

AUSTRALIAN PRODUCT INFORMATION – FYCOMPA® (PERAMPANEL) FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Perampanel (as hemisesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fycompa 2 mg film-coated tablets

Each 2 mg FYCOMPA film-coated tablet contains 2 mg of perampanel (as hemisesquihydrate).

Excipient with known effect:

Each 2 mg tablet contains 78.5 mg of lactose (as monohydrate).

Fycompa 4 mg film-coated tablets

Each 4 mg FYCOMPA film-coated tablet contains 4 mg of perampanel (as hemisesquihydrate).

Excipient with known effect:

Each 4 mg tablet contains 157 mg of lactose (as monohydrate).

Fycompa 6 mg film-coated tablets

Each 6 mg FYCOMPA film-coated tablet contains 6 mg of perampanel (as hemisesquihydrate).

Excipient with known effect:

Each 6 mg tablet contains 151 mg of lactose (as monohydrate).

Fycompa 8 mg film-coated tablets

Each 8 mg FYCOMPA film-coated tablet contains 8 mg of perampanel (as hemisesquihydrate).

Excipient with known effect:

Each 8 mg tablet contains 149 mg of lactose (as monohydrate).

Fycompa 10 mg film-coated tablets

Each 10 mg FYCOMPA film-coated tablet contains 10 mg of perampanel (as hemisesquihydrate).

Excipient with known effect:

Each 10 mg tablet contains 147 mg of lactose (as monohydrate).

Fycompa 12 mg film-coated tablets

Each 12 mg FYCOMPA film-coated tablet contains 12 mg of perampanel (as hemisesquihydrate).

Excipient with known effect:

Each 12 mg tablet contains 145 mg of lactose (as monohydrate).

All film-coated tablets

Excipients with known effect: Sugars (as lactose)

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Film coated tablet

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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FYCOMPA is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in adult and adolescent patients from 12 years of age with epilepsy.

FYCOMPA is indicated for the adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and adolescents

FYCOMPA must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability. FYCOMPA should be taken orally once daily at bedtime.

Partial-Onset Seizures

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

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. It is recommended that FYCOMPA is maintained at the lowest dose that controls symptoms in order to reduce potential adverse events.

Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 Interactions with other medicines and other forms of interactions) 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 Interactions with other medicines and other forms of interactions) should be titrated no more frequently than at 1-week intervals.

Primary Generalised Tonic-Clonic Seizures

FYCOMPA at a dose up to 8 mg/day has been shown to be effective in primary generalised tonic-clonic seizures.

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 Special warnings and precautions for use). It is recommended that FYCOMPA is maintained at the lowest dose that controls symptoms in order to reduce potential adverse events.

Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see Section 4.5 Interactions with other medicines and other forms of interactions) 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 Interactions with other medicines and other forms of interactions) should be titrated no more frequently than at 1-week intervals.

Treatment withdrawal and missed doses

When withdrawing FYCOMPA, the dose should be gradually reduced (see Section 4.4 Special warnings and precautions for use).

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 AEDs, 1 week for patients taking perampanel metabolism-inducing AEDs (see Section 4.5 Interactions With Other Medicines And Other Forms Of Interactions)), 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.

Special Populations

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. FYCOMPA 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 Section 4.4 Special warnings and precautions for use).

Paediatric patients

The safety and efficacy of FYCOMPA 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 Section 5.2 Pharmacokinetic Properties). 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.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 List of excipients.).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Paediatric Use

There is no experience with FYCOMPA in children <12 years. FYCOMPA 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 Section 4.4 Special warnings and precautions for use, Falls). Dizziness occurred in 55.6% of elderly patients given the

8 mg dose and falls occurred in 57.1% given the 12 mg dose. FYCOMPA should be used with caution in the elderly.

