PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

Fycompa 2 mg, film-coated tablets

Fycompa 4 mg, film-coated tablets

Fycompa 6 mg, film-coated tablets

Fycompa 8 mg, film-coated tablets

Fycompa 10 mg, film-coated tablets

Fycompa 12 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fycompa 2 mg:

Each film-coated tablet contains 2 mg perampanel.

Excipient(s) with known effect:

Each 2 mg tablet contains 78,5 mg lactose monohydrate.

Contains sugar (lactose monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 4 mg:

Each film-coated tablet contains 4 mg perampanel.

Excipient(s) with known effect:

Each 4 mg tablet contains 157,0 mg lactose monohydrate.

Contains sugar (lactose monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 6 mg:

Each film-coated tablet contains 6 mg perampanel.

Excipient(s) with known effect:

Each 6 mg tablet contains 151,0 mg lactose monohydrate.

Contains sugar (lactose monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 8 mg:

Each film-coated tablet contains 8 mg perampanel.

Excipient(s) with known effect:

Each 8 mg tablet contains 149,0 mg lactose monohydrate.

Contains sugar (lactose monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 10 mg:

Each film-coated tablet contains 10 mg perampanel.

Excipient(s) with known effect:

Each 10 mg tablet contains 147,0 mg lactose monohydrate.

Contains sugar (lactose monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 12 mg:

Each film-coated tablet contains 12 mg perampanel.

Excipient(s) with known effect:

Each 12 mg tablet contains 145,0 mg lactose monohydrate.

Contains sugar (lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Fycompa 2 mg: Orange, round, biconvex film-coated tablet, engraved with ‘E275’ on one side, and ‘2’ on the other.

Fycompa 4 mg: Red, round, biconvex film-coated tablet, engraved with ‘E277’ on one side, and ‘4’ on the other.

Fycompa 6 mg: Pink, round, biconvex film-coated tablet, engraved with ‘E294’ on one side, and ‘6’ on the other.

Fycompa 8 mg: Purple, round, biconvex film-coated tablet, engraved with ‘E295’ on one side, and ‘8’ on the other.

Fycompa 10 mg: Green, round, biconvex film-coated tablet, engraved with ‘E296’ on one side, and ‘10’ on the other.

Fycompa 12 mg: Blue, round, biconvex film-coated tablet, engraved with ‘E297’ on one side, and ‘12’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fycompa is indicated for the primary or adjunctive treatment of partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age and older.

Fycompa is indicated for adjunctive treatment of primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalised epilepsy (IGE).

4.2 Posology and method of administration

Posology

Fycompa must be titrated, according to individual patient response, in order to optimise the balance between

efficacy and tolerability.

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 Fycompa are available, including an oral suspension.

Partial-Onset Seizures (POS)

Monotherapy or adjunctive therapy

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

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

	Adult/ adolescent (12 years and older)	Children (4-11 years); weighing:		
		≥ 30 kg	20 to < 30 kg	< 20 kg
Recommended starting dose	2 mg/day	2 mg/day	1 mg/day	1 mg/day
Titration (incremental steps)	2 mg/day (no more frequently than weekly intervals)	2 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)
Recommended maintenance dose	4-8 mg/day	4-8 mg/day	4-6 mg/day	2-4 mg/day
Titration (incremental steps)	2 mg/day (no more frequently than weekly intervals)	2 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)	0,5 mg/day (no more frequently than weekly intervals)
Recommended maximum dose	12 mg/day	12 mg/day	8 mg/day	6 mg/day

Adults, adolescents age ≥ 12 years

Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg to 8 mg/day.

Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicines that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-weeks intervals. Patients who are taking concomitant medicines that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 4 to 11 years) weighing ≥ 30 kg

Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 8 mg/day.

Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicines that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicines that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 4 to 11 years) weighing 20 kg and < 30 kg

Treatment with Fycompa should be initiated with a dose of 1 mg/day. The dose may be increased based on clinical response and tolerability by increments of 1 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 6 mg/day.

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

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

Children (from 4 to 11 years) weighing < 20 kg

Treatment with Fycompa should be initiated with a dose of 1 mg/day. The dose may be increased based on clinical response and tolerability by increments of 1 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 2 mg/day to 4 mg/day.

