SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

Each film-coated tablet contains 2 mg perampanel.

Each film-coated tablet contains 4 mg perampanel.

Each film-coated tablet contains 6 mg perampanel.

Each film-coated tablet contains 8 mg perampanel.

Each film-coated tablet contains 10 mg perampanel.

Each film-coated tablet contains 12 mg perampanel.

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

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

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

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

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

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

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

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

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

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

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 12 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.

Posology and method of administration

Posology

Adults and adolescents

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

Perampanel should be taken orally once daily at bedtime.

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.

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 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 has been shown to be effective in primary generalised tonic clonic seizures.

Treatment with Fycompa should be initiated at a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg (either weekly or every 2 weeks, as per half-life considerations described below) to a maintenance dose of up to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased up to 12 mg/day, which may be effective in some patients (see section 4.4). 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.

When withdrawing Fycompa, the dose should be gradually reduced (see section 4.4).

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. Patients should be up-titrated using 2 mg doses no faster than every 2 weeks based on tolerability and effectiveness.

Perampanel dosing for patients with mild and moderate impairment should not exceed 8 mg.

Use in patients with severe hepatic impairment is not recommended.

Paediatric population

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

Method of administration

Fycompa should be taken as single oral dose at bedtime. It may be taken with or without food (see 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 tablets should be swallowed whole without chewing or crushing.

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 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.

Nervous system disorders

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

Oral 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).

End of treatment

It is recommended that discontinuation be undertaken gradually to minimise the potential for rebound seizures (see section 4.2). However, due to its long half-life and subsequent slow

decline in plasma concentrations, perampanel can be discontinued abruptly if absolutely needed.

Falls

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

Aggression

Aggressive and hostile behaviour has been reported in patients receiving perampanel therapy. In perampanel-treated patients in clinical trials, 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 (< 1% in perampanel clinical studies). 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 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 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.

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

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).

Oral contraceptives

In healthy women receiving 12 mg (but not 4 or 8 mg/day) for 21 days concomitantly with a combined oral contraceptive, Fycompa was shown to decrease the levonorgestrel exposure (mean C_{max} and AUC values were each decreased by 40%). Ethinylestradiol AUC was not affected by Fycompa 12 mg whereas C_{max} was decreased by 18%. Therefore, the possibility of decreased efficacy of progestative-containing oral contraceptives should be considered for women needing Fycompa 12 mg/day and an additional reliable 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 and evaluated in the population PK analysis of three pooled Phase 3 studies including patients with partial onset seizures and primary generalised tonic clonic seizures. The effect of these interactions on average steady state concentration is summarised in the following table.

AED coadministered	**Influence of AED on Fycompa concentration**	**Influence of Fycompa on AED concentration**
Carbamazepine	2.75-fold decrease	<10% decrease
Clobazam	No influence	<10% decrease
Clonazepam	No influence	No influence
Lamotrigine	No influence	<10% decrease
Levetiracetam	No influence	No influence
Oxcarbazepine	1.9 fold decrease	35% increase [1)]
Phenobarbital	No influence	No influence
Phenytoin	1.7 fold decrease	No influence
Topiramate	19% decrease	No influence
Valproic Acid	No influence	<10% decrease
Zonisamide	No influence	No influence

Active metabolite monohydroxycarbazepine was not assessed.

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

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

A similar result was seen in a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day and patients with primary generalised tonic clonic seizures receiving perampanel up to 8 mg/day in placebo-controlled clinical trials. The total clearance of Fycompa was increased when administered with carbamazepine (2.75-fold), phenytoin (1.7-fold) and oxcarbazepine (1.9-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.

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

In the epilepsy population pharmacokinetic analysis, perampanel was found to decrease the clearance of oxcarbazepine by 26%. Oxcarbazepine is rapidly metabolised by cytosolic reductase enzyme to the active metabolite, 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.

Effect of cytochrome P450 inducers on perampanel pharmacokinetics

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

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 in the Phase 3 clinical studies, 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.

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 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).

Undesirable effects

Summary of safety profile

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

In the controlled and uncontrolled trial in patients with primary generalised tonic-clonic seizures, 114 subjects have received perampanel of whom 68 have been treated for 6 months and 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%, 4.2% and 13.7% in patients randomised to receive perampanel 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 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% in patients randomized to receive perampanel 8 mg, and 1.2% 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.

