

PRODUCT INFORMATION

Fycompa® perampanel (as hemisesquihydrate) film-coated tablet

NAME OF THE MEDICINE

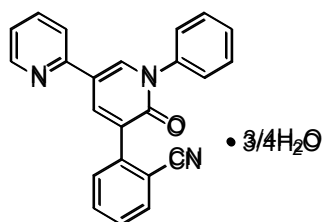
Perampanel (as hemisesquihydrate)

Chemical Structure

The chemical name of perampanel hemisesquihydrate is 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzotrile hydrate (4:3). It has a molecular weight of 362.9.

The empirical formula of perampanel hemisesquihydrate is $C_{23}H_{15}N_3O \cdot 3/4H_2O$

Perampanel hemisesquihydrate has the following structural formula:



CAS Number: 380917-97-5

Perampanel hemisesquihydrate is a crystalline solid and is obtained as a white to yellowish white powder. The pKa value of perampanel hemisesquihydrate is 3.24 and the partition coefficient is 2.86 at 25 °C. Perampanel hemisesquihydrate is freely soluble in *N*-methyl-2-pyrrolidone, 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. In aqueous solutions, perampanel hemisesquihydrate is very slightly soluble in 0.1 mol/L HCl at 37 °C and practically insoluble in pH 2-11 Britton-Robinson buffers at 25 °C, pH 4.5 USP acetate buffer and pH 7.5 USP phosphate buffer at 37 °C.

DESCRIPTION

Each 2, 4, 6, 8, 10, and 12 mg perampanel film-coated tablets contains 2, 4, 6, 8, 10, and 12 mg of perampanel (as hemisesquihydrate).

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Fycompa 2 mg film-coated tablets are orange, round, biconvex tablets, engraved with E275 on one side and '2' on other side.

Fycompa 4 mg film-coated tablets are red, round, biconvex tablets, engraved with E277 on one side and '4' on other side.

Fycompa 6 mg film-coated tablets are pink, round, biconvex tablets, engraved with E294 on one side and '6' on other side

Fycompa 8 mg film-coated tablets are purple, round, biconvex tablets, engraved with E295 on one side and '8' on other side.

Fycompa 10 mg film-coated tablets are green, round, biconvex tablets, engraved with E296 on one side and '10' on other side.

Fycompa 12 mg film-coated tablets are blue, round, biconvex tablets, engraved with E297 on one side and '12' on other side.

The tablets contain the excipients lactose, hypromellose, povidone, magnesium stearate, purified talc, microcrystalline cellulose (6 mg, 8 mg, 10 mg and 12 mg only) magnesium stearate, macrogol 8000, titanium di-oxide, iron oxide yellow (2 mg, 10 mg), iron oxide red (2mg, 4 mg, 6 mg, and 8 mg only), iron oxide black (8 mg only) and indigo carmine aluminium lake (10 mg & 12 mg only).

PHARMACOLOGY

Pharmacodynamic properties

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. Several perampanel metabolites are also AMPA antagonists, although weaker than the parent compound. *In vitro*, perampanel inhibited AMPA-induced (but not NMDA-induced) increase in intracellular calcium in rat cortical neurons. *In vivo*, perampanel displayed anticonvulsant activity in several animal models.

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. Perampanel exposure is correlated

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Attachment 1: Product information for AusPAR Fycompa Perampanel Commercial Eyes Pty Ltd on behalf of Eisai Australia Pty Ltd PM-2013-00324-1-1 Final 14 October 2014. This Product Information was approved at the time this AusPAR was published.

with reduction in seizure frequency.

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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, 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.

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.

Pharmacokinetics

The pharmacokinetics of perampanel have been studied in healthy adult subjects (age range 18 to 79) and subjects with hepatic impairment.

Absorption

Perampanel is around 100% bioavailable. Median T_{max} range from 0.5 to 2.5 hours under fasted conditions.

