SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fycompa Oral suspension
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 Oral suspension

Each ml of oral suspension contains 0.5 mg perampanel

Each bottle of 340 ml contains 170 mg perampanel

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

For the full list of excipients, see section 6.1.

Fycompa 2 mg film-coated tablets

Each film-coated tablet contains 2 mg perampanel.

Excipient with known effect: Each 2 mg tablet contains 78.5 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 4 mg film-coated tablets

Each film-coated tablet contains 4 mg perampanel.

Excipient with known effect: Each 4 mg tablet contains 157.0 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 6 mg film-coated tablets

Each film-coated tablet contains 6 mg perampanel.

Excipient with known effect: Each 6 mg tablet contains 151.0 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 8 mg film-coated tablets

Each film-coated tablet contains 8 mg perampanel.

Excipient with known effect: Each 8 mg tablet contains 149.0 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 10 mg film-coated tablets

Each film-coated tablet contains 10 mg perampanel.

Excipient with known effect: Each 10 mg tablet contains 147.0 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

Fycompa 12 mg film-coated tablets

Each film-coated tablet contains 12 mg perampanel.

Excipient with known effect: Each 12 mg tablet contains 145.0 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

White to off-white suspension

Film-coated tablets:

Fycompa 2 mg film-coated tablets

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

Fycompa 4 mg film-coated tablets

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

Fycompa 6 mg film-coated tablets

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

Fycompa 8 mg film-coated tablets

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

Fycompa 10 mg film-coated tablets

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

Fycompa 12 mg film-coated tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fycompa is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 4 years and older.
Fycompa is indicated for the adjunctive treatment of primary generalized tonic-clonic seizures in patients with epilepsy aged 12 years and older with idiopathic generalised epilepsy.

4.2 Posology and method of administration

Posology
Fycompa must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability.
Perampanel should be taken orally once daily at bedtime. It may be taken with or without food.

The physician should prescribe the most appropriate formulation and strength according to weight and dose.

Switching between the tablet and suspension formulation should be done with caution (see section 5.2).

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

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

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

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

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

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

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

Primary Generalised Tonic-Clonic Seizures
Perampanel at a dose up to 8 mg/day (16 ml/day) has been shown to be effective in primary generalised tonic clonic seizures.

Adults, adolescents age ≥ 12 years
Treatment with Fycompa should be initiated at a dose of 2 mg/day (4 ml/day). The dose may be increased based on clinical response and tolerability by increments of 2 mg (4 ml/day) (either weekly or every 2 weeks, as per half-life considerations described below) to a

maintenance dose of up to 8 mg/day (16 ml/day). Depending upon individual clinical response and tolerability at a dose of 8 mg/day (16 ml/day), the dose may be increased up to 12 mg/day (24 ml/day), which may be effective in some patients (see section 4.4). Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5) should be titrated no more frequently than at 1-week intervals.

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

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

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

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

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

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

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

Paediatric population
Fycompa is not indicated for the treatment of partial-onset seizures in pediatric patients under 4 years old
Fycompa is not indicated for the treatment of primary generalized tonic-clonic seizures in pediatric patients under 12 years old.
The safety and effectiveness of Fycompa for the adjunctive treatment of partial-onset seizures in paediatric patients less than 4 years of age or for the adjunctive treatment of primary generalized tonic-clonic seizures in pediatric patients less than 12 years of age have not been established.

Method of administration

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

It may be taken with or without food. For Fycompa Oral suspension, the product should always be taken under the same conditions.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Severe cutaneous adverse reactions (SCARs)

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

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

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

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

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

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

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

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

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

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

Aggression, psychotic disorder

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

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

Concomitant CYP 3A inducing anti-epileptic medicinal products
Response rates after addition of perampanel at fixed doses were less when patients received concomitant CYP3A enzyme-inducing anti-epileptic medicinal products (carbamazepine, phenytoin, oxcarbazepine) as compared to response rates in patients who received concomitant non-enzyme–inducing anti-epileptic medicinal products. Patient’s response should be monitored when they are switching from concomitant non-inducer anti-epileptic medicinal products to enzyme inducing medicinal products and vice versa. Depending upon individual clinical response and tolerability, the dose may be increased or decreased 2 mg at a time (see section 4.2).