Depending upon individual clinical response and tolerability at a dose of 4 mg/day, the dose may be increased by increments of 0,5 mg/day to 6 mg/day. Patients who are taking concomitant medicines that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicines that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Primary Generalised Tonic-Clonic (PGTC) Seizures

Adjunctive therapy

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

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

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

	intervals)	intervals)	intervals)	intervals)
Recommended maintenance dose	Up to 8 mg/day	4-8 mg/day	4-6 mg/day	2-4 mg/day
Titration (incremental steps)	2 mg/day (no more frequently than weekly intervals)	2 mg/day (no more frequently than weekly intervals)	1 mg/day (no more frequently than weekly intervals)	0,5 mg/day (no more frequently than weekly intervals)
Recommended maximum dose	12 mg/day	12 mg/day	8 mg/day	6 mg/day

Adults, adolescents age ≥ 12 years

Treatment with Fycompa should be initiated at a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks, as per half-life considerations described below) to a maintenance dose of up to 8 mg/day.

Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased up to 12 mg/day, which may be effective in some patients (see section 4.4). Patients who are taking concomitant medicines that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicines that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Children (from 7 to 11 years) weighing ≥ 30 kg

Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 8 mg/day.

Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicines that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week

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

Children (from 7 to 11 years) weighing 20 kg and < 30 kg

Treatment with Fycompa should be initiated with a dose of 1 mg/day. The dose may be increased based on clinical response and tolerability by increments of 1 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 4 mg/day to 6 mg/day.

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

Children (from 7 to 11 years) weighing < 20 kg

Treatment with Fycompa should be initiated with a dose of 1 mg/day. The dose may be increased based on clinical response and tolerability by increments of 1 mg (either weekly or every 2 weeks as per half-life considerations described below) to a maintenance dose of 2 mg/day to 4 mg/day.

Depending upon individual clinical response and tolerability at a dose of 4 mg/day, the dose may be increased by increments of 0,5 mg/day to 6 mg/day. Patients who are taking concomitant medicines that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicines that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

Withdrawal

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

Missed doses

Single missed dose: As perampanel has a long half-life; the patient should wait and take their next dose of Fycompa as scheduled.

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

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

Special populations

Elderly (65 years of age and above)

Clinical studies of Fycompa in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Fycompa should be used with caution in elderly taking into account the medicine interaction potential in polymedicated patients (see section 4.4).

Renal impairment

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

Hepatic impairment

Dose increases in patients with mild 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.

Paediatric population

The safety and efficacy of Fycompa have not yet been established yet in children below 4 years of age in the POS indication or in children below 7 years of age in the PGTCS indication. 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). 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 tablet should be swallowed whole without chewing or crushing.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicine. The available data do not exclude the possibility of an increased risk for Fycompa.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Severe cutaneous adverse reactions (SCARs)

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

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

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

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

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

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

Absence and myoclonic seizures

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

Nervous system disorders

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

Hormonal contraceptives

At doses of 12 mg/day Fycompa may decrease the effectiveness of progestative-containing hormonal contraceptives; in this circumstance, additional non-hormonal forms of contraception are recommended

when using Fycompa (see sections 4.5 and 4.6).

Falls

There is an increased risk of falls, particularly in the elderly.

Aggression

Aggressive and hostile behaviour have been reported in patients receiving Fycompa. Aggression, anger and irritability were reported more frequently at higher doses. Most of the reported events were either mild or moderate and patients recovered either spontaneously or with dose adjustment. However, thoughts of harming others, physical assault or threatening behaviour were observed in some patients. Homicidal ideation has been reported in patients. Patients and caregivers should be counselled to alert a healthcare professional immediately if significant changes in mood or patterns of behaviour are noted. The dosage of Fycompa should be reduced if such symptoms occur and should be discontinued immediately if symptoms are severe.

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.

Concomitant CYP3A inducing anti-epileptic medicines

Response rates after addition of Fycompa at fixed doses were less when patients received concomitant CYP3A enzyme-inducing anti-epileptic medicines (carbamazepine, phenytoin, oxcarbazepine) as compared to response rates in patients who received concomitant non-enzyme-inducing anti-epileptic medicines.

