $t_{½}$ of perampanel was 105 hours. When dosed in combination with the strong CYP3A inducer carbamazepine, the average $t_{½}$was 25 hours.

Linearity/non-linearity

In a population PK analysis on pooled data from twenty Phase 1 studies in healthy subjects receiving perampanel between 0.2 and 36 mg either as single or multiple doses, one Phase 2 and five Phase 3

studies in patients with partial-onset seizure receiving perampanel between 2 and 16 mg/day and two Phase 3 studies in patients with primary generalised tonic-clonic seizures receiving perampanel between 2 and 14 mg/day a linear relationship was found between dose and perampanel plasma concentrations.

Special populations

Hepatic impairment
The pharmacokinetics of perampanel following a single 1 mg dose were evaluated in 12 patients with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 healthy, demographically matched subjects. The mean apparent clearance of unbound perampanel in mildly impaired patients was 188 ml/min vs. 338 ml/min in matched controls, and in moderately impaired patients was 120 ml/min vs. 392 ml/min in matched controls. The $t_{½}$ was longer in mildly impaired (306 h vs. 125 h) and moderately impaired (295 h vs. 139 h) patients compared to matched healthy subjects.

Renal impairment
The pharmacokinetics of perampanel have not been formally evaluated in patients with renal impairment. Perampanel is eliminated almost exclusively by metabolism followed by rapid excretion of metabolites; only trace amounts of perampanel metabolites are observed in plasma. In a population pharmacokinetic analysis of patients with partial-onset seizures having creatinine clearances ranging from 39 to 160 mL/min and receiving perampanel up to 12 mg/day in placebo-controlled clinical trials, perampanel clearance was not influenced by creatinine clearance. In a population pharmacokinetic analysis of patients with primary generalised tonic-clonic seizures receiving perampanel up to 8 mg/day in a placebo-controlled clinical study, perampanel clearance was not influenced by baseline creatinine clearance.

Gender
In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day and patients with primary generalised tonic-clonic seizures receiving perampanel up to 8 mg/day in placebo-controlled clinical trials, perampanel clearance in females (0.54 l/h) was 18% lower than in males (0.66 l/h).

Elderly (65 years of age and above)
In a population pharmacokinetic analysis of patients with partial-onset seizures (age range 12 to 74 years) and primary generalised tonic-clonic seizures (age range 12 to 58 years), and receiving perampanel up to 8 or 12 mg/day in placebo-controlled clinical trials, no significant effect of age on perampanel clearance was found. A dose adjustment in the elderly is not considered to be necessary (see section 4.2).

Paediatric population
In a population pharmacokinetic analysis on pooled data from children aged 4 to 11 years, adolescent patients aged ≥12 years, and adults, perampanel clearance increased with an increase in body weight. Hence, dose adjustment in children aged 4 to 11 years with a body weight < 30 kg is necessary (see section 4.2).

Drug interaction studies

In vitro assessment of drug interactions

Drug metabolising enzyme inhibition
In human liver microsomes, perampanel (30 µmol/l) had a weak inhibitory effect on CYP2C8 and UGT1A9 among major hepatic CYPs and UGTs.

Drug metabolising enzyme induction
Compared with positive controls (including phenobarbital, rifampicin), perampanel was found to weakly induce CYP2B6 (30 μmol/l) and CYP3A4/5 (≥ 3 μmol/l) among major hepatic CYPs and UGTs in cultured human hepatocytes.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

In the fertility study in rats, prolonged and irregular oestrous cycles were observed at the maximum tolerated dose (30 mg/kg) in females; however, these changes did not affect fertility and early embryonic development. There were no effects on male fertility.

The excretion into breast milk was measured in rats at 10 days post-partum. Levels peaked at one hour and were 3.65 times the levels in plasma.

In a pre- and postnatal development toxicity study in rats, abnormal delivery and nursing conditions were observed at maternally toxic doses, and the number of stillbirths was increased in offspring. Behavioural and reproductive development of the offspring was not affected, but some parameters of physical development showed some delay, which is probably secondary to the pharmacology-based CNS effects of perampanel. The placental transfer was relatively low; 0.09% or less of administered dose was detected in the foetus.

Nonclinical data reveal that perampanel was not genotoxic and had no carcinogenic potential. The administration of maximum tolerated doses to rats and monkeys resulted in pharmacologically-based CNS clinical signs and decreased terminal body weight. There were no changes directly attributable to perampanel in clinical pathology or histopathology.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fycompa 2 mg, 4 mg film-coated tablets

Core
Lactose monohydrate
Low-substituted hydroxypropyl cellulose
Povidone K-29/32
Magnesium stearate (E470b)

Fycompa 6 mg, 8 mg, 10 mg, 12 mg film-coated tablets

Core
Lactose monohydrate
Low-substituted hydroxypropyl cellulose
Povidone K-29/32
Microcrystalline cellulose
Magnesium stearate (E470b)

Fycompa 2 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
Ferric oxide, yellow (E172)
Ferric oxide, red (E172)

Fycompa 4 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
Ferric oxide, red (E172)

Fycompa 6 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
Ferric oxide, red (E172)

Fycompa 8 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
Ferric oxide, red (E172)
Ferric oxide, black (E172)

Fycompa 10 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
Ferric oxide, yellow (E172)
FD&C Blue #2 Indigo carmine aluminium lake (E132)

Fycompa 12 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
FD&C Blue #2 Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blisters

Fycompa 2 mg film-coated tablets
Pack of 7 only for first week of dosing, 28 and 98

Fycompa 4 mg film-coated tablets
4 mg – packs of 7, 28, 84 and 98

Fycompa 6 mg film-coated tablets
6 mg – packs of 7, 28, 84 and 98

Fycompa 8 mg film-coated tablets
8 mg – packs of 7, 28, 84 and 98

Fycompa 10 mg film-coated tablets
10 mg – packs of 7, 28, 84 and 98

Fycompa 12 mg film-coated tablets
12 mg – packs of 7, 28, 84 and 98

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany
e-mail: medinfo_de@eisai.net

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/001-023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 July 2012
Date of latest renewal: 6 April 2017

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 0.5 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 0.5 mg perampanel

Each bottle of 340 ml contains 170 mg perampanel

Excipient with known effect:
Each ml of oral suspension contains 175 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension
White to off-white suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fycompa (perampanel) is indicated for the adjunctive treatment of
- partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age and older.
- primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalised epilepsy (IGE).

4.2 Posology and method of administration

Posology

Fycompa must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability.
Perampanel suspension should be taken orally once daily at bedtime.
It may be taken with or without food, but preferably always under the same conditions. Switching between the tablet and suspension formulation should be done with caution (see section 5.2).
The physician should prescribe the most appropriate formulation and strength according to weight and dose.

Partial-Onset Seizures
Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective therapy in partial-onset seizures.