Other concomitant (non- anti-epileptic) cytochrome P450 inducing or inhibiting medicinal products
Patients should be closely monitored for tolerability and clinical response when adding or removing cytochrome P450 inducers or inhibitors, since perampanel plasma levels can be decreased or increased; the dose of perampanel may need to be adjusted accordingly.

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

Excipients
Fructose intolerance
Fycompa Oral suspension contains sorbitol (E420), each mL of Fycompa contains 175 mg sorbitol.
Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

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

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

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

Lactose 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 this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

Hormonal contraceptives

In healthy women receiving 12 mg (but not 4 or 8 mg/day) for 21 days concomitantly with a combined oral contraceptive, Fycompa was shown to decrease the levonorgestrel exposure (mean C_{max} and AUC values were each decreased by 40%). Ethinylestradiol AUC was not affected by 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 4.4).

Interactions between Fycompa and other anti-epileptic medicinal products
Potential interactions between Fycompa (up to 12 mg once daily) and other anti-epileptic drugs (AEDs) were assessed in clinical studies. A population PK analysis of three pooled Phase 3 studies in adolescent and adult patients with partial-onset seizures evaluated the effect of Fycompa (up to 12 mg once daily) on the PK of other AEDs. In another population PK analysis of pooled data from twenty Phase 1 studies in healthy subjects, with Fycompa up to 36 mg, and one Phase 2 and six Phase 3 studies in paediatric, adolescent and adult

patients with partial-onset seizures or primary generalised tonic-clonic seizures, with Fycompa up to 16 mg once daily, evaluated the effect of concomitant AEDs of perampanel clearance.
The effect of these interactions on average steady state concentration is summarised in the following table.

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

1) Active metabolite monohydroxycarbazepine was not assessed.

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

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

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

Perampanel is dosed to clinical effect regardless of other AEDs.

<u>Effect of perampanel on CYP3A substrates</u>
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.

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

Effect of cytochrome P450 inhibitors on perampanel pharmacokinetics
In healthy subjects, the CYP3A4 inhibitor ketoconazole (400 mg once daily for 10 days) increased perampanel AUC by 20% and prolonged perampanel half-life by 15% (67.8 h vs 58.4 h). Larger effects cannot be excluded when perampanel is combined with a CYP3A inhibitor with longer half-life than ketoconazole or when the inhibitor is given for a longer treatment duration.

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

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and contraception in males and females
Fycompa is not recommended in women of childbearing potential not using contraception unless clearly necessary. Fycompa s 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. 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.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

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

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

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

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

System Organ Class	Very common	Common	Uncommon	Not known
Metabolism and nutrition disorders		Decreased appetite Increased appetite		
Psychiatric disorders		Aggression Anger	Suicidal ideation	

System Organ Class	Very common	Common	Uncommon	Not known
		Anxiety Confusional state	Suicide attempt Hallucinations Psychotic disorder	
Nervous system disorders	Dizziness Somnolence	Ataxia Dysarthria Balance disorder Irritability		
Eye disorders		Diplopia Vision blurred		
Ear and labyrinth disorders		Vertigo		
Gastrointestinal disorders		Nausea		
Skin and subcutaneous tissue disorders				Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)* Stevens - Johnson Syndrome (SJS)*
Musculoskeletal and connective tissue disorders		Back pain		
General disorders		Gait disturbance Fatigue		
Investigations		Weight increased		
Injury, poisoning and procedural complications		Fall		

* See section 4.4

Paediatric population

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

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

Available data in children did not suggest any clinically significant effects of perampanel on growth and development parameters including body weight, height, thyroid function, insulin-like growth factor-1 (IGF-1) level, cognition (as assessed by Aldenkamp-Baker neuropsychological assessment schedule [ABNAS]), behaviour (as assessed by Child Behavior Checklist [CBCL]), and dexterity (as assessed by Lafayette Grooved Pegboard

Test [LGPT]). However, long term effects [greater than 1 year] on learning, intelligence, growth, endocrine function, and puberty in children remain unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

There have been post-marketing cases of intentional and accidental overdose in paediatric patients with doses of perampanel up to 36 mg and in adult patients with doses up to 300 mg. The adverse reactions observed included altered mental status, agitation, aggressive behaviour, coma and depressed level of consciousness. The patients recovered without sequelae.
There is no available specific antidote to the effects of perampanel.
General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. In view of its long half-life, the effects caused by perampanel could be prolonged. Because of low renal clearance special interventions such as forced diuresis, dialysis or haemoperfusion are unlikely to be of value.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Perampanel is a first-in-class selective, non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-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. Activation of AMPA receptors by glutamate is thought to be responsible for most fast excitatory synaptic transmission in the brain. In *in vitro* studies, perampanel did not compete with AMPA for binding to the AMPA receptor, but perampanel binding was displaced by noncompetitive AMPA receptor antagonists, indicating that perampanel is a noncompetitive AMPA receptor antagonist. *In vitro*, perampanel inhibited AMPA-induced (but not NMDA-induced) increase in intracellular calcium. *In vivo*, perampanel significantly prolonged seizure latency in an AMPA-induced seizure model.