Patients' response should be monitored when they are switching from concomitant non-inducer anti-epileptic medicines to enzyme inducing medicines and vice versa. Depending upon individual clinical response and tolerability, the dose may be increased or decreased 2 mg at a time (see **s**ection 4.2).

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

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

Hepatotoxicity

Cases of hepatotoxicity (mainly hepatic enzyme increased) with Fycompa in combination with other anti-epileptic medicines have been reported. If hepatic enzymes elevation is observed, monitoring of liver function should be considered.

Excipients

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

4.5 Interaction with other medicines and other forms of interaction

Hormonal contraceptives

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

Interactions between Fycompa and other anti-epileptic medicines

Potential interactions between Fycompa and other anti-epileptic medicines (AEDs) were assessed in clinical studies. A population PK analysis of three pooled Phase 3 studies in adolescent and adult patients with partial-onset seizures evaluated the effect of Fycompa (up to 12 mg once daily) on the PK of other AEDs.

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

AED co-administered	**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 (phenobarbitone)	20 % decrease	No influence
Phenytoin	2-fold decrease	No influence
Topiramate	20 % decrease	No influence
Valproic acid	No influence	< 10 % decrease
Zonisamide	No influence	No influence

[1)] Active metabolite monohydroxycarbazepine was not assessed.

Based on the results from the population pharmacokinetic analysis of patients with partial-onset seizures and patients with primary generalised tonic-clonic seizures the total clearance of Fycompa was increased when co-administered with carbamazepine (3-fold), and phenytoin or oxcarbazepine (2-fold), which are known inducers of enzymes of metabolism (see section 5.2). This effect should be taken into account and managed when adding or withdrawing these anti-epileptic medicines 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 (phenobarbitone), 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.

Effect of Fycompa on CYP3A substrates

In healthy subjects, Fycompa (6 mg once daily for 20 days) decreased midazolam AUC by 13 %. A larger decrease in exposure of midazolam (or other sensitive CYP3A substrates) at higher Fycompa doses cannot be excluded. (See section 4.4).

Effect of cytochrome P450 inducers on Fycompa pharmacokinetics

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

Effect of cytochrome P450 inhibitors on Fycompa 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.

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

Paediatric population

Interaction studies have only been performed in adults.

In a population pharmacokinetic analysis of adolescent patients age ≥ 12 years and children age 4 to 11 years, there were no notable differences compared to the adult population.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Women of childbearing potential and contraception in males and females

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

Pregnancy

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

Breastfeeding

Studies in lactating rats have shown excretion of perampanel and/or its metabolites in milk (for details see section 5.3). It is not known whether perampanel is excreted in human milk. A risk to the newborns/infants cannot be excluded. Fycompa is not recommended during breastfeeding.

Fertility

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

4.7 Effects on ability to drive and use machines

Fycompa may impair the patient's ability to drive and use machines.

Fycompa may cause dizziness and somnolence. Patients are advised not to drive a vehicle, operate machinery or engage in other potentially hazardous activities until it is known whether Fycompa affects their ability to perform these tasks (see sections 4.4 and 4.5).

4.8 Undesirable effects

Summary of safety profile

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

In the controlled and uncontrolled trials in patients with primary generalised tonic-clonic seizures, 114

subjects have received Fycompa of whom 68 have been treated for 6 months and 36 for longer than 12 months.

Adverse reactions leading to discontinuation:

In the controlled Phase 3 partial-onset seizures clinical trials, the rate of discontinuation as a result of an adverse event was 1,7 %, 4,2 % and 13,7 % in patients randomised to receive Fycompa at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 1,4 % in patients randomised to receive placebo. The adverse events most commonly (≥ 1 % in the total Fycompa group and greater than placebo) leading to discontinuation were dizziness and somnolence.

In the controlled Phase 3 primary generalised tonic-clonic seizures clinical trial, the rate of discontinuation as a result of an adverse reaction was 4,9 % in patients randomised to receive Fycompa 8 mg, and 1,2 % in patients randomised to receive placebo. The adverse reaction most commonly leading to discontinuation (≥ 2 % in the Fycompa group and greater than placebo) was dizziness.