The following table summarises the recommended posology for adults, adolescents and children from 4 years of age. More details are provided below the table.

	Adult/adolescent (12 years and older)	Children (4 – 11 years); weighing:		
		≥ 30 kg	20 - < 30 kg	< 20 kg
Recommended starting dose	2 mg/day (4 ml/day)	2 mg/day (4 ml/day)	1 mg/day (2 ml/day)	1 mg/day (2 ml/day)
Titration (incremental steps)	2 mg/day (4 ml/day) (no more frequently than weekly intervals)	2 mg/day (4 ml/day) (no more frequently than weekly intervals)	1 mg/day (2 ml/day) (no more frequently than weekly intervals)	1 mg/day (2 ml/day) (no more frequently than weekly intervals)
Recommended maintenance dose	4 – 8 mg/day (8 – 16 ml/day)	4 – 8 mg/day (8 – 16 ml/day)	4 – 6 mg/day (8 – 12 ml/day)	2 – 4 mg/day (4 – 8 ml/day)
Titration (incremental steps)	2 mg/day (4 ml/day) (no more frequently than weekly intervals)	2 mg/day (4 ml/day) (no more frequently than weekly intervals)	1 mg/day (2 ml/day) (no more frequently than weekly intervals)	0.5 mg/day (1 ml/day) (no more frequently than weekly intervals)
Recommended maximum dose	12 mg/day (24 ml/day)	12 mg/day (24 ml/day)	8 mg/day (16 ml/day)	6 mg/day (12 ml/day)

Adults, adolescents age ≥ 12 years
Treatment with Fycompa should be initiated with a dose of 2 mg/day (4 ml/day). The dose may be increased based on clinical response and tolerability by increments of 2 mg (4 ml) (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day (8 ml/day) to 8 mg/day (16 ml/day). Depending upon individual clinical response and tolerability at a dose of 8 mg/day (16 ml/day), the dose may be increased by increments of 2 mg/day (4 ml/day) to 12 mg/day (24 ml/day). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 4 to 11 years) weighing ≥ 30 kg
Treatment with Fycompa should be initiated with a dose of 2 mg/day (4 ml/day). The dose may be increased based on clinical response and tolerability by increments of 2 mg (4 ml/day) (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day (8 ml/day) to 8 mg/day (16 ml/day). Depending upon individual clinical response and tolerability at a dose of 8 mg/day (16 ml/day), the dose may be increased by increments of 2 mg/day (4 ml/day) to 12 mg/day (24 ml/day). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 4 to 11 years of age) weighing 20 kg and < 30 kg
Treatment with Fycompa should be initiated with a dose of 1 mg/day (2 ml/day). The dose may be increased based on clinical response and tolerability by increments of 1 mg (2 ml/day) (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day (8 ml/day) to 6 mg/day (12 ml/day). Depending upon individual clinical response and tolerability at a dose of 6 mg/day (12 ml/day), the dose may be increased by increments of 1 mg/day (2 ml/day) to 8 mg/day (16 ml/day). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 4 to 11 years of age) weighing < 20 kg
Treatment with Fycompa should be initiated with a dose of 1 mg/day (2 ml/day). The dose may be increased based on clinical response and tolerability by increments of 1 mg (2 ml/day) (either weekly

or every 2 weeks as per half-life considerations described below) to a maintenance dose of 2 mg/day (4 ml/day) to 4 mg/day (8 ml/day). Depending upon individual clinical response and tolerability at a dose of 4 mg/day (8 ml/day), the dose may be increased by increments of 0.5 mg/day (1 ml/day) to 6 mg/day (12 ml/day). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Primary Generalised Tonic-Clonic Seizures
Perampanel at a dose up to 8 mg/day has been shown to be effective in primary generalised tonic-clonic seizures.

The following table summarises the recommended posology for adults, adolescents and children from 7 years of age. More details are provided below the table.

	Adult/adolescent (12 years and older)	Children (7 – 11 years); weighing:		
		≥ 30 kg	20 - < 30 kg	< 20 kg
Recommended starting dose	2 mg/day (4 ml/day)	2 mg/day (4 ml/day)	1 mg/day (2 ml/day)	1 mg/day (2 ml/day)
Titration (incremental steps)	2 mg/day (4 ml/day) (no more frequently than weekly intervals)	2 mg/day (4 ml/day) (no more frequently than weekly intervals)	1 mg/day (2 ml/day) (no more frequently than weekly intervals)	1 mg/day (2 ml/day) (no more frequently than weekly intervals)
Recommended maintenance dose	Up to 8 mg/day (Up to 16 ml/day)	4 – 8 mg/day (8 – 16 ml/day)	4 – 6 mg/day (8 – 12 ml/day)	2 – 4 mg/day (4 – 8 ml/day)
Titration (incremental steps)	2 mg/day (4 ml/day) (no more frequently than weekly intervals)	2 mg/day (4 ml/day) (no more frequently than weekly intervals)	1 mg/day (2 ml/day) (no more frequently than weekly intervals)	0.5 mg/day (1 ml/day) (no more frequently than weekly intervals)
Recommended maximum dose	12 mg/day (24 ml/day)	12 mg/day (24 ml/day)	8 mg/day (16 ml/day)	6 mg/day (12 ml/day)

Adults, adolescents age ≥ 12 years
Treatment with Fycompa should be initiated at a dose of 2 mg/day (4 ml/day). The dose may be increased based on clinical response and tolerability by increments of 2 mg (4 ml/day) (either weekly or every 2 weeks, as per half-life considerations described below) to a maintenance dose of up to 8 mg/day (16 ml/day). Depending upon individual clinical response and tolerability at a dose of 8 mg/day (16 ml/day), the dose may be increased up to 12 mg/day (24 ml/day), which may be effective in some patients (see section 4.4). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 7 to 11 years) weighing ≥ 30 kg
Treatment with Fycompa should be initiated with a dose of 2 mg/day (4 ml/day). The dose may be increased based on clinical response and tolerability by increments of 2 mg (4 ml) (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day (8 ml/day) to 8 mg/day (16 ml/day). Depending upon individual clinical response and tolerability at a dose of 8 mg/day (16 ml/day), the dose may be increased by increments of 2 mg/day (4 ml/day) to 12 mg/day (24 ml/day). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week

intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 7 to 11 years of age) weighing 20 kg and < 30 kg
Treatment with Fycompa should be initiated with a dose of 1 mg/day (2 ml/day). The dose may be increased based on clinical response and tolerability by increments of 1 mg (2 ml) (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day (8 ml/day) to 6 mg/day (12 ml/day). Depending upon individual clinical response and tolerability at a dose of 6 mg/day, the dose may be increased by increments of 1 mg/day (2 ml/day) to 8 mg/day (16 ml/day). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 7 to 11 years of age) weighing < 20 kg
Treatment with Fycompa should be initiated with a dose of 1 mg/day (2 ml/day). The dose may be increased based on clinical response and tolerability by increments of 1 mg (2 ml) (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 2 mg/day (4 ml/day) to 4 mg/day (8 ml/day). Depending upon individual clinical response and tolerability at a dose of 4 mg/day (8 ml/day), the dose may be increased by increments of 0.5 mg/day (1 ml/day) to 6 mg/day (12 ml/day). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Withdrawal
It is recommended that discontinuation be undertaken gradually to minimise the potential for rebound seizures. However, due to its long half-life and subsequent slow decline in plasma concentrations, perampanel can be discontinued abruptly if absolutely needed.

