NEW ZEALAND DATA SHEET

1 PRODUCT NAME

FYCOMPA 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg film coated tablets and FYCOMPA 2 mg/4 mL oral suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 FILM-COATED TABLETS

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 film-coated tablet contains 78.5mg 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.

2.2 ORAL SUSPENSION

Each bottle of 340 mL oral suspension contains 170 mg perampanel (as hemisesquihydrate).
Each 4 mL of oral suspension contains 2 mg perampanel (as hemisesquihydrate).
Excipient with known effect:
Each 4 mL of oral suspension contains:
1000 mg sorbitol solution (70%) (crystallising),
4.40 mg sodium benzoate.

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

3 PHARMACEUTICAL FORM

3.1 FILM COATED TABLETS

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.

3.2 ORAL SUSPENSION

FYCOMPA oral suspension appears as a white to off-white suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FYCOMPA is indicated for the adjunctive treatment of

- Partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age with epilepsy.
- Primary generalised tonic-clonic seizures (PGTCS) in patients from 7 years of age with idiopathic generalised epilepsy.

4.2 DOSE AND METHOD OF ADMINISTRATION

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.

The physician should prescribe the most appropriate formulation and strength according to weight and dose. Alternate formulations of perampanel are available, including oral suspension.

Dose and Titration for all patients

Table 1 summarises the recommended posology for patients with Partial-Onset Seizures from 4 years of age and patients with Primary Generalised Tonic Clonic Seizures from 7 years of age.

Treatment with FYCOMPA should be initiated with the lowest dose specified in Table 1 for the patient's age and weight. The dose may be increased based on clinical response and tolerability by increments according to age and weight as specified in Table 1 (no more frequently than either weekly or every 2-4 weeks as per half-life considerations described below) to a maintenance dose according to age and weight as specified in Table 1.Real world experience suggests that slower titration may lead to improved tolerability. Depending upon individual clinical response and tolerability at the recommended maintenance dose, the dose may be increased by increments no more frequently than either weekly or every 2-4 weeks according to age and weight as specified in Table 1 to the Recommended Maximum Dose specified in Table 1, 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.

Concomitant medicines, such as moderate and strong CYP3A4 inducers, including enzyme-inducing AEDs such as phenytoin, carbamazepine, and oxcarbazepine, may impact the half-life of perampanel (see Section 4.5 Interactions with other medicines and other forms of interactions). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel should be titrated no more frequently than every 2-4 weeks. 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 weekly intervals.

Table 1: Recommended posology for patients with Partial-Onset Seizures (from 4 years of age) and Primary Generalised Tonic Clonic Seizures (from 7 years of age)

	Adult/adolescent (12 years and older)	**Children (<12 years); weighing:**		
		≥ 30 kg	**20 - < 30 kg**	**< 20 kg**
Recommended starting dose	2 mg/day (4 ml/day)	2 mg/day (4 ml/day)	1 mg/day (2 ml/day)	1 mg/day (2 ml/day)
Titration increments up to maintenance dose[a]	2 mg/day (4 ml/day)	2 mg/day (4 ml/day)	1 mg/day (2 ml/day)	1 mg/day (2 ml/day)
Recommended maintenance dose	4 – 8 mg/day (8 – 16 ml/day)	4 – 8 mg/day (8 – 16 ml/day)	4 – 6 mg/day (8 – 12 ml/day)	2 – 4 mg/day (4 – 8 ml/day)
Titration increments up to maximum dose[a]	2 mg/day (4 ml/day)	2 mg/day (4 ml/day)	1 mg/day (2 ml/day)	0.5 mg/day (1 ml/day)
Recommended maximum dose	12 mg/day (24 ml/day)	12 mg/day (24 ml/day)	8 mg/day (16 ml/day)	6 mg/day (12 ml/day)

a: Titration for patients taking medicinal products that do not shorten the half-life of perampanel should occur no more frequently than every 2-4 weeks.
Titration for patients taking medicinal products that shorten the half-life of perampanel should occur no more frequently than weekly 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.

Dosage adjustment in 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.

Dosage adjustment in hepatic impairment

Dose increases in adult and adolescent patients with mild and moderate hepatic impairment should be based on clinical response and tolerability.

For adult and adolescent patients with mild or moderate hepatic impairment, dosing can be initiated at the starting dose specified in Table 1. Patients should be up-titrated slowly and no faster than every 2 weeks based on tolerability and effectiveness. FYCOMPA dosing for patients with mild and moderate impairment should not exceed the maintenance dose specified in Table 1.

No data is available in children <12 years with mild or moderate hepatic impairment. No dosing recommendation can be made for these children.

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

There is limited long term safety data in children below 12 years of age. The safety and efficacy of FYCOMPA in children below 4 years of age with POS and 7 years of age with PGTCS have not been established yet.