Post-marketing experience

The following adverse reactions have been identified during post approval use of Fycompa.

Skin and subcutaneous tissue disorders: Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

Tabulated summary of adverse reactions

In the table below, adverse reactions were identified based on review of the full Fycompa clinical studies safety database.

The following convention has been used for the classification of adverse reactions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 10 000), not known (cannot be estimated from the available data).

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

System Organ	**Very common**	**Common**	**Uncommon**	**Not known**

Class				
Metabolism and nutrition disorders		Decreased appetite, increased appetite		
Psychiatric disorders		Aggression, anger, anxiety, confusional state	Suicidal ideation, suicide attempt, hallucinations	
Nervous system disorders	Dizziness, somnolence	Ataxia, dysarthria, balance disorder, irritability		
Eye disorders		Diplopia, vision blurred		
Ear and labyrinth disorders		Vertigo		
Gastrointestinal disorders		Nausea		
Skin and subcutaneous tissue disorders				Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)*, Stevens – Johnson Syndrome (SJS)*
Musculoskeletal and connective tissue disorders		Back pain		
General disorders and administrative site conditions		Gait disturbance, fatigue		
Investigations		Weight increased		
Injury, poisoning and procedural		Fall		

complications				

* See section 4.4.

Paediatric population

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

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

Available data in children did not suggest any clinically significant effects of Fycompa 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)). However, long term effects (greater than 1 year) on learning, intelligence, growth, endocrine function, and puberty in children remain unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There have been post-marketing cases of intentional and accidental overdose in paediatric patients with

doses of Fycompa up to 36 mg and in adult patients with doses up to 300 mg. The adverse reactions observed included altered mental status, agitation, aggressive behaviour, coma and depressed level of consciousness. The patients recovered without sequelae.

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

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 Fycompa 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

A 2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics, ATC code: N03AX22.

Mechanism of action

Perampanel is a selective, non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons.

In *in vitro* studies, perampanel inhibited AMPA-induced (but not NMDA-induced) increase in intracellular calcium.

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

Pharmacodynamic effects

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

Psychomotor performance

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

Cognitive function

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

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

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

Alertness and mood

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

Cardiac electrophysiology

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

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.

A 19-week, randomised, double-blind, placebo-controlled study with an open-label extension phase (Study 235) was performed to assess the short-term effects on cognition of Fycompa (target dose range of 8 to 12 mg once daily) as adjunctive therapy in 133 (Fycompa n = 85, placebo n = 48) adolescent patients, aged 12 to less than 18 years old, with inadequately controlled partial-onset seizures. Cognitive function was assessed by the Cognitive Drug Research (CDR) System Global Cognition t-Score, which is a composite score derived from 5 domains testing Power of Attention, Continuity of Attention, Quality of Episodic Secondary Memory, Quality of Working Memory, and Speed of Memory. The mean change (SD) from baseline to end of double-blind treatment (19 weeks) in CDR System Global Cognition t-Score was 1,1 (7,14) in the placebo group and (minus) -1,0 (8,86) in the perampanel group, with the difference between the treatment groups in LS means (95 % CI) = (minus) -2,2 (-5,2, 0,8). There was no statistically significant difference between the treatment groups (p = 0,145). CDR System Global Cognition t-Scores for placebo and perampanel were 41,2 (10,7) and 40,8 (13,0), respectively at the baseline. For patients with perampanel in the open label extension (n = 112), the mean change (SD) from baseline to end of open-label treatment (52 weeks) in CDR System Global Cognition t-Score was (minus) -1,0 (9,91). This was not statistically significant (p = 0,96). After up to 52 weeks of treatment with perampanel (n = 114), no effect on bone growth was observed. No effects on weight, height and sexual development were seen following up to 104 weeks of treatment (n = 114).

An open-label, uncontrolled study (Study 311) was performed to assess the exposure-efficacy relationship of perampanel as adjunctive therapy in 180 paediatric patients (aged 4 to 11 years old) with inadequately

controlled partial-onset seizures or primary generalised tonic-clonic seizures. Patients were titrated over 11 weeks to a target dose of 8 mg/day or the maximum tolerated dose (not to exceed 12 mg/day) for patients not taking concomitant CYP3A-inducing anti-epileptic 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 anti-epileptic medicine. Fycompa dose achieved at the end of titration was maintained for 12 weeks (for a total of 23 weeks of exposure) at the completion of the core study. Patients who entered into Extension Phase were treated for an additional 29 weeks for a total exposure duration of 52 weeks.