Missed doses
Single missed dose: As perampanel has a long half-life, the patient should wait and take their next dose as scheduled.

If more than 1 dose has been missed, for a continuous period of less than 5 half-lives (3 weeks for patients not taking perampanel metabolism-inducing anti-epileptic drugs (AED), 1 week for patients taking perampanel metabolism-inducing AEDs (see section 4.5)), consideration should be given to re-start treatment from the last dose level.

If a patient has discontinued perampanel for a continuous period of more than 5 half-lives, it is recommended that initial dosing recommendations given above should be followed.

Elderly (65 years of age and above)
Clinical studies of Fycompa in epilepsy did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Analysis of safety information in 905 perampanel-treated elderly patients (in double-blind studies conducted in non-epilepsy indications) revealed no age-related differences in the safety profile. In combination with the lack of age-related difference in perampanel exposure, the results indicate that dose-adjustment in the elderly is not required. Perampanel should be used with caution in elderly taking into account the drug interaction potential in polymedicated patients (see section 4.4).

Renal impairment
Dose adjustment is not required in patients with mild renal impairment. Use in patients with moderate or severe renal impairment or patients undergoing haemodialysis is not recommended.

Hepatic impairment
Dose increases in patients with mild and moderate hepatic impairment should be based on clinical response and tolerability. For patients with mild or moderate hepatic impairment, dosing can be initiated at 2 mg (4 ml). Patients should be up-titrated using 2 mg (4 ml) doses no faster than every 2 weeks based on tolerability and effectiveness.
Perampanel dosing for patients with mild and moderate impairment should not exceed 8 mg.
Use in patients with severe hepatic impairment is not recommended.

Paediatric population
The safety and efficacy of perampanel have not yet been established in children below 4 years of age in the POS indication or in children below 7 years of age in the PGTCS indication.

Method of administration

Fycompa is for oral use.

Preparation: The press-in-bottle adapter (PIBA) which is supplied in the product carton should be inserted firmly into the neck of the bottle before use and remain in place for the duration of the usage of the bottle. The oral syringe should be inserted into the PIBA and the dose withdrawn from the inverted bottle. The cap should be replaced after each use. The cap fits properly when the PIBA is in place.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicinal products in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for perampanel.
Therefore, patients (children, adolescents, and adults) should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens - Johnson Syndrome (SJS), which can be life-threatening or fatal, have been reported (frequency unknown; see section 4.8) in association with perampanel treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

Symptoms of DRESS include typically, although not exclusively, fever, rash associated with other organ system involvement, lymphadenopathy, liver function tests abnormalities and eosinophilia. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

Symptoms of SJS include typically although not exclusively, skin detachment (epidermal necrosis/blister) < 10%, erythematous skin (confluent), rapid progression, painful atypical target-like

lesions and/or purpuric macules in wide dissemination or large erythema (confluent), bullous/erosive involvement of more than 2 mucous membranes.

If signs and symptoms suggestive of these reactions appear, perampanel should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS or DRESS with the use of perampanel, treatment with perampanel must not be restarted in this patient at any time.

Absence and myoclonic seizures

Absence and myoclonic seizures are two common generalised seizure types that frequently occur in IGE patients. Other AEDs are known to induce or aggravate these seizure types. Patients with myoclonic seizures and absence seizures should be monitored while on Fycompa.

Nervous system disorders

Perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines (see section 4.7).

Hormonal contraceptives

At doses of 12 mg/day Fycompa may decrease the effectiveness of progestative-containing hormonal contraceptives; in this circumstance additional non-hormonal forms of contraception are recommended when using Fycompa (see sections 4.5 and 4.6).

Falls

There appears to be an increased risk of falls, particularly in the elderly; the underlying reason is unclear.

Aggression, psychotic disorder

Aggressive, hostile, and abnormal behaviours have been reported in patients receiving perampanel therapy. In perampanel-treated patients in clinical trials, aggression, anger, irritability, and psychotic disorder were reported more frequently at higher doses. Most of the reported events were either mild or moderate, and patients recovered either spontaneously or with dose adjustment. However, thoughts of harming others, physical assault, or threatening behaviour were observed in some patients (<1% in perampanel clinical trials). Homicidal ideation has been reported in patients. Patients and caregivers should be counselled to alert a healthcare professional immediately if significant changes in mood or patterns of behaviour are noted. The dosage of perampanel should be reduced if such symptoms occur and discontinuation should be considered if symptoms are severe (see section 4.2).

Abuse potential

Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of perampanel abuse.

Concomitant CYP 3A inducing anti-epileptic medicinal products

Response rates after addition of perampanel at fixed doses were less when patients received concomitant CYP3A enzyme-inducing anti-epileptic medicinal products (carbamazepine, phenytoin, oxcarbazepine) as compared to response rates in patient who received concomitant non-enzyme-inducing anti-epileptic medicinal products. Patients' response should be monitored when they are switching from concomitant non-inducer anti-epileptic medicinal products to enzyme inducing medicinal products and vice versa. Depending upon individual clinical response and tolerability, the dose may be increased or decreased 2 mg at a time (see section 4.2).

Other concomitant (non- anti-epileptic) cytochrome P450 inducing or inhibiting medicinal products

Patients should be closely monitored for tolerability and clinical response when adding or removing cytochrome P450 inducers or inhibitors, since perampanel plasma levels can be decreased or increased; the dose of perampanel may need to be adjusted accordingly.

Hepatotoxicity

Cases of hepatotoxicity (mainly hepatic enzyme increased) with perampanel in combination with other antiepileptic drugs have been reported. If hepatic enzymes elevation is observed, monitoring of liver function should be considered.

Excipients

Fructose intolerance
Fycompa contains sorbitol (E420), each mL of Fycompa contains 175 mg sorbitol.

Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

Caution should be exercised when combining Fycompa oral suspension with other antiepileptic medications containing sorbitol, since a combined intake of over 1 gram of sorbitol may affect absorption of some drugs.

Benzoic Acid (E210) and Sodium Benzoate (E211)
Fycompa contains benzoic acid (E210) and sodium benzoate (E211), each mL of Fycompa contains <0.005 mg benzoic acid and 1.1 mg sodium benzoate.

Benzoic acid and benzoates can displace bilirubin from albumin. Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus.