Perampanel is readily absorbed after oral administration with no evidence of marked first-pass metabolism. Food does not affect the extent of absorption, but slows the rate of absorption. When administered with food, peak plasma concentrations are reduced and delayed by 2 hours compared with dosing in a fasted state.

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).

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Biotransformation

Perampanel is extensively metabolised via primary oxidation and sequential glucuronidation. Primary oxidative metabolism is mediated by CYP3A based on results of *in vitro* studies using recombinant human CYPs and human liver microsomes. However, the metabolism has not been completely elucidated and other pathways cannot be excluded.

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

Elimination

Following administration of a radiolabeled perampanel dose to 8 healthy elderly subjects, 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 $t_{1/2}$ of perampanel was 105 hours. When dosed in combination with the strong CYP3A inducer carbamazepine, the average $t_{1/2}$ was 25 hours.

Linearity/non-linearity

In healthy subjects, plasma concentrations of perampanel increased in direct proportion to administered doses over the range of 2 to 12 mg. In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day in placebo-controlled clinical trials, 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 subjects 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 subjects was 188 ml/min vs. 338 ml/min in matched controls, and in moderately impaired subjects was 120 ml/min vs. 392 ml/min in matched controls. The $t_{1/2}$ was longer in mildly impaired (306 h vs. 125 h) and moderately impaired (295 h vs. 139 h) subjects 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. Apparent clearance of perampanel 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 corresponding 37% increase in AUC.

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Gender

In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day in placebo-controlled clinical trials, perampanel clearance in females (0.605 l/h) was 17% lower than in males (0.730 l/h).

Elderly (65 years of age and above)

Perampanel was given to 31 patients with epilepsy aged 65 years or older. While large differences in the pharmacokinetics of perampanel were not apparent, due to the adverse events experienced by these patients perampanel should be used with caution in the elderly.

Paediatric population

Juvenile animal data

Oral administration of perampanel to juvenile rats for 12 weeks from post natal day 7 of life at doses of 1, 3 and 3/10/30 mg/kg/day (high-dose escalations after 4 and 8 weeks) was associated with CNS clinical signs and decreased hindlimb grip strength/foot splay (all doses), reduced growth and neurobehavioural impairment (mid/high doses), and delayed sexual maturation (high dose). A no-effect doses was not determined. Oral administration of perampanel to juvenile dogs for 33 weeks from post natal day 42 of life at doses of 1,5 and 5/10 mg/kg/day (high dose escalation after 2 weeks) was associated with CNS clinical signs at all dose. The CNS clinical signs were due to exaggerated pharmacologic effects of perampanel.

In a population pharmacokinetic analysis of the adolescent patients in the Phase 3 clinical studies, there were no notable differences between this population and the overall population.

CLINICAL TRIALS

The efficacy of Fycompa in partial-onset seizures was established in three adjunctive therapy 19 week, randomised, double-blind, placebo-controlled, multicentre trials in adult and adolescent patients. Subjects 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, subjects were required to have more than five seizures with no seizure-free period exceeding 25 days. In these three trials, subjects 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 Fycompa 8 and 12 mg/day with placebo and the third study (study 306) compared doses of Fycompa 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, subjects were randomised and titrated to the randomised dose. During the Titration Phase in all three trials, treatment was initiated at 2 mg/day and

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increased in weekly increments of 2 mg/day to the target dose. Subjects 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 Fycompa.

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 Fycompa 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). 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.

Analysis Window Responder	Placebo (N=441) %	2 mg (N=180) %	4 mg (N=172) %	8 mg (N=431) %	12 mg (N=254) %
Maintenance - LOCF					
Yes	19.3	20.6	28.5	35.3	35.0
No	80.7	79.4	71.5	64.7	65.0

Therefore the NNT with any dose of perampanel for 4 mg to 12 mg to achieve a 50% reduction in seizure frequency was 6.25 to 10.9.

Data from placebo-controlled studies demonstrate that improvement in seizure control is observed with a once-daily Fycompa 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.