Method of administration

FYCOMPA should be taken as single oral dose at bedtime. It may be taken with or without food (see Section 5.2Pharmacokinetic properties).

The film-coated tablet should be swallowed whole with a glass of water. It should not be chewed, crushed or split. The film-coated 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.

The oral suspension should be shaken vigorously for at least 5 seconds before every administration. The press in-bottle adapter (PIBA) which is supplied in the product carton should be inserted firmly into the neck of the bottle before use and remain in place for the duration of the usage of the bottle. The oral syringe should be inserted into the PIBA and the dose withdrawn from the inverted bottle. The provided adaptor and graduated oral dosing syringe should be used to administer the oral suspension. A household teaspoon or tablespoon

is not an adequate measuring device. The cap should be replaced after each use. The cap fits properly when the PIBA is in place.
Discard any unused FYCOMPA oral suspension remaining 90 days after first opening the bottle.

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

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 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 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 aetiology 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 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.

Hepatotoxicity

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

Galactose Intolerance

FYCOMPA film-coated tablets contains lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take FYCOMPA film-coated tablets.

Sorbitol

FYCOMPA oral suspension contains sorbitol; therefore patients with rare hereditary problems of fructose intolerance should not take FYCOMPA oral suspension.

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

Use in hepatic impairment

See Section 4.2 Dose and method of administration, Patients with 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, Renal impairment and Section 5.2 Pharmacokinetic Properties, Special Populations, Renal Impairment.

Effect on laboratory tests

No data available.

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 (see Section 4.2 Dose and method of administration and Section 4.8 Adverse effects, Other Special Populations).

Paediatric use

The safety and efficacy of FYCOMPA in children below 4 years of age with POS and 7 years of age with PGTCS have not been established yet. FYCOMPA is not recommended for use in children aged less than 4 years of age.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

FYCOMPA is not considered as 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 Cmax and AUC values were each decreased by 40%). Ethinyloestradiol AUC was not affected by FYCOMPA 12 mg whereas Cmax 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 and other anti-epileptic drugs (AEDs) were assessed in clinical studies. A population PK analysis of three pooled Phase 3 studies in adolescent and adult patients with partial-onset seizures evaluated the effect of Fycompa (up to 12 mg once daily) on the PK of other AEDs. In another population PK analysis of pooled data from twenty Phase 1 studies in healthy subjects, with Fycompa up to 36 mg, and one Phase 2 and six Phase 3 studies in paediatric, adolescent and adult patients with partial-onset seizures or primary generalised tonic-clonic seizures, with Fycompa up to 16 mg once daily, evaluated the effect of concomitant AEDs of perampanel clearance. The effect of these interactions on average steady state concentration is summarised in Table 3.

Table 3: 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	3 -fold decrease	<10% decrease

Clobazam	No influence	<10% decrease
Clonazepam	No influence	No influence
Lamotrigine	No influence	<10% decrease
Levetiracetam	No influence	No influence
Oxcarbazepine	2- fold decrease	35% increase[1)]
Phenobarbital	20% decrease	No influence
Phenytoin	2- fold decrease	No influence
Topiramate	20% decrease	No influence
Valproic Acid	No influence	<10% decrease
Zonisamide	No influence	No influence

1) Active metabolite monohydroxycarbazepine was not assessed.

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

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

FYCOMPA 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 Cmax 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.

Paediatric population

Interaction studies have only been performed in adults.

In a population pharmacokinetic analysis of the adolescent patients age ≥12 years and children age 4 to <12 years, there were no notable differences compared to the adult 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 (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 UNDESIRABLE EFFECTS

Clinical Trials

Partial-Onset Seizures in adults and adolescents

A total of 1,038 in adult and adolescent 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

(≥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 4 below gives the incidence in the Phase 3 controlled trials of the adverse reactions that occurred in ≥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 (≥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 4. Adverse Reactions in Pooled Double-blind Trials in Patients with Partial-Onset Seizures (Reactions ≥ 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

Body weight of subjects was recorded during vital signs monitoring at various time points during the conduct of Phase 3 studies. 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, based on body weight measurements, 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, based on body weight measurements, 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

Primary Generalised Tonic-Clonic Seizures in adults and adolescents

A total of 81 adult and adolescent 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 (≥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 (≥2% in the FYCOMPA group and greater than placebo) were vomiting and dizziness.