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 initial review was done by considering all treatment emergent adverse events (TEAEs) in the double-blind Phase 3 epilepsy studies that occurred in ≥2% of patients in the total Fycompa group. The following were also considered: incidence rates higher than with placebo; severity, seriousness, and rates of discontinuation due to the events; analyses of exposure and dose-response; and consistency with Fycompa pharmacology. TEAEs that occurred in less frequency and met the same criteria as for the more frequent TEAEs were also considered. 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).

The dose of 2 mg/day was not included in this assessment because it is not considered to be an effective dose, and the rates of TEAEs in that dose group were generally comparable to, or lower than, those in the placebo group.

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

System Organ Class	Very common	Common	Uncommon
Metabolism and nutrition disorders		Decreased appetite Increased appetite	
Psychiatric disorders		Aggression Anger Anxiety	Suicidal ideation Suicide attempt

		Confusional state	
Nervous system disorders	Dizziness Somnolence	Ataxia Dysarthria Balance disorder Irritability	
Eye disorders		Diplopia Vision blurred	
Ear and labyrinth disorders		Vertigo	
Gastrointestinal disorders		Nausea	
Musculoskeletal and connective tissue disorders		Back pain	
General disorders		Gait disturbance Fatigue	
Investigations		Weight increased	
Injury, poisoning and procedural complications		Fall	

Paediatric population

Based on the clinical trial database of 165 adolescents, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults.

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:

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

There is limited clinical experience with perampanel overdose in humans. In a report of an intentional overdose that could have resulted in a dose up to 264 mg, the patient experienced events of altered mental status, agitation and aggressive behaviour and recovered without sequelae. There is no available specific antidote to the effects of perampanel. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. In view of its long half-life, the effects caused by perampanel could be prolonged. Because of low renal clearance special interventions such as forced diuresis, dialysis or haemoperfusion are unlikely to be of value.

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.

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.

Clinical efficacy and safety

Partial Onset Seizures

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

Two studies (studies 304 and 305) compared doses of Fycompa 8 and 12 mg/day with placebo and the third study (study 306) compared doses of Fycompa 2, 4 and 8 mg/day with placebo. In all three trials, following a 6-week Baseline Phase to establish baseline seizure frequency prior to randomisation, subjects were randomised and titrated to the randomised dose. During the Titration Phase in all three trials, treatment was initiated at 2 mg/day and increased in weekly increments of 2 mg/day to the target dose. Subjects experiencing intolerable adverse events could remain on the same dose or have their dose decreased to

the previously tolerated dose. In all three trials, the Titration Phase was followed by a Maintenance Phase that lasted 13 weeks, during which patients were to remain on a stable dose of Fycompa.

The pooled 50% responder rates were placebo 19%, 4 mg 29%, 8 mg 35% and 12 mg 35%. A statistically significant effect on the reduction in 28-day seizure frequency (Baseline to Treatment Phase) as compared to the placebo group was observed with Fycompa treatment at doses of 4 mg/day (Study 306), 8 mg/day (Studies 304, 305 and 306), and 12 mg/day (Studies 304 and 305). The 50% responder rates in the 4 mg, 8 mg and 12 mg groups were respectively 23.0%, 31.5%, and 30.0% in combination with enzyme inducing anti-epileptic medicinal products and were 33.3%, 46.5% and 50.0% when 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 Fycompa dose of 4 mg and this benefit is enhanced as the dose is increased to 8 mg/day. No efficacy benefit was observed at the dose of 12 mg as compared to the dose of 8 mg in the overall population. Benefit at the dose of 12 mg was observed in some patients who tolerate the dose of 8 mg and when the clinical response to that dose was insufficient. A clinically meaningful reduction in seizure frequency relative to placebo was achieved as early as the second week of dosing when patients reached a daily dose of 4 mg.

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. There are no data regarding the effects of withdrawal of concomitant anti-epileptic medicinal products to achieve monotherapy with perampanel.

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.