4.5 Interaction with other medicinal products and other forms of interaction

Fycompa is not considered a strong inducer or inhibitor of cytochrome P450 or UGT enzymes (see section 5.2).

Hormonal contraceptives

In healthy women receiving 12 mg (but not 4 or 8 mg/day) for 21 days concomitantly with a combined oral contraceptive, Fycompa was shown to decrease the levonorgestrel exposure (mean C_{max} and AUC values were each decreased by 40%). Ethinylestradiol AUC was not affected by Fycompa 12 mg whereas C_{max} was decreased by 18%. Therefore, the possibility of decreased efficacy of hormonal progestative-containing contraceptives should be considered for women needing Fycompa 12 mg/day and an additional reliable method (intra-uterine device (IUD), condom) is to be used (see section 4.4).

Interactions between Fycompa and other anti-epileptic medicinal products

Potential interactions between Fycompa and other anti-epileptic drugs (AEDs) were assessed in clinical studies. A population PK analysis of three pooled Phase 3 studies in adolescent and adult patients with partial-onset seizures evaluated the effect of Fycompa (up to 12 mg once daily) on the PK of other AEDs. In another population PK analysis of pooled data from twenty Phase 1 studies in healthy subjects, with Fycompa up to 36 mg, and one Phase 2 and six Phase 3 studies in paediatric, adolescent and adult patients with partial-onset seizures or primary generalised tonic-clonic seizures, with Fycompa up to 16 mg once daily, evaluated the effect of concomitant AEDs of perampanel clearance. The effect of these interactions on average steady state concentration is summarised in the following table.

AED coadministered	Influence of AED on Fycompa concentration	Influence of Fycompa on AED concentration
Carbamazepine	3 fold decrease	<10% decrease
Clobazam	No influence	<10% decrease
Clonazepam	No influence	No influence
Lamotrigine	No influence	<10% decrease
Levetiracetam	No influence	No influence
Oxcarbazepine	2 fold decrease	35% increase [1)]
Phenobarbital	20% decrease	No influence
Phenytoin	2 fold decrease	No influence
Topiramate	20% decrease	No influence
Valproic Acid	No influence	<10% decrease
Zonisamide	No influence	No influence

1) Active metabolite monohydroxycarbazepine was not assessed.

Based on the results from the population pharmacokinetic analysis of patients with partial-onset seizures and patients with primary generalised tonic-clonic seizures the total clearance of Fycompa was increased when co-administered with carbamazepine (3-fold), and phenytoin or oxcarbazepine (2-fold), which are known inducers of enzymes of metabolism (see section 5.2). This effect should be taken into account and managed when adding or withdrawing these anti-epileptic drugs from a patient's treatment regimen. Clonazepam, levetiracetam, phenobarbital, topiramate, zonisamide, clobazam, lamotrigine and valproic acid did not affect to a clinically relevant manner the clearance of Fycompa.

In a population pharmacokinetic analysis of patients with partial-onset seizures, Fycompa did not affect to a clinically relevant manner the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, zonisamide, carbamazepine, clobazam, lamotrigine and valproic acid, at the highest perampanel dose evaluated (12 mg/day).

Perampanel was found to decrease the clearance of oxcarbazepine by 26%. Oxcarbazepine is rapidly metabolised by cytosolic reductase enzyme to the active metabolite, monohydroxycarbazepine. The effect of perampanel on monohydroxycarbazepine concentrations is not known.

Perampanel is dosed to clinical effect regardless of other AEDs.

Effect of perampanel on CYP3A substrates

In healthy subjects, Fycompa (6 mg once daily for 20 days) decreased midazolam AUC by 13%. A larger decrease in exposure of midazolam (or other sensitive CYP3A substrates) at higher Fycompa doses cannot be excluded.

Effect of cytochrome P450 inducers on perampanel pharmacokinetics

Strong inducers of cytochrome P450, such as rifampicin and hypericum, are expected to decrease perampanel concentrations and the potential for higher plasma concentrations of reactive metabolites in their presence has not been excluded. Felbamate has been shown to decrease the concentrations of some medicinal products and may also reduce perampanel concentrations.

Effect of cytochrome P450 inhibitors on perampanel pharmacokinetics

In healthy subjects, the CYP3A4 inhibitor ketoconazole (400 mg once daily for 10 days) increased perampanel AUC by 20% and prolonged perampanel half--life by 15% (67.8 h vs 58.4 h). Larger effects cannot be excluded when perampanel is combined with a CYP3A inhibitor with longer half-life than ketoconazole or when the inhibitor is given for a longer treatment duration.

Levodopa
In healthy subjects, Fycompa (4 mg once daily for 19 days) had no effect on C_{max} or AUC of levodopa.

Alcohol

The effects of perampanel on tasks involving alertness and vigilance such as driving ability were additive or supra-additive to the effects of alcohol itself, as found in a pharmacodynamic interaction study in healthy subjects. Multiple dosing of perampanel 12 mg/day increased levels of anger, confusion, and depression as assessed using the Profile of Mood State 5-point rating scale (see section 5.1). These effects may also be seen when Fycompa is used in combination with other central nervous system (CNS) depressants.

Paediatric population

Interaction studies have only been performed in adults.
In a population pharmacokinetic analysis of adolescent patients age ≥ 12 years and children age 4 to 11 years, there were no notable differences compared to the adult population.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and contraception in males and females

Fycompa is not recommended in women of childbearing potential not using contraception unless clearly necessary. Fycompa may decrease the effectiveness of progestative-containing hormonal contraceptives. An additional non-hormonal form of contraception is, therefore recommended (see sections 4.4 and 4.5).

Pregnancy

There are limited amounts of data (less than 300 pregnancy outcomes) from the use of perampanel in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats at maternally toxic doses (see section 5.3). Fycompa is not recommended during pregnancy.

Breast-feeding

Studies in lactating rats have shown excretion of perampanel and/or its metabolites in milk (for details see section 5.3). It is not known whether perampanel is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fycompa therapy taking into account the benefit of breast--feeding for the child and the benefit of therapy for the woman.

Fertility

In the fertility study in rats, prolonged and irregular oestrous cycles were observed at high-dose (30 mg/kg) in females; however, these changes did not affect the fertility and early embryonic development. There were no effects on male fertility (see section 5.3). The effect of perampanel on human fertility has not been established.

4.7 Effects on ability to drive and use machines

Fycompa has moderate influence on the ability to drive and use machines.
Perampanel may cause dizziness and somnolence and, therefore, may influence the ability to drive or use machines. Patients are advised not to drive a vehicle, operate complex machinery or engage in other potentially hazardous activities until it is known whether perampanel affects their ability to perform these tasks (see sections 4.4 and 4.5).