Other special populations

Paediatric Population

Based on the clinical trial database of 196 adolescents exposed to FYCOMPA from double-blind studies for POS and PGTCS, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults, except for aggression, which was observed more frequently in adolescents than in adults.
Based on the clinical trial database of 180 children (4 to <12 years) with POS and PGTCS, exposed to perampanel from a multicentre open label study, the overall safety profile in children were similar to that of adolescents and adults, except for somnolence (26.1%, 14.8% adolescents and 14.2% adults,), irritability (12.8%, 6.6% adolescents, and 7.4% adults,), aggression (8.9%, 7.7% adolescents, 1.0% adults), and agitation (4.4%, 0.5% adolescents and 0.4% adults) which were observed more frequently in children than in adolescents and adults. Table 5 provides a summary of the adverse events observed in the core study occurring in more than 5% of the subjects.

Table 5: TEAEs in Paediatric Trial in Patients with POS or PGTC (TEAEs ≥ 5% of Patients)

	Total (N=180) n (%)
Somnolence	47 (26.1)
Nasopharyngitis	35 (19.4)
Dizziness	23 (12.8)
Irritability	23 (12.8)
Pyrexia	23 (12.8)
Vomiting	20 (11.1)
Aggression	16 (8.9)
Influenza	15 (8.3)
Headache	13 (7.2)
Gastroenteritis	13 (7.2)
Upper Respiratory Tract Infection	11 (6.1)
Diarrhoea	11 (6.1)
Fatigue	9 (5.0)

TEAEs leading to dose reduction were observed in 40.6% of children. Common TEAEs leading to dose reduction in children included somnolence (13.3%), dizziness (5.6%), irritability (4.4%), and aggression (4.4%). TEAEs leading to discontinuation were observed in 9.4% of children. Reasons for discontinuation occurring in more than one subject were irritability (1.7%), aggression (1.7%), seizure (1.1%), and balance disorder (1.1%).

In the core and extension phase of this study, 76.7% of subjects received Fycompa for more than 24 weeks and 33.9% of subjects received Fycompa for more than 52 weeks.

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

Post-Marketing Experience

The following adverse reactions have been identified during post approval use of FYCOMPA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous tissue disorders

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antiepileptics, carboxamide derivatives; ATC code: N03AF03.

Mechanism of action

Perampanel is a first-in-class selective, non-competitive antagonist of the ionotropic α-amino-3hydroxy-5-methyl-4-isoxazoleproprionic 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.

In an open label uncontrolled study conducted in paediatric patients, no clinically important changes in cognition relative to baseline as measured by ABNAS were observed following adjunctive perampanel therapy (see Section 5.1 Paediatric population). Long-term cognitive effects of perampanel in children are unknown.

Cardiac electrophysiology

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

Clinical efficacy and safety

Partial-Onset Seizures in adults and adolescents

The efficacy of FYCOMPA in partial-onset seizures in adults and adolescents 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 6: Pooled 50% responder rate during the maintenance period (LOCF) for placebo and Fycompa dose

Treatment Responder status	**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 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 in adults and adolescents

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 in adults and adolescents

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 Pre-randomization 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. The efficacy of FYCOMPA in the treatment of absence and myoclonic seizures has not been demonstrated.

Conversion to monotherapy

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

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 efficacy of perampanel in children down to the age of 4 years for POS and 7 years for PGTCS has been extrapolated from data of adolescents and adults with POS or PGTCS. A similar clinical response is expected in these patients based on the paediatric posology (see Section 4.2 Dose and method of administration) established to achieve plasma concentrations in the range observed in adolescents and adults taking efficacious doses (see Section 5.2 Pharmacokinetic properties). Data supporting the extrapolation principle and the safety of perampanel adjunctive therapy in children (aged 4 to <12 years old) have been evaluated in an open-label, uncontrolled study (Study 311). A total of 180 paediatric patients (aged 4 to <12 years old) with inadequately controlled partial-onset seizures or primary generalised tonic-clonic seizures. Patients were titrated over 11 weeks to a target dose of 8 mg/day or the maximum tolerated dose (not to exceed 12 mg/day) for patients not taking concomitant CYP3A-inducing antiepileptic drugs (carbamazepine, oxcarbazepine, eslicarbazepine and phenytoin) or 12 mg/day or the maximum tolerated dose (not to exceed 16 mg/day) for patients taking a concomitant CYP3A-inducing antiepileptic drug. Perampanel dose achieved at the end of titration was maintained for 12 weeks (for a total of 23 weeks of exposure) at the completion of the core study. Patients who entered into Extension Phase were treated for an additional 29 weeks for a total exposure duration of 52 weeks. The approved dose for children weighing <30 kg is lower than the dose used in this study. Efficacy results observed in the core and extension phase of the Study are presented in Table 7. Overall, the treatment effects on the median reduction in seizure frequency, 50% responder rate, and seizure-free rate were sustained following 52 weeks of perampanel treatment.

Table 7: Summary of Efficacy Endpoint Data in Children Aged 4 to <12 Years from Open-Label Study 311.