Suicidal ideation and behaviour

Antiepileptic drugs (AED), including FYCOMPA, 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 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 varying mechanisms of action and across a range of 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 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: 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 FYCOMPA 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.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including FYCOMPA. DRESS may be fatal or life-threatening. If signs or symptoms of DRESS are present, the patient should be evaluated immediately and FYCOMPA should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Nervous system disorders

Dizziness and gait disturbance

FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination (see Section 4.8 Adverse Effects (Undesirable effects)). In the controlled Phase 3 epilepsy clinical trials, dizziness and vertigo were reported in 35% and 47% of patients randomised 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 randomised 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 FYCOMPA-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 randomised 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 randomised 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 FYCOMPA-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 randomised 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. Falls occurred in 11.1% of elderly patients given the 8 mg dose and 57.1% given the 12 mg dose. FYCOMPA 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 Section 4.2 Dose and method of administration). However, due to its long half-life and subsequent slow decline in plasma concentrations, FYCOMPA 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. Aggression was observed more frequently in adolescents than adults. 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 FYCOMPA treated patients and twice as frequently as in placebo-treated patients. Other symptoms that were observed with FYCOMPA 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 FYCOMPA 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 FYCOMPA significantly worsened mood and increased anger. Patients taking FYCOMPA should avoid the use of alcohol.

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 FYCOMPA-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 FYCOMPA 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 FYCOMPA 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

FYCOMPA 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.

Use in hepatic impairment

See Section 4.2 Dose and method of administration, Dosage adjustment in hepatic impairment and Section 5.2 Pharmacokinetic Properties, Special Populations, Hepatic Impairment.

Use in renal impairment

See Section 4.2 Dose and method of administration, Dosage adjustment in renal impairment and Section 5.2 Pharmacokinetic Properties, Special Populations, Renal Impairment.

Effect on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

FYCOMPA is not considered a strong inducer or inhibitor of cytochrome P450 or UGT enzymes (see Section 5.2 Pharmacokinetic Properties).

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.)

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 Section 4.6 Fertility, Pregnancy And Lactation, Use In Pregnancy).

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 four pooled Phase 3 studies including patients with partial-onset seizures and primary generalised tonic-clonic seizures. The effect of these interactions on average steady state concentration is summarised in Table 2.

Table 2: The effect of interactions on average steady state concentrations of other AEDs

AED coadministered	Influence of AED on FYCOMPA concentration	Influence of FYCOMPA on AED concentration
Carbamazepine	2.8 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	1.9 fold decrease	35% increase ¹⁾
Phenobarbital	No influence	No influence
Phenytoin	1.7 fold decrease	No influence
Topiramate	19% decrease	No influence
Valproic Acid	No influence	<10% decrease
Zonisamide	No influence	No influence

1) Active metabolite monohydroxycarbazepine was not assessed.

Some AEDs known as enzyme inducers (carbamazepine, phenytoin, oxcarbazepine) have been shown to increase perampanel clearance and consequently to decrease plasma concentrations of perampanel reducing its half life.

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 FYCOMPA up to 12 mg/day and patients with primary generalised tonic-clonic seizures receiving FYCOMPA up to 8 mg/day in placebo-controlled clinical trials. The total clearance of FYCOMPA was increased when administered with carbamazepine (2.8-fold), phenytoin (1.7-fold) and oxcarbazepine (1.9-fold), which are known inducers of enzymes of metabolism (see Section 5.2 Pharmacokinetic Properties). This effect should be taken into account and managed when adding or withdrawing these AEDs from a patient's treatment regimen.

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 FYCOMPA 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, monohydroxycarbazepine. The effect of FYCOMPA on monohydroxycarbazepine concentrations is not known.

FYCOMPA is dosed to clinical effect regardless of other AEDs (see Section 4.2 Dose and method of administration).

Effect of perampanel on CYP3A substrates

Concomitant CYP3A inducing AEDs

Partial-Onset Seizures

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 AEDs (see Section 5.1 Pharmacodynamic properties, Clinical trials). 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 Dose and method of administration).