4.8 Undesirable effects

Summary of the safety profile

In all controlled and uncontrolled trials in patients with partial-onset seizures, 1,639 patients have received perampanel of whom 1,147 have been treated for 6 months and 703 for longer than 12 months.

In the controlled and uncontrolled study in patients with primary generalised tonic-clonic seizures, 114 patients have received perampanel of whom 68 have been treated for 6 months and 36 for longer than 12 months.

Adverse reactions leading to discontinuation:
In the controlled Phase 3 partial-onset seizures clinical trials, the rate of discontinuation as a result of an adverse reaction was 1.7% (3/172), 4.2% (18/431) and 13.7% (35/255) in patients randomised to receive perampanel at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 1.4% (6/442) in patients randomised to receive placebo. The adverse reactions most commonly (≥ 1% in the total perampanel group and greater than placebo) leading to discontinuation were dizziness and somnolence.

In the controlled Phase 3 primary generalised tonic-clonic seizures clinical trial, the rate of discontinuation as a result of an adverse reaction was 4.9% (4/81) in patients randomised to receive perampanel 8 mg, and 1.2% (1/82) in patients randomised to receive placebo. The adverse reaction most commonly leading to discontinuation (≥ 2% in the perampanel group and greater than placebo) was dizziness.

Post-marketing use

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with perampanel treatment (see section 4.4).

Tabulated list of adverse reactions

In the table below, adverse reactions, which were identified based on review of the full Fycompa clinical studies safety database, are listed by System Organ Class and frequency. The following convention has been used for the classification of adverse reactions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), not known (cannot be estimated from the available data).

Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Very common	Common	Uncommon	Not known
Metabolism and nutrition disorders		Decreased appetite Increased appetite		
Psychiatric disorders		Aggression Anger Anxiety Confusional state	Suicidal ideation Suicide attempt Hallucinations Psychotic disorder	
Nervous system disorders	Dizziness Somnolence	Ataxia Dysarthria Balance disorder Irritability		
Eye disorders		Diplopia Vision blurred		

System Organ Class	Very common	Common	Uncommon	Not known
Ear and labyrinth disorders		Vertigo		
Gastrointestinal disorders		Nausea		
Skin and subcutaneous tissue disorders				Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)* Stevens - Johnson Syndrome (SJS)*
Musculoskeletal and connective tissue disorders		Back pain		
General disorders		Gait disturbance Fatigue		
Investigations		Weight increased		
Injury, poisoning and procedural complications		Fall		

* See section 4.4

Paediatric population

Based on the clinical trial database of 196 adolescents exposed to perampanel from double-blind studies for partial-onset seizures and primary generalised tonic-clonic seizures, the overall safety profile in adolescents was similar to that of adults, except for aggression, which was observed more frequently in adolescents than in adults.

Based on the clinical trial database of 180 paediatric patients exposed to perampanel from a multicentre, open label study, the overall safety profile in children was similar to that established for adolescents and adults, except for somnolence, irritability, aggression, and agitation, which were observed more frequently in the paediatric study compared to studies in adolescents and adults.

Available data in children did not suggest any clinically significant effects of perampanel on growth and development parameters including body weight, height, thyroid function, insulin-like growth factor-1 (IGF-1) level, cognition (as assessed by Aldenkamp-Baker neuropsychological assessment schedule [ABNAS]), behaviour (as assessed by Child Behavior Checklist [CBCL]), and dexterity (as assessed by Lafayette Grooved Pegboard Test [LGPT]). However, long term effects [greater than 1 year] on learning, intelligence, growth, endocrine function, and puberty in children remain unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There have been post-marketing cases of intentional and accidental overdose in paediatric patients with doses of perampanel up to 36 mg and in adult patients with doses up to 300 mg. The adverse reactions observed included altered mental status, agitation, aggressive behaviour, coma and depressed level of consciousness. The patients recovered without sequelae.

There is no available specific antidote to the effects of perampanel.

General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. In view of its long half-life, the effects caused by perampanel could be prolonged. Because of low renal clearance special interventions such as forced diuresis, dialysis or haemoperfusion are unlikely to be of value.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX22

Mechanism of action

Perampanel is a first-in-class selective, 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 overexcitation. Activation of AMPA receptors by glutamate is thought to be responsible for most fast excitatory synaptic transmission in the brain. In *in vitro* studies, perampanel did not compete with AMPA for binding to the AMPA receptor, but perampanel binding was displaced by noncompetitive AMPA receptor antagonists, indicating that perampanel is a noncompetitive AMPA receptor antagonist. *In vitro*, perampanel inhibited AMPA-induced (but not NMDA-induced) increase in intracellular calcium. *In vivo*, perampanel significantly prolonged seizure latency in an AMPA-induced seizure model.

The precise mechanism by which perampanel exerts its antiepileptic effects in humans remains to be fully elucidated.

Pharmacodynamic effects

A pharmacokinetic-pharmacodynamic (efficacy) analysis was performed based on the pooled data from the 3 efficacy trials for partial-onset seizures. In addition, a pharmacokinetic-pharmacodynamic (efficacy) analysis was performed in one efficacy trial for primary generalised tonic-clonic seizures. In both analyses, perampanel exposure is correlated with reduction in seizure frequency.

Psychomotor performance
Single and multiple doses of 8 mg and 12 mg impaired psychomotor performance in healthy volunteers in a dose-related manner. The effects of perampanel on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol. Psychomotor performance testing returned to baseline within 2 weeks of cessation of perampanel dosing.

Cognitive function
In a healthy volunteer study to assess the effects of perampanel on alertness, and memory using a standard battery of assessments, no effects of perampanel were found following single and multiple doses of perampanel up to 12 mg/day.

In a placebo-controlled study conducted in adolescent patients, no significant changes in cognition relative to placebo as measured by Cognitive Drug Research (CDR) System Global Cognition Score were observed for perampanel. In the open label extension, no significant changes were observed in global CDR system score after 52 weeks of perampanel treatment (see section 5.1 Paediatric population).

In an open-label uncontrolled study conducted in paediatric patients, no clinically important changes in cognition relative to baseline as measured by ABNAS were observed following adjunctive perampanel (see section 5.1 Paediatric population).

Alertness and mood
Levels of alertness (arousal) decreased in a dose-related manner in healthy subjects dosed with perampanel from 4 to 12 mg/day. Mood deteriorated following dosing of 12 mg/day only; the changes in mood were small and reflected a general lowering of alertness. Multiple dosing of perampanel 12 mg/day also enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion and depression as assessed using the Profile of Mood State 5-point rating scale.

Cardiac electrophysiology
Perampanel did not prolong the QTc interval when administered in daily doses up to 12 mg/day, and did not have a dose-related or clinically important effect on QRS duration.