Primary Tonic-Clonic Seizures

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

The 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 subjects 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% of subjects have a modal daily perampanel dose of greater than 4 to 8 mg/day and 16.7% 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% of subjects 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

There are no data regarding the effects of withdrawal of concomitant anti-epileptic medicinal products to achieve monotherapy with perampanel.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Fycompa in one or more subsets of the paediatric population in treatment-resistant epilepsies (localisation-related and age-related epilepsy syndromes) (see section 4.2 for information on adolescent use).

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.

5.2 Pharmacokinetic properties

The pharmacokinetics of perampanel have been studied in healthy adult subjects (age range 18 to 79), adults and adolescents 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. Food does not affect the extent of absorption, but slows the rate of absorption. When administered with food, peak plasma concentrations are reduced and delayed by 2 hours compared with dosing in a fasted state.

Distribution

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

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

Biotransformation

Perampanel is extensively metabolised via primary oxidation and sequential glucuronidation. Primary oxidative metabolism is mediated by CYP3A based on results of *in vitro* studies using recombinant human CYPs and human liver microsomes.

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

Elimination

Following administration of a radiolabeled perampanel dose to 8 healthy elderly subjects, 30% of recovered radioactivity was found in the urine and 70% in the faeces. In urine and faeces, recovered radioactivity was primarily composed of a mixture of oxidative and conjugated metabolites. In a population pharmacokinetic analysis of pooled data from 19 Phase 1 studies, the average $t_{1/2}$ of perampanel was 105 hours. When dosed in combination with the strong CYP3A inducer carbamazepine, the average $t_{1/2}$ was 25 hours.

Linearity/non-linearity

In healthy subjects, plasma concentrations of perampanel increased in direct proportion to administered doses over the range of 2 to 12 mg. In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day and patients with primary generalised tonic clonic seizures receiving perampanel up to 8 mg/day in placebo-controlled clinical trials, a linear relationship was found between dose and perampanel plasma concentrations.

Special populations

Hepatic impairment

The pharmacokinetics of perampanel following a single 1 mg dose were evaluated in 12 subjects with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 healthy, demographically matched subjects. The mean apparent clearance of unbound perampanel in mildly impaired subjects was 188 ml/min vs. 338 ml/min in matched controls, and in moderately impaired subjects was 120 ml/min vs. 392 ml/min in matched controls. The $t_{1/2}$ was longer in mildly impaired (306 h vs. 125 h) and moderately impaired (295 h vs. 139 h) subjects compared to matched healthy subjects.

Renal impairment

The pharmacokinetics of perampanel have not been formally evaluated in patients with renal impairment. Perampanel is eliminated almost exclusively by metabolism followed by rapid excretion of metabolites; only trace amounts of perampanel metabolites are observed in plasma. 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) 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 8 or up to 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 of the adolescent patients in the Phase 3 clinical studies, there were no notable differences between this population and the overall population.

Drug interaction studies

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

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

Fycompa 2 mg- 5 years

Fycompa 4 mg- 5 years

Fycompa 6 mg- 5 years

Fycompa 8 mg- 5 years

Fycompa 10 mg- 5 years

Fycompa 12 mg- 5 years

6.4 Special precautions for storage

Store below 30°C

Nature and contents of container

PVC/aluminium blisters

Fycompa 2 mg – pack of 7, 10, 14, 28, 84, 98

Fycompa 4 mg – packs of 7, 10, 14, 28, 84, 98

Fycompa 6 mg – packs of 7, 10, 14, 28, 84, 98

Fycompa 8 mg – packs of 7, 10, 14, 28, 84, 98

Fycompa 10 mg – packs of 7, 10, 14, 28, 84, 98

Fycompa 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.

7. MANUFACTURER:

Eisai Manufacturing Limited,

Hetfield, Hertfordshire, UK

8. MARKETING AUTHORISATION HOLDER

Megapharm Ltd,

P.O.B 519 Hod Hasharon 4510501, Israel

8. MARKETING AUTHORISATION NUMBER(S)

Fycompa 2mg – 150-46-33189

Fycompa 4mg – 150-47-33791

Fycompa 6mg - 150-48-33792

Fycompa 8mg – 150-49-33793

Fycompa 10mg – 150-50-33794

Fycompa 12mg – 150-51-33795

The format of this leaflet was determained by the ministry of health and its content was checked and approved in Febuary 2016.