Open label extension study

Ninety-seven percent of the patients who completed the randomised trials 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.

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.

31 patients aged 65 and over received perampanel in these studies. Due to high rates of dizziness and falls in these patients, perampanel should be used with caution in the elderly.

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Paediatric population

The safety and efficacy of perampanel in children below 12 years of age have not been established yet. No data are available.

INDICATIONS

Fycompa is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see DESCRIPTION)

PRECAUTIONS

Pediatric Use

There is no experience with perampanel in children <12 years. Perampanel is not recommended children aged less than 12 years

Use in the Elderly

Twenty patients aged 65 and over received perampanel in the double blind phase 3 epilepsy studies. Dizziness and falls were particularly frequent in these patients and the incidence of falls was increased in elderly patients taking perampanel (see FALLS). Dizziness occurred in 55.6% of elderly patients given the 8 mg dose and all occurred in 57.1% given the 12 mg dose. Perampanel should be used with caution in the elderly.

Suicidal ideation and behaviour

Antiepileptic drugs (AED), including perampanel, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% ci:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment

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duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treatment patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in the placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analyses. The finding of increased risk with AEDs of vary mechanisms of action and across a range indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs

Table 2: Risk by indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other indications, but the absolute risk differences were similar for epilepsy and psychiatric conditions.

Anyone considering prescribing perampanel or any other AED must balance the risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

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Nervous system disorders

Dizziness and gait disturbance

Fycompa caused dose-related increases in events related to dizziness and disturbance in gait or coordination (see ADVERSE REACTIONS). In the controlled Phase 3 epilepsy clinical trials, dizziness and vertigo were reported in 35% and 47% of patients randomized to receive Fycompa at doses of 8 mg and 12 mg/day, respectively, compared to 10% of placebo-treated patients. The gait disturbance related events (including ataxia, gait disturbance, balance disorder, and coordination abnormal) were reported in 12% and 16% of patients randomized to receive Fycompa at doses of 8 mg and 12 mg/day, respectively, compared to 2% of placebo-treated patients.

These adverse reactions occurred mostly during the titration phase and led to discontinuation in 3% of perampanel-treated subjects compared to 1% of placebo-treated patients. Elderly patients had an increased risk of these adverse reactions compared to younger adults and adolescents.

Somnolence and Fatigue

Fycompa caused dose-dependent increases in somnolence and fatigue-related events (including fatigue, asthenia, and lethargy).

In the controlled Phase 3 epilepsy clinical trials, 16% and 18% of patients randomized to receive Fycompa at doses of 8 mg and 12 mg/day, respectively, reported somnolence compared to 7% of placebo patients. In the controlled Phase 3 epilepsy clinical trials, 12% and 15% of patients randomized to receive Fycompa at doses of 8 mg and 12 mg/day, respectively, reported fatigue-related events compared to 5% of placebo patients. Somnolence or fatigue-related events led to discontinuation in 2% of perampanel-treated patients and 0.5% of placebo-treated patients. Elderly patients had an increased risk of these adverse reactions compared to younger adults and adolescents.

Falls

An increased risk of falls, in some cases leading to serious injuries including head injuries and bone fracture, occurred in patients being treated with Fycompa (with and without concurrent seizures). In the controlled Phase 3 epilepsy clinical trials, falls were reported in 5% and 10% of patients randomized to receive Fycompa at doses of 8 mg and 12 mg/day, respectively, compared to 3% of placebo-treated patients. Falls were reported as serious and led to discontinuation more frequently in Fycompa-treated patients than placebo-treated patients.

Twenty patients aged 65 and over years received perampanel in the double blind phase 3 epilepsy studies, Dizziness and falls were particularly frequent in these patients. Dizziness occurred in 55.6% of elderly patients given the 8 mg dose and 42.9% given the 12 mg dose.

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Falls occurred in 11.1% of elderly patients given the 8 mg dose and 57.1% given the 12 mg dose. Perampanel should be used with caution in the elderly.