Primary Generalised Tonic-Clonic Seizures

Response rates after addition of perampanel at a fixed dose of 8 mg were less when patients received concomitant CYP3A enzyme-inducing AEDs (carbamazepine, phenytoin, oxcarbazepine) as compared to response rates in patients who received concomitant non-enzyme–inducing AEDs (see Section 5.1 Pharmacodynamic properties, Clinical trials). Patients' response should be monitored when they are switching from concomitant non-inducer AEDs to enzyme-inducing AEDs, and vice versa. Depending upon individual clinical response and tolerability, the dose may be increased by increments of 2 mg up to 12 mg/day.

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 FYCOMPA 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 58.4 h). Larger effects cannot be excluded when FYCOMPA 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.

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 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 FYCOMPA on human fertility has not been established.

Use in Pregnancy

Pregnancy Category B3.

FYCOMPA is not recommended during pregnancy. There are limited amounts of data (less than 300 pregnancy outcomes) from the use of FYCOMPA 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 10mg/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.

Women of childbearing potential

FYCOMPA is not recommended in women of childbearing potential not using contraception unless clearly necessary.

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 Section 4.6 Fertility, Pregnancy And Lactation, 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

FYCOMPA has moderate influence on the ability to drive and use machines.

FYCOMPA 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 FYCOMPA affects their ability to perform these tasks.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

In the controlled and uncontrolled trial in patients with primary generalised tonic-clonic seizures, 114 subjects have received perampanel of whom 68 have been treated for 6 months and 34 for longer than 12 months.

Partial-Onset Seizures

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 randomised to receive FYCOMPA at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 5% in patients randomised 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

Table 3 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 more often led to dose reduction or discontinuation.

Table 3. 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
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 partial onset seizures, 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.

Across the entire perampanel treatment duration in the open label extension study for partial onset seizures, 43.9% of subjects had an increase in body weight of >7%, and 15.3% had a decrease in body weight of >7%. The mean change from baseline in body weight at the end of treatment was 2.54 kg. The mean duration of perampanel exposure was 115.41 weeks.

In subjects with primary generalised tonic-clonic seizures who completed the controlled clinical trial and subsequently entered the open-label extension phase, 27.9% had a clinically notable increase (>7%) in body weight across the entire perampanel treatment duration. The mean duration of perampanel exposure was 40.3 weeks.

Other Adverse Reactions

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.

Primary Generalised Tonic-Clonic Seizures

A total of 81 patients on perampanel constituted the safety population in the Phase 3 placebo-controlled trial in patients with primary generalised tonic-clonic seizures. Approximately 57% of patients were female, and the mean age was 27 years.

In the controlled Phase 3 primary generalised tonic-clonic seizures clinical trial, the adverse event profile was similar to that noted for the controlled Phase 3 partial-onset seizures trials.

The most frequently reported adverse reactions in patients receiving FYCOMPA ($\geq 10\%$ and higher than in the placebo group) included dizziness (32.1%), fatigue (14.8%), headache (12.3%), somnolence (11.1%), and irritability (11.1%). The adverse reactions most commonly leading to discontinuation ($\geq 2\%$ in the FYCOMPA group and greater than placebo) were vomiting and dizziness.

Post-Marketing Experience

Skin and Subcutaneous tissue disorders

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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

Pharmacokinetic-pharmacodynamic (efficacy) analyses have shown that within the recommended dose range there is a positive correlation between serum levels of FYCOMPA and seizure frequency for partial-onset seizures and primary generalised tonic-clonic seizures.

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.

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 Trials

Partial-Onset Seizures

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 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). 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 FYCOMPA was given in combination with non-enzyme-inducing anti-epileptic medicinal products. These studies show that once-daily administration of FYCOMPA at doses of 4 mg to 12 mg was significantly more efficacious than placebo as adjunctive treatment in this population.

Table 4: Pooled 50% responder rate during the maintenance period (LOCF) for placebo and Fycompa dose

Treatment	Placebo (N=441)	2 mg (N=180)	4 mg (N=172)	8 mg (N=431)	12 mg (N=254)
Responder status	%	%	%	%	%
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 number needed to treat (NNT) with any dose of FYCOMPA 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 for Partial Onset Seizures

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.

Elderly Patients in Clinical Trials for Partial Onset Seizures

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

Primary Generalised Tonic-Clonic Seizures

FYCOMPA 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 FYCOMPA or placebo. The population included 164 patients (FYCOMPA 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 primary endpoint was the percent change from baseline in primary generalised tonic-clonic seizure frequency per 28 days during the treatment period (titration + maintenance) as compared to the baseline period. The median percent change in primary generalised tonic-clonic seizure frequency per 28 days during the Titration and Maintenance Periods (combined) relative to Prerandomization was greater with FYCOMPA (-76.5%) than with placebo (-38.4%), $P < 0.0001$. The 50% primary generalised tonic-clonic seizures responder rate during the Maintenance Period was significantly higher in the FYCOMPA group (64.2%) than in the placebo group (39.5%), $P = 0.0019$. The 50% responder rates were 58.0% for the FYCOMPA group and 35.8% for the placebo group ($P = 0.0059$) when discontinued patients were considered non-responders. The 50% responder rate was 22.2% when FYCOMPA was used in combination with enzyme inducing anti-epileptic medicinal products and 69.4% when FYCOMPA was given in combination with non-enzyme-inducing anti-epileptic medicinal products. The number of FYCOMPA subjects taking enzyme inducing anti-epileptic medicinal products was small ($n = 9$).

During the 3 month maintenance period, 30.9% of the patients on FYCOMPA in the clinical studies became free of PGTC seizures compared with 12.3% on placebo. Freedom from all seizures was achieved in 23.5% of patients on FYCOMPA compared to 4.9% of patients on placebo. There are no data regarding the effects of withdrawal of concomitant anti-epileptic medicinal products to achieve monotherapy with FYCOMPA. The efficacy of FYCOMPA in the treatment of absence and myoclonic seizures has not been demonstrated.

Paediatric population

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.

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

5.2 PHARMACOKINETIC PROPERTIES

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).

Metabolism

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.

Excretion

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

The pharmacokinetics of perampanel are linear within the dose range 2 to 12 mg daily.

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. Considering the substantial overlap in the exposure between normal and mildly impaired patients, no dosage adjustment is necessary for patients with mild renal impairment. FYCOMPA has not been studied in patients with severe renal impairment and patients undergoing haemodialysis (see Section 4.2 Dose and method of administration).

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)

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

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.

5.3 PRECLINICAL SAFETY DATA

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 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.

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.

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 dose 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The film-coated tablets contain the excipients lactose monohydrate, hypromellose, povidone, magnesium stearate, purified talc, microcrystalline cellulose (6 mg, 8 mg, 10 mg and 12 mg only), macrogol 8000, titanium dioxide, 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).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

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.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

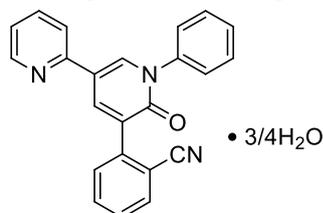
Perampanel hemisesquihydrate is a crystalline solid and is obtained as a white to yellowish white powder. The pKa value of perampanel hemisesquihydrate is 3.24 and the partition coefficient is 2.86 at 25°C. Perampanel hemisesquihydrate is freely soluble in N-methyl-2-pyrrolidone, sparingly soluble in 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 M 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.

Chemical structure

The chemical name of perampanel hemisesquihydrate is 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile 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:

CAS Number: 380917-97-5

7 MEDICINE SCHEDULE (POISON STANDARD)

Schedule 4 – Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

23 May 2014

10 DATE OF REVISION

15 April 2020

Summary Table of changes

Version Number	Section changed	Summary of new information
3.2	All	Reformatted to new TGA template. No change to content.