Clinical efficacy and safety

Partial-Onset Seizures
The efficacy of perampanel in partial-onset seizures was established in three adjunctive therapy 19 week, randomised, double-blind, placebo-controlled, multicentre trials in adult and adolescent patients. Patients had partial-onset seizures with or without secondary generalisation and were not adequately controlled with one to three concomitant AEDs. During a 6-week baseline period, patients were required to have more than five seizures with no seizure-free period exceeding 25 days. In these three trials, patients had a mean duration of epilepsy of approximately 21.06 years. Between 85.3% and 89.1% of patients were taking two to three concomitant AEDs with or without concurrent vagal nerve stimulation.

Two studies (studies 304 and 305) compared doses of perampanel 8 and 12 mg/day with placebo and the third study (study 306) compared doses of perampanel 2, 4 and 8 mg/day with placebo. In all three trials, following a 6-week Baseline Phase to establish baseline seizure frequency prior to randomisation, patients were randomised and titrated to the randomised dose. During the Titration Phase in all three trials, treatment was initiated at 2 mg/day and increased in weekly increments of 2 mg/day to the target dose. Patients experiencing intolerable adverse events could remain on the same dose or have their dose decreased to the previously tolerated dose. In all three trials, the Titration Phase was followed by a Maintenance Phase that lasted 13 weeks, during which patients were to remain on a stable dose of perampanel.

The pooled 50% responder rates were placebo 19%, 4 mg 29%, 8 mg 35% and 12 mg 35%. A statistically significant effect on the reduction in 28-day seizure frequency (Baseline to Treatment Phase) as compared to the placebo group was observed with perampanel treatment at doses of 4 mg/day (Study 306), 8 mg/day (Studies 304, 305 and 306), and 12 mg/day (Studies 304 and 305). The 50% responder rates in the 4 mg, 8 mg and 12 mg groups were respectively 23.0%, 31.5%, and 30.0% in combination with enzyme-inducing anti-epileptic medicinal products and were 33.3%, 46.5% and 50.0% when perampanel was given in combination with non-enzyme-inducing anti-epileptic medicinal products. These studies show that once-daily administration of perampanel at doses of 4 mg to 12 mg was significantly more efficacious than placebo as adjunctive treatment in this population.

Data from placebo-controlled studies demonstrate that improvement in seizure control is observed with a once-daily perampanel dose of 4 mg and this benefit is enhanced as the dose is increased to 8 mg/day. No efficacy benefit was observed at the dose of 12 mg as compared to the dose of 8 mg in the overall population. Benefit at the dose of 12 mg was observed in some patients who tolerate the dose of 8 mg and when the clinical response to that dose was insufficient. A clinically meaningful reduction in seizure frequency relative to placebo was achieved as early as the second week of dosing when patients reached a daily dose of 4 mg.

1.7 to 5.8% of the patients on perampanel in the clinical studies became seizure free during the 3 month maintenance period compared with 0%-1.0% on placebo.

Open label extension study
Ninety-seven percent of the patients who completed the randomised trials in patients with partial-onset seizures were enrolled in the open label extension study (n = 1186). Patients from the randomised trial were converted to perampanel over 16 weeks followed by a long-term maintenance period (≥ 1 year). The mean average daily dose was 10.05 mg.

Primary Generalised Tonic-Clonic Seizures
Perampanel as adjunctive therapy in patients 12 years of age and older with idiopathic generalised epilepsy experiencing primary generalised tonic-clonic seizures was established in a multicentre, randomised, double-blind, placebo-controlled study (Study 332). Eligible patients on a stable dose of 1 to 3 AEDs experiencing at least 3 primary generalised tonic-clonic seizures during the 8-week baseline period were randomised to either perampanel or placebo. The population included 164 patients (perampanel N = 82, placebo N = 82). Patients were titrated over four weeks to a target dose of 8 mg per day or the highest tolerated dose and treated for an additional 13 weeks on the last dose level achieved at the end of the titration period. The total treatment period was 17 weeks. Study drug was given once per day.

The 50% primary generalised tonic-clonic seizures responder rate during the Maintenance Period was significantly higher in the perampanel group (58.0%) than in the placebo group (35.8%), P = 0.0059. The 50% responder rate was 22.2% in combination with enzyme-inducing anti-epileptic medicinal products and was 69.4% when perampanel was given in combination with non-enzyme-inducing anti-epileptic medicinal products. The number of perampanel patients taking enzyme-inducing anti-epileptic medicinal products was small (n = 9). The median percent change in primary generalised tonic-clonic seizure frequency per 28 days during the Titration and Maintenance Periods (combined) relative to Prerandomisation was greater with perampanel (-76.5%) than with placebo (-38.4%), P < 0.0001. During the 3 months maintenance period, 30.9% (25/81) of the patients on perampanel in the clinical studies became free of PGTC seizures compared with 12.3% (10/81) on placebo.

Other subtypes of idiopathic generalised seizure
The efficacy and safety of perampanel in patients with myoclonic seizures have not been established. The available data are insufficient to reach any conclusions.
The efficacy of perampanel in the treatment of absence seizures has not been demonstrated.
In Study 332, in patients with PGTC seizures who also had concomitant myoclonic seizures, freedom from seizures was achieved in 16.7% (4/24) on perampanel compared to 13.0% (3/23) in those on placebo. In patients with concomitant absence seizures, freedom from seizures was achieved in 22.2% (6/27) on perampanel compared to 12.1% (4/33) on placebo. Freedom from all seizures was achieved in 23.5% (19/81) of patients on perampanel compared to 4.9% (4/81) of patients on placebo.

Open label extension phase
Of the 140 patients who completed the Study 332, 114 patients (81.4%) had entered the Extension phase. Patients from the randomised trial were converted to perampanel over 6 weeks followed by a long-term maintenance period (≥ 1 year). In the Extension Phase, 73.7% (84/114) of patients have a modal daily perampanel dose of greater than 4 to 8 mg/day and 16.7% (19/114) had a modal daily dose of greater than 8 to 12 mg/day. A decrease in PGTC seizure frequency of at least 50% was seen in 65.9% (29/44) of patients after 1 year of treatment during the Extension Phase (relative to their pre-perampanel baseline seizure frequency). These data were consistent with those for percent change in seizure frequency and showed that the PGTC 50% responder rate was generally stable across time from about week 26 through the end of year 2. Similar results were seen when all seizures and absence vs. myoclonic seizures were evaluated over time.

Conversion to monotherapy
In a retrospective study of clinical practice, 51 patients with epilepsy who received perampanel as adjunctive treatment converted to perampanel monotherapy. The majority of these patients had a history of partial onset seizures. Of these, 14 patients (27%) reverted to adjunctive therapy in the following months. Thirty four (34) patients were followed up for at least 6 months and, of these, 24 patients (71%) remained on perampanel monotherapy for at least 6 months. Ten (10) patients were

followed up for at least 18 months and, of these, 3 patients (30%) remained on perampanel monotherapy for at least 18 months.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Fycompa in one or more subsets of the paediatric population in treatment-resistant epilepsies (localisation-related and age-related epilepsy syndromes) (see section 4.2 for information on adolescent and paediatric use).