End of treatment

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

Serious Psychiatric and Behavioural Reactions

Serious or life-threatening psychiatric and behavioural adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking Fycompa. Monitor patients for these reactions as well as for changes in mood, behaviour, or personality that are not typical for the patient, particularly during the titration period and at higher doses. Fycompa should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening.

In controlled Phase 3 epilepsy clinical trials, hostility and aggression related adverse reactions occurred in 12% and 20% of patients randomised to receive Fycompa at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment although new events continued to be observed through more than 37 weeks. Fycompa - treated patients experienced more hostility and aggression related adverse reactions that were serious, severe, and led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients.

In general, in the placebo-controlled Phase 3 epilepsy trials, neuropsychiatric events were reported more frequently in patients being treated with Fycompa than in patients taking placebo. These events included irritability, aggression, anger and anxiety which occurred in 2% or greater of perampanel treated patients and twice as frequently as in placebo-treated patients. Other symptoms that were observed with perampanel treatment and more common than with placebo, included belligerence, affect lability, agitation, and physical assault. Some of these events were reported as serious and life-threatening, Homicidal ideation and/or threat were exhibited in 0.1% of 4,368 perampanel treated patients in controlled and open label studies, including non-epilepsy studies.

In the Phase 3 epilepsy trials these events occurred in patients with and without prior psychiatric history, prior aggressive behaviour, or concomitant use of medications associated with hostility and aggression. Some patients experienced worsening of their pre-existing psychiatric conditions. Patients with active psychotic disorders and unstable recurrent affective disorders were excluded from the clinical trials. The combination of alcohol and perampanel significantly worsened mood and increased anger. Patients taking Fycompa should avoid the use of alcohol.

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In healthy volunteers taking Fycompa , observed psychiatric events included paranoia, euphoric mood, agitation, anger, mental status changes and disorientation confusional state.

In the non-epilepsy trials, psychiatric events that occurred in perampanel-treated subjects more often than placebo-treated subjects included disorientation, delusion and paranoia.

Patients, their caregivers, and families should be informed that Fycompa may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least one month after the last dose of Fycompa , and especially when taking higher doses and during the initial few weeks of drug therapy (titration period), or at others times of dose increases. The dose of Fycompa should be reduced if these symptoms occur. Permanently discontinue Fycompa for persistent severe or worsening psychiatric symptoms or behaviours and refer for psychiatric evaluation.

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.

In a clinical trial of 40 volunteers with a history of polydrug use supra-therapeutic doses of Fycompa (24 mg and 36 mg) produced responses for “Euphoria” that were similar to alprazolam 3 mg, and lower than ketamine 100 mg. The incidence of euphoria reported as an adverse event in this study following Fycompa administration 8 mg, 24 mg and 36 mg was 37%, 46%, 46%, respectively, which was higher than alprazolam 3mg (13%) but lower than ketamine 100mg (89%).

“Drug liking”, Overall Drug Liking”, and “Take Drug Again” for Fycompa were each statistically lower than for ketamine 100mg. In addition, for “Bad Drug Effects”, Fycompa 24 mg and 36 mg produced responses significantly higher than ketamine 100mg. For “Sedation”, Fycompa 24 and 36 mg produced responses similar to alprazolam 3 mg and higher than ketamine 100 mg. On the “Take Drug Again” scale all doses of perampanel produced lower scores than 1.5 mg and 3 mg alprazolam, and most of the differences were statistically significant.

The potential for Fycompa to produce withdrawal symptoms has not been adequately evaluated.

Monotherapy

Perampanel has not been assessed as monotherapy in patients with epilepsy. Monotherapy is not recommended.

Galactose Intolerance

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

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Use in pregnancy (Category B3)

Fycompa is not recommended in women of childbearing potential not using contraception unless clearly necessary. Fycompa is not recommended during pregnancy. There are limited amounts of data (less than 300 pregnancy outcomes) from the use of perampanel in pregnant women.