In patients with partial-onset seizures (n = 148 patients), the median change in seizure frequency per 28 days, the 50 % or greater responder rate, and seizure-free rate following 23 weeks of perampanel treatment were -40,1 %, 46,6 % (n = 69/148), and 11,5 % (n = 17/148), respectively, for total partial-onset seizures. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 108 patients, -69,4 %), 50 % responder rate (Weeks 40-52: 62,0 %, n = 67/108), and seizure-free rate (Weeks 40-52: 13,0 %, n = 14/108) were sustained following 52 weeks of Fycompa treatment.

In a subset of partial-onset seizure patients with secondarily generalised seizures (n = 54 patients), the corresponding values were -58,7 %, 64,8 % (n = 35/54), and 18,5 % (n = 10/54), respectively, for secondarily generalised tonic-clonic seizures. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 41 patients, -73,8 %), 50 % responder rate (Weeks 40-52: 80,5 %, n = 33/41), and seizure-free rate (Weeks 40-52: 24,4 %, n = 10/41) were sustained following 52 weeks of Fycompa treatment.

In patients with primary generalised tonic-clonic seizures (n = 22 patients, with 19 patients aged 7 to < 12 years and 3 patients aged 4 to < 7 years), the median change in seizure frequency per 28 days, the 50 % or greater responder rate, and seizure-free rate were -69,2 %, 63,6 % (n = 14/22), and 54,5 % (n = 12/22), respectively. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 13 patients, -100,0 %), 50 % responder rate (Weeks 40-52: 61,5 %, n = 8/13), and seizure-free rate (Weeks 40-52: 38,5 %, n = 5/13) were sustained following 52 weeks of Fycompa treatment. These results should be considered cautiously as the number of patients is very small.

Similar results were obtained in a subset of patients with primary generalised tonic-clonic seizures of idiopathic generalised epilepsy (IGE) (n = 19 patients, with 17 patients aged 7 to < 12 years and 2 patients aged 4 to < 7 years; the corresponding values were -56,5 %, 63,2 % (n = 12/19), and 52,6 % (n = 10/19), respectively. The treatment effects on the median reduction in seizure frequency (Weeks 40-52: n = 11 patients, -100,0 %), 50 % responder rate (Weeks 40-52: 54,5 %, n = 6/11), and seizure-free rate (Weeks 40-52: 36,4 %, n = 4/11) were sustained following 52 weeks of Fycompa treatment. These results should be considered cautiously as the number of patients is very small.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Perampanel is approximately 95 % bound to plasma proteins.

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

Biotransformation

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

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

Elimination

Following administration of a radiolabelled perampanel dose either to 8 healthy adults or elderly subjects, approximately 30 % of recovered radioactivity was found in the urine and 70 % in the faeces. In urine and faeces, recovered radioactivity was primarily composed of a mixture of oxidative and conjugated metabolites. The average $t_{1/2}$ of perampanel is 105 hours. When dosed in combination with the strong CYP3A inducer carbamazepine, the average $t_{1/2}$ is 25 hours.

Linearity/non-linearity

In a population PK analysis on pooled data from twenty Phase 1 studies 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 seizures receiving perampanel between 2 and 16 mg/day and two Phase 3 studies in patients with primary generalised tonic-clonic seizures receiving perampanel between 2 and 14 mg/day a linear relationship was found between dose and perampanel plasma concentrations.

Special populations

Hepatic impairment:

The pharmacokinetics of perampanel following a single 1 mg dose were evaluated in 12 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. In a population pharmacokinetic analysis of patients with partial-onset seizures having creatinine clearances ranging from 39 to 160 mL/min and receiving perampanel up to 12 mg/day in placebo-controlled clinical trials, perampanel clearance was not influenced by creatinine clearance. In a population pharmacokinetic analysis of patients with primary generalised tonic-clonic seizures receiving Fycompa up to 8 mg/day in a placebo-controlled clinical study, perampanel clearance was not influenced by baseline creatinine clearance.

Gender:

In a population, pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day and patients with primary generalised tonic-clonic seizures receiving perampanel up to 8 mg/day in placebo-controlled clinical trials, perampanel clearance in females (0,54 L/h) was 18 % lower than in males (0,66 L/h).

Elderly (65 years of age and above):

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

Paediatric population

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

Medicine interaction studies

In vitro assessment of drug interactions

Medicine metabolising enzyme inhibition:

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

Medicine metabolising enzyme induction:

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

5.3 Preclinical safety data

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

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

The excretion into breastmilk was measured in rats at 10 days post-partum. Levels peaked at one hour and were 3,65 times the levels in plasma.

In a pre- and postnatal development toxicity study in rats, abnormal delivery and nursing conditions were observed at maternally toxic doses, and the number of stillbirths was increased in offspring. Behavioural and reproductive development of the offspring was not affected, but some parameters of physical development showed some delay, which is probably secondary to the pharmacology-based CNS effects of perampanel. The placental transfer was relatively low; 0,09 % or less of administered dose was detected in the foetus.

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

perampanel in clinical pathology or histopathology.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Fycompa 2 mg, 4 mg film-coated tablets:

Lactose monohydrate

Low-substituted hydroxypropyl cellulose

Povidone

Magnesium stearate (E470b)

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

Lactose monohydrate

Low-substituted hydroxypropyl cellulose

Povidone

Microcrystalline cellulose

Magnesium stearate (E470b)

Film-coating

Fycompa 2 mg film-coated tablets:

Hypromellose 2910

Talc

Macrogol 8000

Titanium dioxide (E171)

Ferric oxide, yellow (E172)

Ferric oxide, red (E172)

Fycompa 4 mg film-coated tablets:

Hypromellose 2910

Talc

Macrogol 8000

Titanium dioxide (E171)

Ferric oxide, red (E172)

Fycompa 6 mg film-coated tablets:

Hypromellose 2910

Talc

Macrogol 8000

Titanium dioxide (E171)

Ferric oxide, red (E172)

Fycompa 8 mg film-coated tablets:

Hypromellose 2910

Talc

Macrogol 8000

Titanium dioxide (E171)

Ferric oxide, red (E172)

Ferric oxide, black (E172)

Fycompa 10 mg film-coated tablets:

Hypromellose 2910

Talc

Macrogol 8000

Titanium dioxide (E171)

Ferric oxide, yellow (E172)

FD&C Blue #2 Indigo carmine aluminium lake (E132)

Fycompa 12 mg film-coated tablets:

Hypromellose 2910

Talc

Macrogol 8000

Titanium dioxide (E171)

FD&C Blue #2 Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store at or below 30 °C.

Keep blisters in outer carton until required for use.

6.5 Nature and contents of container

Fycompa 2 mg: Packs of 7, 28 and 98 tablets in clear PVC/ silver aluminium blisters.

Fycompa 4 mg: Packs of 7, 28, 84 and 98 tablets in clear PVC/ silver aluminium blisters.

Fycompa 6 mg: Packs of 7, 28, 84 and 98 tablets in clear PVC/ silver aluminium blisters.

Fycompa 8 mg: Packs of 7, 28, 84 and 98 tablets in clear PVC/ silver aluminium blisters.

Fycompa 10 mg: Packs of 7, 28, 84 and 98 tablets in clear PVC/ silver aluminium blisters.

Fycompa 12 mg: Packs of 7, 28, 84 and 98 tablets in clear PVC/ silver aluminium blisters.

Blister strips are packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eisai Pharmaceuticals Africa (Pty) Ltd.

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8 REGISTRATION NUMBERS

Fycompa 2 mg: 47/2.5/1196

Fycompa 4 mg: 47/2.5/1197

Fycompa 6 mg: 47/2.5/1198

Fycompa 8 mg: 47/2.5/1199

Fycompa 10 mg: 47/2.5/1200

Fycompa 12 mg: 47/2.5/1201

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 February 2017

10 DATE OF REVISION OF THE TEXT