Disease Cohort	POS		PGTCS	
	Total (N=148)	Subset of POS with SGS (N=54)	Total (N=22)	Subset of PGTCS of IGE (N=19)
Median change in seizure frequency per 28 days from baseline				
Treatment duration: 23 weeks	-40.1%	-58.7%	-69.2%	-56.5%
Treatment duration: 52 weeks	-46.1%	-62.8%	-47.9%	-39.7%
50% Responder Rate				
Treatment duration: 23 weeks	46.6%	64.8%	63.6%	63.2%
Treatment duration: 52 weeks	45.9%	66.7%	45.5%	42.1%

Following 23 weeks of perampanel treatment, 42.6% of patients with partial-onset seizures, 43.7% in the subset of partial-onset seizure patients with secondarily generalized seizures, 34.8% of patients with primary generalized tonic-clonic seizures, and 35.3% in the subset of primary generalized tonic-clonic seizures of idiopathic generalized epilepsy (IGE) patients were very much improved or much improved compared to baseline, as assessed by Clinical Global Impression of Change (CGIC). The treatment effects on the CGIC observed above were sustained following 52 weeks of perampanel treatment.

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

There is limited long term safety data in children below 12 years of age. The safety and efficacy of FYCOMPA in children below 4 years of age have not been established yet.

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

Perampanel is around 100% bioavailable. Median Tmax 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.

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

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

Distribution

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

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

Biotransformation

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

Special populations

Hepatic impairment

The pharmacokinetics of perampanel following a single 1 mg dose were evaluated in 12 adults with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 healthy, demographically matched adults. 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 t1/2 was longer in mildly impaired (306 h vs. 125 h) and moderately impaired (295 h vs. 139 h) subjects compared to matched healthy subjects. FYCOMPA has not been studied in paediatric patients with hepatic impairment (see Section 4.2 Dose and method of administration).

Renal impairment

The pharmacokinetics of perampanel have not been formally evaluated in adults and children with renal impairment (see Section 4.2 Dose and method of administration).

Perampanel is eliminated almost exclusively by metabolism followed by rapid excretion of metabolites; only trace amounts of perampanel metabolites are observed in plasma. In a population pharmacokinetics analysis of adults and adolescents, 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 adult and adolescent patients, no dosage adjustment is necessary for adult or adolescent patients with mild renal impairment. Based on the pharmacokinetic properties of perampanel, no dosage adjustment is recommended for paediatric patients with mild renal impairment.

FYCOMPA has not been studied in adults and children with severe renal impairment and adults and children 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 on pooled data from children aged 4 to <12 years, adolescent patients aged ≥12 years, and adults, perampanel clearance decreased with an reduction in body weight. Hence, dose adjustment for children aged 4 to <12 years with a body weight <30kg is necessary (see Section 4.2 Dose and method of administration)

5.3 PRECLINICAL SAFETY DATA

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 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.

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

Film-coated tablets

The 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).

Oral suspension

The oral suspension contains sorbitol solution (70%) (crystallising), Avicel RC – 591, poloxamer, dimeticone 500, polysorbate 65, methylcellulose, silicon dioxide, PEG-40 stearate, benzoic acid, sorbic acid, sulfuric acid, citric acid, sodium benzoate, purified water.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

FYCOMPA 2, 4, 6, 8, 10, 12 mg film coated tablets: 60 months.
FYCOMPA oral suspension: 24 months

The oral suspension should be used within 90 days of first opening.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

FYCOMPA film coated tablets

Store below 30°C. Store in original container.

FYCOMPA oral suspension

Store below 30°C. Do not freeze. Use within 90 days after the first opening of the bottle

6.5 NATURE AND CONTENTS OF CONTAINER

Film-coated tablets

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.

Not all pack sizes may be marketed.

Oral suspension

FYCOMPA oral suspension is supplied in a polyethylene terephthalate (PET) bottle with a child-resistant (CR) polypropylene (PP) closure; each bottle contains 340 mL of suspension and is packaged in an outer cardboard carton.

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.
Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

03 September 2020

10 DATE OF REVISION OF THE TEXT

29 November 2021

Summary Table of changes

Version Number	Section changed	Summary of new information
2	2, 3, 4.2, 4.4,5.2, 6.1, 6.3, 6.5,	Updated to include information regarding a new oral suspension dosage form. Information updated includes composition, presentation, dosing information, special warnings and precautions regarding oral suspension ingredients, pharmacokinetics information, and excipients.
2	4.1, 4.2, 4.4, 4.8, 5.1, 5.2.	Updated to include information to support an indication extension to include paediatric patients aged from 4 to 11. Information updated includes the indication, the dosing information, special warnings and precautions for use in paediatric patients, pharmacodynamic information regarding the paediatric data.
2	5.1	Addition of clinical information regarding withdrawal of background therapies to perampanel monotherapy.
2	5.1	Addition of clinical information regarding adolescent data