The three pivotal double-blind placebo-controlled phase 3 studies included 143 adolescents between the ages of 12 and 18. The results in these adolescents were similar to those seen in the adult population.

Study 332 included 22 adolescents between the ages of 12 and 18. The results in these adolescents were similar to those seen in the adult population.

A 19-week, randomised, double-blind, placebo-controlled study with an open-label extension phase (Study 235) was performed to assess the short-term effects on cognition of Fycompa (target dose range of 8 to 12 mg once daily) as adjunctive therapy in 133 (Fycompa n = 85, placebo n = 48) adolescent patients, aged 12 to less than 18 years old, with inadequately controlled partial-onset seizures. Cognitive function was assessed by the Cognitive Drug Research (CDR) System Global Cognition t-Score, which is a composite score derived from 5 domains testing Power of Attention, Continuity of Attention, Quality of Episodic Secondary Memory, Quality of Working Memory, and Speed of Memory. The mean change (SD) from baseline to end of double-blind treatment (19 weeks) in CDR System Global Cognition t-Score was 1.1 (7.14) in the placebo group and (minus) –1.0 (8.86) in the perampanel group, with the difference between the treatment groups in LS means (95% CI) = (minus) -2.2 (-5.2, 0.8). There was no statistically significant difference between the treatment groups (p = 0.145). CDR System Global Cognition t-Scores for placebo and perampanel were 41.2 (10.7) and 40.8 (13.0), respectively at the baseline. For patients with perampanel in the open label extension (n = 112), the mean change (SD) from baseline to end of open-label treatment (52 weeks) in CDR System Global Cognition t-Score was (minus) -1.0 (9.91). This was not statistically significant (p = 0.96). After up to 52 weeks of treatment with perampanel (n = 114), no effect on bone growth was observed. No effects on weight, height and sexual development were seen following up to 104 weeks of treatment (n = 114).

An open-label, uncontrolled study (Study 311) was performed to assess the exposure-efficacy relationship of perampanel as adjunctive therapy in 180 paediatric patients (aged 4 to 11 years old) with inadequately controlled partial-onset seizures or primary generalised tonic-clonic seizures. Patients were titrated over 11 weeks to a target dose of 8 mg/day or the maximum tolerated dose (not to exceed 12 mg/day) for patients not taking concomitant CYP3A-inducing antiepileptic drugs (carbamazepine, oxcarbazepine, eslicarbazepine and phenytoin) or 12 mg/day or the maximum tolerated dose (not to exceed 16 mg/day) for patients taking a concomitant CYP3A-inducing antiepileptic drug. Perampanel dose achieved at the end of titration was maintained for 12 weeks (for a total of 23 weeks of exposure) at the completion of the core study. Patients who entered into Extension Phase were treated for an additional 29 weeks for a total exposure duration of 52 weeks.

In patients with partial-onset seizures (n = 148 patients), the median change in seizure frequency per 28 days, the 50% or greater responder rate, and seizure-free rate following 23 weeks of perampanel treatment were -40.1%, 46.6% (n = 69/148), and 11.5% (n = 17/148), respectively, for total partial-onset seizures. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 108 patients, -69.4%), 50% responder rate (Weeks 40-52: 62.0%, n = 67/108), and seizure-free rate (Weeks 40-52: 13.0%, n = 14/108) were sustained following 52 weeks of perampanel treatment.

In a subset of partial-onset seizure patients with secondarily generalised seizures, the corresponding values were -58.7%, 64.8% (n = 35/54), and 18.5% (n = 10/54), respectively, for secondarily

generalised tonic-clonic seizures. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 41 patients, -73.8%), 50% responder rate (Weeks 40-52: 80.5%, n = 33/41), and seizure-free rate (Weeks 40-52: 24.4%, n = 10/41) were sustained following 52 weeks of perampanel treatment.

In patients with primary generalised tonic-clonic seizures (n = 22 patients, with 19 patients aged 7-<12 years and 3 patients aged 4-<7 years), the median change in seizure frequency per 28 days, the 50% or greater responder rate, and seizure-free rate were -69.2%, 63.6% (n = 14/22), and 54.5% (n = 12/22), respectively. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 13 patients, -100.0%), 50% responder rate (Weeks 40-52: 61.5%, n = 8/13), and seizure-free rate (Weeks 40-52: 38.5%, n = 5/13) were sustained following 52 weeks of perampanel treatment. These results should be considered cautiously as the number of patients is very small.

Similar results were obtained in a subset of patients with primary generalised tonic-clonic seizures of idiopathic generalised epilepsy (IGE) (n = 19 patients, with 17 patients aged 7-<12 years and 2 patients aged 4-<7 years; the corresponding values were -56.5%, 63.2% (n = 12/19), and 52.6% (n = 10/19), respectively. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 11 patients, -100.0%), 50% responder rate (Weeks 40-52: 54.5%, n = 6/11), and seizure-free rate (Weeks 40-52: 36.4%, n = 4/11) were sustained following 52 weeks of perampanel treatment. These results should be considered cautiously as the number of patients is very small.

5.2 Pharmacokinetic properties

The pharmacokinetics of perampanel have been studied in healthy adult subjects (age range 18 to 79), adults, adolescents, and paediatric patients with partial-onset seizures and primary generalised tonic-clonic seizures, adults with Parkinson's disease, adults with diabetic neuropathy, adults with multiple sclerosis, and patients with hepatic impairment.

Absorption

Perampanel is readily absorbed after oral administration with no evidence of marked first-pass metabolism.

Perampanel oral suspension is bioequivalent on a mg per mg basis to perampanel tablets under fasted conditions. When a single 12-mg dose of both formulations was administered with a high fat meal, perampanel oral suspension achieves equivalent $AUC_{0\text{-}inf}$ and approximately 23 % lower C_{max} and 2 hours delay in time to peak exposure (t_{max}) compared to the tablet formulation. However, population pharmacokinetic analysis demonstrated that under simulated steady state exposure conditions, C_{max} and $AUC_{(0\text{-}24h)}$, of perampanel oral suspension were bioequivalent to the tablet formulation under both fasted and fed conditions.

When coadministered with a high fat meal, C_{max} and $AUC_{0\text{-}inf}$ of a single 12-mg dose of perampanel oral suspension were approximately 22% and 13%, respectively, lower compared to fasted conditions.

Distribution

Data from *in vitro* studies indicate that perampanel is approximately 95% bound to plasma proteins.

In vitro studies show that perampanel is not a substrate or significant inhibitor of organic anion transporting polypeptides (OATP) 1B1 and 1B3, organic anion transporters (OAT) 1, 2, 3, and 4, organic cation transporters (OCT) 1, 2, and 3, and the efflux transporters P-glycoprotein and Breast Cancer Resistance Protein (BCRP).