Perampanel and/or its metabolites cross the placenta in rats. Oral administration of perampanel to pregnant rats throughout organogenesis at doses of 1, 3 and 10 mg/kg/day was associated with a dose-related increase in diverticulum of the intestine; a no effect dose was not established. These doses are 0.8, 2 and 8 times respectively the MRHD of 12 mg/day based on body surface area.

There were no effects on embryofetal development following oral administration of perampanel to pregnant rabbits throughout organogenesis at doses of 1, 3 and 10 mg/kg/day (1.4, 4 and 14 times respectively the MRHD of 12 mg/day based on body surface area). Exposure (plasma AUC) at all doses was less than anticipated clinical exposure.

Oral administration of perampanel to rats from early gestation to weaning at doses of 1, 3 or 10 mg/kg/day (0.8, 2 and 8 times the MRHD of 12 mg/day based on body surface area) was associated with increased stillbirths and abnormal delivery and nursing behaviour at the mid- and high-doses; the no-effect dose was 1 mg/kg/day. Behavioural development and reproductive function of the offspring were not affected.

Use in lactation

Studies in lactating rats have shown excretion of perampanel and/or its metabolites in milk. The excretion into breast milk was measured in rats at 10 days post-partum. Levels peaked at one hour and were about 4 times the levels in plasma. Studies in rats with perampanel administration from early gestation to weaning have shown adverse effects (see Use in pregnancy).

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 breastfeeding or to discontinue/abstain from Fycompa therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Genotoxicity

Perampanel was negative in the bacterial reverse mutation and mouse lymphoma *tk* assays *in vitro*, and in the micronucleus test in rats *in vivo*.

Carcinogenicity

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

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treatment-related tumours in either species. Estimated exposures (plasma AUC) to perampanel at the highest doses tested were less than anticipated clinical exposure at the MRHD of 12 mg/day.

Effects on Fertility

There were no clear effects on fertility or early embryonic development in male or female rats treated with perampanel at oral doses of 1, 10, or 30 mg/kg/day (0.8, 8 and 23 times respectively the MRHD of 12 mg/day based on body surface area). Prolonged and/or irregular estrous cycles were observed at all doses but particularly at the high-dose. The effect of perampanel on human fertility has not been established.

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.

INTERACTIONS WITH OTHER MEDICINES

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

Drug interaction studies

In vitro assessment of drug interactions

Drug metabolising enzyme

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

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

Transporters

Perampanel was not a substrate or significant inhibitor of several influx **or** efflux transporters *in vitro* (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.)

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Oral 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 progestative-containing oral contraceptives should be considered for women needing Fycompa 12 mg/day and an additional reliable non-hormonal method (for example intra-uterine device (IUD), condom) form of contraceptive is to be used (see PRECAUTIONS).

Interactions between Fycompa and other anti-epileptic medicinal products

Potential interactions between Fycompa (up to 12 mg once daily) and other anti-epileptic drugs (AEDs) were assessed in clinical studies and evaluated in the population PK analysis of three pooled Phase 3 studies. 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	No influence	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 monohydroxycarbamazepine was not assessed.

Some anti-epileptic drugs known as enzyme inducers (carbamazepine, phenytoin, oxcarbazepine) have been shown to increase perampanel clearance and consequently to decrease plasma concentrations of perampanel.

Carbamazepine, a known potent enzyme inducer, reduced perampanel levels by two-thirds in a study performed on healthy subjects.

A similar result was seen in a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day in placebo-controlled clinical trials. The total clearance of Fycompa was increased when administered with carbamazepine (3-fold), phenytoin (2-fold) and oxcarbazepine (2-fold), which are known inducers of enzymes of metabolism (see Pharmacokinetics). This effect should be taken into account and managed when adding or withdrawing these anti-epileptic drugs from a patient's treatment regimen.

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In a population pharmacokinetic analysis of patients with partial-onset seizures receiving Fycompa up to 12 mg/day in placebo-controlled clinical trials, 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).

In the epilepsy population pharmacokinetic analysis, perampanel was found to decrease the clearance of oxcarbazepine by 26%. Oxcarbazepine is rapidly metabolised by cytosolic reductase enzyme to the active metabolite, monohydroxycarbamazepine. The effect of perampanel on monohydroxycarbamazepine concentrations is not known.

Perampanel is dosed to clinical effect regardless of other AEDs.

Effect of perampanel on CYP3A substrates

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. 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. Patient's 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 DOSAGE AND ADMINISTRATION).

Effect of cytochrome P450 inducing or inhibiting medicinal products on perampanel pharmacokinetics

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

Effect of cytochrome P450 inducers on perampanel pharmacokinetics

Strong inducers of cytochrome P450, such as rifampicin and hypericum, are expected to decrease perampanel concentrations. Felbamate has been shown to decrease the concentrations of some drugs 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

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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. Strong inhibitors of other cytochrome P450 isoforms could potentially also increase perampanel concentrations.

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

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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 Pharmacodynamic Properties). These effects may also be seen when Fycompa is used in combination with other central nervous system (CNS) depressants.

Interaction studies have only been performed in adults. In a population pharmacokinetic analysis of the adolescent patients in the Phase 3 clinical studies, there were no notable differences between this population and the overall population.

ADVERSE EFFECTS

Clinical Trials

Summary of safety profile

In all controlled and uncontrolled trials in patients with partial-onset seizures, 1,639 subjects have received perampanel of whom 1,174 have been treated for 6 months and 703 for longer than 12 months.

A total of 1,038 patients on perampanel (2, 4, 8, or 12 mg once daily) constituted the safety population in the pooled analysis of Phase 3 placebo controlled studies in patients with partial onset seizures. Approximately 51% of patients were female and the mean age was 35 years.

Adverse Reactions Leading to Discontinuation

In controlled Phase 3 clinical trials the rate of discontinuation as a result of an adverse reaction was 3%, 8% and 19% in patients randomized to receive Fycompa at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 5% in patients randomized to receive placebo. The adverse events most commonly leading to discontinuation ($\geq 1\%$ in the 8 mg or 12 mg Fycompa group and greater than placebo) were dizziness, somnolence, vertigo, aggression, anger, ataxia, blurred vision, irritability, and dysarthria.

Most Common Adverse Reactions

The Table below gives the incidence in the Phase 3 controlled trials of the adverse reactions that occurred in $\geq 2\%$ of patients with partial-onset seizures in any Fycompa dose group. Overall, the most frequently reported dose-related adverse reactions in patients receiving Fycompa at doses of 8 mg or 12 mg ($\geq 4\%$ and occurring at least 1% higher than the placebo group) included dizziness (36%), somnolence (16%), fatigue (10%), irritability (9%), falls (7%), nausea (7%), ataxia (5%), balance disorder (4%), gait disturbance (4%), vertigo (4%), and weight gain (4%). For almost every adverse reaction, rates were higher on 12 mg and

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more often led to dose reduction or discontinuation.

Table 2. Adverse Reactions in Pooled Double-blind Trials in Patients with Partial-Onset Seizures (Reactions \geq 2% of Patients in Highest Fycompa Dose (12 mg) Group and More Frequent than Placebo)

	Placebo n=442 %	Fycompa		
		4 mg n=172 %	8 mg n=431 %	12 mg n=255 %
Ear and Labyrinth Disorders				
Vertigo	1	4	3	5
Eye Disorders				
Diplopia	1	1	1	3
Blurred vision	1	1	3	4
Gastrointestinal Disorders				
Constipation	2	2	2	3
Nausea	5	3	6	8
Vomiting	3	2	3	4
Infections and Infestations				
Upper respiratory tract infection	3	3	3	4
Injury, Poisoning and Procedural Complications				
Contusion	1	0	2	2
Falls	3	2	5	10
Head injury	1	1	1	3
Limb injury	<1	1	1	2
Skin laceration	1	0	2	2
Investigations				
Weight gain	1	4	4	4
Metabolism & Nutrition disorders				
Hyponatremia	<1	0	0	2
Musculoskeletal and Connective Tissue disorders				
Arthralgia	1	0	3	2
Back pain	2	2	2	5
Musculoskeletal pain	1	1	1	2
Myalgia	2	1	1	3
Pain in extremity	1	0	2	3
Peripheral edema	1	1	1	2
Nervous system disorders				
Asthenia	1	1	2	2
Ataxia	0	1	3	8
Balance disorder	1	0	5	3
Coordination abnormal	0	1	<1	2
Dizziness	9	16	32	43
Dysarthria	0	1	3	4
Fatigue	5	8	8	12
Gait disturbance	1	1	4	4
Headache	11	11	11	13
Hypersomnia	0	1	2	3

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Hypoaesthesia	1	0	0	3
Memory impairment	1	0	1	2
Paraesthesia	1	0	1	2
Somnolence	7	9	16	18
Psychiatric disorders				
Aggression	1	1	2	3
Anger	<1	0	1	3
Anxiety	1	2	3	4
Confusional state	<1	1	1	2
Euphoric mood	0	0	<1	2
Irritability	3	4	7	12
Mood altered	<1	1	<1	2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3	1	1	4
Oropharyngeal pain	1	2	2	2

Weight Gain

In controlled clinical trials in patients with epilepsy clinically significant weight gain (i.e. >7% BW) occurred in 14%, 15.3% and 15.4% of patients given perampanel 4 mg, 8 mg and 12 mg respectively compared to 7.1% given placebo

The following adverse reactions are discussed in more detail in the precautions section of the prescribing information:

- Psychiatric reactions including aggression
- Suicidal ideation and behaviour
- Abuse potential
- Dizziness and gait disturbance
- Falls
- Somnolence and fatigue

Paediatric population

Based on the clinical trial database of 143 adolescents, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults.

DOSAGE AND ADMINISTRATION

Adults and adolescents

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

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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/day 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 INTERACTIONS WITH OTHER MEDICINES) 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 INTERACTIONS WITH OTHER MEDICINES) should be titrated no more frequently than at 1-week intervals.

When withdrawing Fycompa, the dose should be gradually reduced (see PRECAUTIONS).

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 INTERACTIONS WITH OTHER MEDICINES), consideration should be given to restart 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.

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.

Patients with 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.

Elderly patients

Fycompa should be used with caution in the elderly (see PRECAUTIONS).

Paediatric patients

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The safety and efficacy of perampanel in children below 12 years of age have not been established yet. No data are available.

Method of administration

Fycompa should be taken as single oral dose at bedtime. It may be taken with or without food (see Pharmacokinetics). 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. To ensure the patient receives the entire dose the tablets should be swallowed whole without chewing or crushing.

OVERDOSAGE

Contact the Poisons Information Centre on telephone 13 11 26 for advice on management of overdose.

There is limited clinical experience with perampanel overdose in humans. In a report of an intentional overdose that could have resulted in a dose up to 264 mg, the patient experienced events of altered mental status, agitation and aggressive behaviour and 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.

PRESENTATION AND STORAGE CONDITIONS

Presentations

Fycompa 2 mg film coated tablet is available in PVC/aluminium blisters of 7.

Fycompa 4 mg film coated tablet is available in PVC/aluminium blisters of 28.

Fycompa 6 mg film coated tablet is available in PVC/aluminium blisters of 28.

Fycompa 8 mg film coated tablet is available in PVC/aluminium blisters of 28.

Fycompa 10 mg film coated tablet is available in PVC/aluminium blisters of 28.

Fycompa 12 mg film coated tablet is available in PVC/aluminium blisters of 28.

Storage

Store below 30°C.

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NAME AND ADDRESS OF THE SPONSOR

Villa 2
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Claremont
WA 6010

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

23 May 2014

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