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

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

Psychomotor performance

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

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

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

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

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

<u>Clinical efficacy and safety</u>

Partial-Onset Seizures

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

Two studies (studies 304 and 305) compared doses of perampanel8 and 12 mg/day with placebo and the third study (study 306) compared doses of perampanel2, 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. Patients experiencing intolerable adverse events could remain on the same dose or have their dose decreased to the previously tolerated dose. In all three trials, the Titration Phase was followed by a Maintenance Phase that lasted 13 weeks, during which patients were to remain on a stable dose of perampanel.

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

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

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

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

Pediatric Use
Safety and effectiveness of Fycompa for the treatment of partial-onset seizures have been established in pediatric patients 4 years of age and older.

The safety and effectiveness of Fycompa in patients 12 years of age and older was established by three randomized double-blind, placebo-controlled, multicenter studies, which included 72 pediatric patients between 12 and 16 years of age exposed to Fycompa.

Use of Fycompa for the treatment of partial-onset seizures in pediatric patients 4 years to less than 12 years of age is supported by evidence from adequate and well-controlled studies of Fycompa in patients 12 years of age and older with partial onset seizures, pharmacokinetic data from adult and pediatric patients, and safety data in 225 pediatric patients 4 years to less than 12 years of age treated with Fycompa.
The safety and efficacy of Fycompa for the adjunctive therapy of primary generalized tonic-clonic seizures in pediatric patients 12 years of age and older was established in a single randomized double-blind, placebo-controlled, multicenter trial (n=164), which included 11 pediatric patients 12 to 16 years of age exposed to Fycompa; an additional 6 patients were treated with Fycompa in the open-label extension of the study.

The safety and effectiveness of Fycompa for the treatment of partial-onset seizures in pediatric patients less than 4 years of age or for the treatment of primary generalized tonic-clonic seizures in pediatric patients less than 12 years of age have not been established.

The safety and effectiveness of Fycompa in patients 12 years of age and older was established by three randomized double-blind, placebo-controlled, multicenter studies, which included 72 pediatric patients between 12 and 16 years of age exposed to Fycompa. Use of

Fycompa for the treatment of partial-onset seizures in pediatric patients 4 years to less than 12 years of age is supported by evidence from adequate and well-controlled studies of Fycompa in patients 12 years of age and older with partial onset seizures, pharmacokinetic data from adult and pediatric patients, and safety data in 225 pediatric patients 4 years to less than 12 years of age treated with Fycompa.

In a population pharmacokinetic analysis of healthy subjects and pediatric and adult patients with partial onset seizures, including 123 children 4 years to less than 12 years of age, 226 adolescents 12 years to less than 18 years of age, and 1912 adults 18 years of age and older, no significant effect of age or body weight on perampanel clearance was found.

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

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

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

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

across time from about week 26 through the end of year 2 Similar results were seen when all seizures and absence vs. myoclonic seizures were evaluated over time.

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

Paediatric population

The 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, ages 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).

5.2 Pharmacokinetic properties

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

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

Perampanel oral suspension is bioequivalent on a mg per mg basis to perampanel tablets under fasted conditions. When a single 12-mg dose of both formulations was administered

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

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

Distribution

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

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

Biotransformation

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

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

Elimination

Following administration of a radiolabeled perampanel dose to either 8 healthy adults or elderly subjects, approximately 30% of recovered radioactivity was found in the urine and 70% in the faeces. In urine and faeces, recovered radioactivity was primarily composed of a mixture of oxidative and conjugated metabolites. In a population pharmacokinetic analysis of pooled data from 19 Phase 1 studies, the average $t_{1/2}$ 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.

Special populations

Hepatic impairment
The pharmacokinetics of perampanel following a single 1 mg dose were evaluated in 12 patients with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 healthy, demographically matched subjects. The mean apparent clearance of unbound perampanel in mildly impaired 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 perampanel up to 8 mg/day in a placebo-controlled clinical study, perampanel clearance was not influenced by baseline creatinine clearance.

Gender
In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day and patients with primary generalised tonic-clonic seizures receiving perampanel up to 8 mg/day in placebo-controlled clinical trials, perampanel clearance in females (0.54 l/h) was18% 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 rang 12 to 74 years) and primary generalised tonic-clonic seizures (age range 12 to 58 years) and receiving perampanel up to 8 or 12 mg/day in placebo-controlled clinical trials, no significant effect of age on perampanel clearance was found. A dose adjustment in the elderly is not considered to be necessary (see section 4.2).

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

<u>Drug interaction studies</u>

In vitro assessment of drug interactions

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

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

5.3 Preclinical safety data

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

2 mg tablet
Core
Lactose monohydrate, Low-substituted hydroxypropyl cellulose, Povidone, Magnesium stearate
Film coating
Hypromellose 2910; Talc; Macrogol 8000; Titanium dioxide; Ferric oxide, yellow; Ferric oxide, red

4 mg tablet
Core
Lactose monohydrate, Low-substituted hydroxypropyl cellulose, Povidone , Magnesium stearate
Film coating
Hypromellose 2910; Talc; Macrogol 8000; Titanium dioxide ; Ferric oxide, red

6 mg tablet
Core
Lactose monohydrate, Low-substituted hydroxypropyl cellulose, Povidone , Microcrystalline cellulose, Magnesium stearate
Film coating
Hypromellose 2910; Talc; Macrogol 8000; Titanium dioxide ; Ferric oxide, red

8 mg tablet
Core
Lactose monohydrate, Low-substituted hydroxypropyl cellulose, Povidone, Microcrystalline cellulose, Magnesium stearate
Film coating
Hypromellose 2910; Talc; Macrogol 8000; Titanium dioxide; Ferric oxide, red; Ferric oxide, black

10 mg tablet
Core
Lactose monohydrate, Low-substituted hydroxypropyl cellulose, Povidone, Microcrystalline cellulose, Magnesium stearate
Film coating
Hypromellose 2910; Talc; Macrogol 8000; Titanium dioxide; Ferric oxide, yellow; FD&C Blue #2 Indigo carmine aluminium lake

12 mg tablet
Core
Lactose monohydrate, Low-substituted hydroxypropyl cellulose, Povidone, Microcrystalline cellulose, Magnesium stearate
Film coating
Hypromellose 2910; Talc; Macrogol 8000; Titanium dioxide; FD&C Blue #2 Indigo carmine aluminium lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Fycompa Oral suspension
After first opening: Use within 90 days and not later than the expiry date indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C. Do not freeze.

6.5 Nature and contents of container

Fycompa Oral suspension
Polyethylene terephthalate (PET) bottle with a child-resistant (CR) polypropylene (PP) closure; each bottle contains 340 ml of suspension in an outer cardboard carton.
Each carton contains one bottle, two 20 mL graduated oral dosing syringes and an LDPE press-in bottle adapter (PIBA). The oral dosing syringes are graduated in 0.5 ml increments.

Film-coated tablets
PVC/aluminium blisters
2 mg – pack of 7, 10, 14, 28, 84, 98
4 mg – packs of 7, 10, 14, 28, 84, 98
6 mg – packs of 7, 10, 14, 28, 84, 98
8 mg – packs of 7, 10, 14, 28, 84, 98
10 mg – packs of 7, 10, 14, 28, 84, 98
12 mg – packs of 7, 10, 14, 28, 84, 98

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER:

Eisai Manufacturing Limited, Hatfield, Hertfordshire, UK

8. MARKETING AUTHORISATION HOLDER

Eisai Israel Ltd., PO Box 8049, Kfar Saba, 4418001 Israel

9. MARKETING AUTHORISATION NUMBER(S)

Fycompa Oral suspension 173-16-36621-99
Fycompa 2mg film-coated tablets – 150-46-33189

Fycompa 4mg film-coated tablets – 150-47-33791

Fycompa 6mg film-coated tablets - 150-48-33792

Fycompa 8mg film-coated tablets – 150-49-33793

Fycompa 10mg film-coated tablets – 150-50-33794

Fycompa 12mg film-coated tablets – 150-51-33795

This leaflet was Revised in May 2023 in accordance with Ministry of Health guidelines.