Biotransformation

Perampanel is extensively metabolised via primary oxidation and sequential glucuronidation. The metabolism of perampanel is mediated primarily by CYP3A based on clinical study results in healthy subjects administered radiolabelled perampanel and supported by *in vitro* studies using recombinant human CYPs and human liver microsomes.

Following administration of radiolabelled perampanel, only trace amounts of perampanel metabolites were observed in plasma.

Elimination

Following administration of a radiolabelled perampanel dose to either 8 healthy adults or elderly subjects, approximately 30% of recovered radioactivity was found in the urine and 70% in the faeces. In urine and faeces, recovered radioactivity was primarily composed of a mixture of oxidative and conjugated metabolites. In a population pharmacokinetic analysis of pooled data from 19 Phase 1 studies, the average $t_{½}$ of perampanel was 105 hours. When dosed in combination with the strong CYP3A inducer carbamazepine, the average $t_{½}$was 25 hours.

Linearity/non-linearity

In a population PK analysis on pooled data from twenty Phase 1 studies in healthy subjects receiving perampanel between 0.2 and 36 mg either as single or multiple doses, one Phase 2 and five Phase 3 studies in patients with partial-onset seizure receiving perampanel between 2 and 16 mg/day and two Phase 3 studies in patients with primary generalised tonic-clonic seizures receiving perampanel between 2 and 14 mg/day a linear relationship was found between dose and perampanel plasma concentrations.

Special populations

Hepatic impairment
The pharmacokinetics of perampanel following a single 1 mg dose were evaluated in 12 patients with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 healthy, demographically matched subjects. The mean apparent clearance of unbound perampanel in mildly impaired patients was 188 ml/min vs. 338 ml/min in matched controls, and in moderately impaired patients was 120 ml/min vs. 392 ml/min in matched controls. The $t_{½}$ was longer in mildly impaired (306 h vs. 125 h) and moderately impaired (295 h vs. 139 h) patients compared to matched healthy subjects.

Renal impairment
The pharmacokinetics of perampanel have not been formally evaluated in patients with renal impairment. Perampanel is eliminated almost exclusively by metabolism followed by rapid excretion of metabolites; only trace amounts of perampanel metabolites are observed in plasma. In a population pharmacokinetic analysis of patients with partial-onset seizures having creatinine clearances ranging from 39 to 160 mL/min and receiving perampanel up to 12 mg/day in placebo-controlled clinical trials, perampanel clearance was not influenced by creatinine clearance. In a population pharmacokinetic analysis of patients with primary generalised tonic-clonic seizures receiving perampanel up to 8 mg/day in a placebo-controlled clinical study, perampanel clearance was not influenced by baseline creatinine clearance.

Gender
In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day and patients with primary generalised tonic-clonic seizures receiving perampanel up to 8 mg/day in placebo-controlled clinical trials, perampanel clearance in females (0.54 l/h) was 18% lower than in males (0.66 l/h).

Elderly (65 years of age and above)
In a population pharmacokinetic analysis of patients with partial-onset seizures (age range 12 to 74 years) and primary generalised tonic-clonic seizures (age range 12 to 58 years), and receiving perampanel up to 8 or 12 mg/day in placebo-controlled clinical trials, no significant effect of age on perampanel clearance was found. A dose adjustment in the elderly is not considered to be necessary (see section 4.2).

Paediatric population
In a population pharmacokinetic analysis on pooled data from children aged 4 to 11 years, adolescent patients aged ≥12 years, and adults, perampanel clearance increased with an increase in body weight. Hence, dose adjustment in children aged 4 to 11 years with a body weight < 30 kg is necessary (see section 4.2).

Drug interaction studies

In vitro assessment of drug interactions

Drug metabolising enzyme inhibition
In human liver microsomes, perampanel (30 μmol/l) had a weak inhibitory effect on CYP2C8 and UGT1A9 among major hepatic CYPs and UGTs.

Drug metabolising enzyme induction
Compared with positive controls (including phenobarbital, rifampicin), perampanel was found to weakly induce CYP2B6 (30 μmol/l) and CYP3A4/5 (≥ 3 μmol/l) among major hepatic CYPs and UGTs in cultured human hepatocytes.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

In the fertility study in rats, prolonged and irregular oestrous cycles were observed at the maximum tolerated dose (30 mg/kg) in females; however, these changes did not affect fertility and early embryonic development. There were no effects on male fertility.

The excretion into breast milk was measured in rats at 10 days post-partum. Levels peaked at one hour and were 3.65 times the levels in plasma.

In a pre- and postnatal development toxicity study in rats, abnormal delivery and nursing conditions were observed at maternally toxic doses, and the number of stillbirths was increased in offspring. Behavioural and reproductive development of the offspring was not affected, but some parameters of physical development showed some delay, which is probably secondary to the pharmacology-based CNS effects of perampanel. The placental transfer was relatively low; 0.09% or less of administered dose was detected in the foetus.

Nonclinical data reveal that perampanel was not genotoxic and had no carcinogenic potential. The administration of maximum tolerated doses to rats and monkeys resulted in pharmacologically-based CNS clinical signs and decreased terminal body weight. There were no changes directly attributable to perampanel in clinical pathology or histopathology.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420) liquid (crystallising)
Microcrystalline cellulose (E460)
Carmellose sodium (E466)
Poloxamer 188
Simethicone emulsion 30%, containing purified water, silicone oil, polysorbate 65, methylcellulose, silica gel, macrogol stearate, sorbic acid, benzoic acid (E210) and sulfuric acid
Citric acid, anhydrous (E330)
Sodium benzoate (E211)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

After first opening: 90 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyethylene terephthalate (PET) bottle with a child-resistant (CR) polypropylene (PP) closure; each bottle contains 340 ml of suspension in an outer cardboard carton.

Each carton contains one bottle, two 20 mL graduated oral dosing syringes and an LDPE press-in bottle adapter (PIBA). The oral dosing syringes are graduated in 0.5 ml increments.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany
e-mail: medinfo_de@eisai.net

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 July 2012
Date of latest renewal: 6 April 2017

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton of 7, 28 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 2 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/001
EU/1/12/776/017
EU/1/12/776/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fycompa 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack (PVC/Aluminium blister)

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 2 mg tablets
Perampanel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cartons of 7, 28, 84 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 4 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
84 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/002
EU/1/12/776/003
EU/1/12/776/004
EU/1/12/776/019

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fycompa 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack (PVC/Aluminium blister)

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 4 mg tablets
Perampanel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cartons of 7, 28,84 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 6 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 6 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
84 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/005
EU/1/12/776/006
EU/1/12/776/007
EU/1/12/776/020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fycompa 6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack (PVC/Aluminium blister)

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 6 mg tablets
Perampanel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cartons of 7, 28,84 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 8 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 8 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
84 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS