表 1.6.2-1 外国における添付文書

	欧州	米国
	作用に対する特異的な解毒剤はない。バイタルサインのモニタリング及び患者の臨床状態の観察を含む一般的な対症療法を行うこと。半減期が長いことから，ペランパネルによる作用は持続する可能性がある。腎クリアランスが低いため，強制利尿，透析，血液灌流などの特別な介入法が奏効する可能性は低い。	作用は治療用量での副作用と同様であり，浮動性めまいが最も多く報告された。後遺症の報告はなかった。 FYCOMPA の過量投与に伴う反応に対する特異的な解毒剤はない。過量投与が生じた場合は，薬剤にかかわらず過量投与に対して行われている標準的な医学的管理手順に従うべきである。十分な気道，酸素供給及び換気を確保すべきであり，心律動及びバイタルサインをモニタリングすることが推奨される。認定された中毒管理センターに連絡を取り，FYCOMPA の過量投与の管理に関する最新情報を求めるべきである。半減期が長いため，FYCOMPA による反応が持続する可能性がある。
自動車運転及び機械操作の能力に及ぼす影響	Fycompa は自動車運転及び機械操作の能力に中等度の影響を及ぼす。ペランパネルは浮動性めまい及び傾眠を誘発する可能性があるため，自動車運転又は機械操作の能力に影響を及ぼす可能性がある。これらの作業を行う能力に対するペランパネルの影響の有無が明らかになるまで，患者は自動車の運転，複雑な機械の操作及び他の潜在的に危険な作業を行うべきでない。	－（自動車運転等に関する注意喚起は「警告及び使用上の注意 神経学的作用」及び「薬物相互作用 アルコール及びその他の中枢神経抑制剤」に記載）
薬物乱用及び薬物依存	－（乱用の可能性については「特別な警告及び使用上の注意」に記載）	**規制薬物** FYCOMPA はペランパネルを含有しており，スケジュール III の規制薬物に指定されている。 **乱用** 処方薬の乱用とは，1 回でも，その薬物から得られる心理的又は生理的作用を求めて，意図的に治療目的外でその薬物を使用することである。薬物乱用の反復により形成される薬物嗜癖の特徴は，有害な影響にもかかわらず薬物を求める強い欲望がある，使用のコントロールが困難である，義務よりも薬物の使用に高い優先順位を付ける，耐性が高くなる，場合により身体的離脱症状がみられる，などである。薬物乱用と薬物嗜癖は別のものであり，身体的依存とは異なる（例えば，乱用は身体的依存を伴わない場合がある）。 ヒト乱用性試験において，快楽的多剤使用者における FYCOMPA（8 mg，24 mg 及び 36 mg）の乱用性が，アルプラゾラム C-IV（1.5 mg 及び 3 mg）及び経口ケタミン C-III（100 mg）との比較により評価された。FYCOMPA の使用により，治療用量を超える用量の 24 mg 及び 36 mg で，「多幸症」に関してケタミン 100 mg 及びアルプラゾラム 3 mg と同程度の反応が認められた。「高揚感」については，FYCOMPA 24 mg 及び 36 mg で，視覚的アナログ尺度（VAS）においてケタミン 100 mg と同程度の反応，アルプラゾラムの両用量より有意に高い反応が認められた。「薬物嗜好性」，「総合的薬物嗜好性」及び「薬物再度摂取」の評価は，ケタミン 100 mg に比べて

表 1.6.2-1 外国における添付文書

	欧州	米国
		FYCOMPA の方がそれぞれ統計学上有意に低かった。さらに，「薬物悪影響」については，FYCOMPA 24 mg 及び 36 mg でケタミン 100 mg より有意に高い反応が認められた。「鎮静」については，FYCOMPA 24 mg 及び 36 mg でアルプラゾラム 3 mg と同程度の反応，ケタミン 100 mg より高い反応が認められた。 さらに，「浮遊感」，「ぼんやりとする」，「超然としている」などの解離現象に関連する VAS 項目について，FYCOMPA の治療用量を超える用量でケタミン 100 mg と同程度の反応，アルプラゾラムの両検討用量より高い反応が認められた。注意すべき点として，傾眠のため，多くの被験者で FYCOMPA の Tmax 付近のデータが欠落した。FYCOMPA の影響に関する上記のデータは過小評価となっている可能性がある。ほとんどの評価項目について，高用量 FYCOMPA の影響の持続時間はアルプラゾラム 3 mg 及びケタミン 100 mg に比べてかなり長かった。 本試験における FYCOMPA 8 mg，24 mg 及び 36 mg 投与後の多幸症の発現率はそれぞれ 37%，46%及び 46%であり，これらの発現率はアルプラゾラム 3 mg 投与後（13%）より高かったが，ケタミン 100 mg 投与後（89%）より低かった。 **依存** 身体的依存は，薬物の急な中止又は大幅な用量減量後にみられる離脱症状を特徴とする。 ラット非臨床試験において，ハンドリングに対する多動，筋固縮，摂餌量及び体重の低下等の離脱症状が観察された。 FYCOMPA は依存及び離脱症状（不安，神経過敏，易刺激性，疲労，嗜眠，無力症，気分動揺，不眠を含む）を起こすことがある。
市販後データ	好酸球増加と全身症状を伴う薬物反応（DRESS）を含む重症皮膚有害反応（SCARs）がペランパネル投与に関連して報告されている。	FYCOMPA は市販後に以下の副作用が報告されている。市販後における副作用の自発報告は母数が不明確なため発現頻度や薬剤との因果関係を正確に評価することは困難な場合がある。 皮膚症状：好酸球増加と全身症状を伴う薬物反応（DRESS） 精神症状：急性精神病，幻覚，妄想，妄想症，譫妄，錯乱状態，失見当識，記憶障害

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FYCOMPA® safely and effectively. See full prescribing information for FYCOMPA®.

FYCOMPA® (perampanel) tablets, for oral use, CIII
FYCOMPA® (perampanel) oral suspension, CIII
Initial U.S. Approval: 2012

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS
See full prescribing information for complete boxed warning.

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA (5.1)**
- **Monitor patients for these reactions as well as for changes in mood, behavior, or personality that are not typical for the patient, particularly during the titration period and at higher doses (5.1)**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening (5.1)**

RECENT MAJOR CHANGES

Indications and Usage (1.1)	9/2018
Dosage and Administration (2.1, 2.3)	9/2018

INDICATIONS AND USAGE

FYCOMPA, a non-competitive AMPA glutamate receptor antagonist, is indicated for:

- Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 4 years of age and older (1.1)
- Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older (1.2)

DOSAGE AND ADMINISTRATION

Dosing in the absence of moderate or strong CYP3A4 inducers

- Starting dose: 2 mg once daily orally at bedtime (2.1, 2.2)
- May increase dose based on clinical response and tolerability by increments of 2 mg once daily no more frequently than at weekly intervals (2.1, 2.2)
- Recommended maintenance dose in monotherapy or adjunctive therapy for partial-onset seizures: 8 mg to 12 mg once daily at bedtime (2.1)
- Recommended maintenance dose in adjunctive therapy for primary generalized tonic-clonic seizures: 8 mg once daily at bedtime (2.2)
- Measure oral suspension using provided adaptor and dosing syringe (2.7)

Dosing in the presence of concomitant moderate or strong CYP3A4 inducers: see section 2.3

Specific Populations

- Mild and Moderate Hepatic Impairment: Maximum recommended daily dose is 6 mg (mild) and 4 mg (moderate) once daily at bedtime (2.4)
- Severe Hepatic Impairment: Not recommended (2.4)
- Severe Renal Impairment or on Hemodialysis: Not recommended (2.5)
- Elderly: Increase dose no more frequently than every 2 weeks (2.6)

DOSAGE FORMS AND STRENGTHS

- Tablets: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg (3)
- Oral Suspension: 0.5 mg/mL (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Suicidal Behavior and Ideation: Monitor for suicidal thoughts or behavior (5.2)
- Neurologic Effects: Monitor for dizziness, gait disturbance, somnolence, and fatigue (5.3)
  Patients should use caution when driving or operating machinery (5.3)
- Falls: Monitor for falls and injuries (5.4)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-Organ Hypersensitivity: Discontinue if no alternate etiology (5.5)
- Withdrawal of Antiepileptic Drugs: In patients with epilepsy, there may be an increase in seizure frequency (5.6)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and ≥1% higher than placebo) include dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, headache, vomiting, contusion, abdominal pain, and anxiety (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Contraceptives: 12 mg once daily may decrease the effectiveness of hormonal contraceptives containing levonorgestrel (7.1)
- Moderate and Strong CYP3A4 Inducers (including carbamazepine, oxcarbazepine, and phenytoin): increase clearance of perampanel and decrease perampanel plasma concentrations. When moderate or strong CYP3A4 inducers are introduced or withdrawn, monitor patients closely. Dose adjustment of FYCOMPA may be necessary (2.3, 7.2)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA (5.1).**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression (5.1).**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA (5.1).**
- **Closely monitor patients particularly during the titration period and at higher doses (5.1).**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening (5.1).**

1 INDICATIONS AND USAGE

1.1 Partial-Onset Seizures

FYCOMPA is indicated for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 4 years of age and older.

1.2 Primary Generalized Tonic-Clonic Seizures

FYCOMPA is indicated as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Partial-Onset Seizures

Monotherapy or Adjunctive Therapy

The recommended starting dosage of FYCOMPA in adults and pediatric patients 4 years of age and older is 2 mg once daily taken orally at bedtime. Increase dosage no more frequently than at weekly intervals by increments of 2 mg once daily based on individual clinical response and tolerability.

The recommended maintenance dose range is 8 mg to 12 mg once daily, although some patients may respond to a dose of 4 mg daily. A dose of 12 mg once daily resulted in somewhat greater reductions in seizure rates than the dose of 8 mg once daily, but with a substantial increase in adverse reactions.

Dosage adjustment is recommended with concomitant use of moderate or strong CYP3A4 enzyme inducing drugs, which include certain antiepileptic drugs (AEDs) *[see Dosage and Administration (2.3)]*.

2.2 Dosage for Primary Generalized Tonic-Clonic Seizures

Adjunctive Therapy

The recommended starting dosage of FYCOMPA in adults and pediatric patients 12 years of age and older is 2 mg once daily taken orally at bedtime. Increase dosage no more frequently than at weekly intervals by increments of 2 mg once daily based on individual clinical response and tolerability.

The recommended maintenance dose is 8 mg once daily taken at bedtime. Patients who are tolerating FYCOMPA at 8 mg once daily and require further reduction of seizures may benefit from a dose increase up to 12 mg once daily if tolerated.

Dosage adjustment is recommended with concomitant use of moderate or strong CYP3A4 enzyme inducing drugs, which include certain AEDs *[see Dosage and Administration (2.3)]*.

2.3 Dosage Modifications with Concomitant Use of Moderate or Strong CYP3A4 Enzyme Inducers
Moderate and strong CYP3A4 inducers, including enzyme-inducing AEDs such as phenytoin, carbamazepine, and oxcarbazepine, cause a reduction in FYCOMPA plasma levels *[see Drug Interactions (7.2), Clinical Pharmacology (12.3)]*. Therefore, in adults and pediatric patients 4 years of age and older receiving these concomitant enzyme-inducing drugs, the recommended starting dosage of FYCOMPA is 4 mg once daily taken orally at bedtime.

Increase dosage by increments of 2 mg once daily based on individual clinical response and tolerability, no more frequently than at weekly intervals. A maintenance dose has not been established in clinical trials. The highest dose studied in patients on concomitant enzyme-inducing AEDs was 12 mg once daily.

When moderate or strong CYP3A4 inducers are introduced or withdrawn from a patient's treatment regimen, the patient should be closely monitored for clinical response and tolerability. Dose adjustment of FYCOMPA may be necessary.

2.4 Dosage Adjustment in Patients with Hepatic Impairment
In patients with mild and moderate hepatic impairment, the starting dose of FYCOMPA is 2 mg once daily. Increase dosage by increments of 2 mg once daily no more frequently than every 2 weeks. The maximum recommended daily dose is 6 mg for patients with mild hepatic impairment and 4 mg for patients with moderate hepatic impairment. FYCOMPA is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.5 Dosage Information for Patients with Renal Impairment
FYCOMPA can be used in patients with moderate renal impairment with close monitoring. A slower titration may be considered, based on clinical response and tolerability. FYCOMPA is not recommended in patients with severe renal impairment or patients undergoing hemodialysis *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.6 Dosage Information for Elderly Patients
In elderly patients, increase dosage no more frequently than every 2 weeks during titration *[see Use in Specific Populations (8.5)]*.

2.7 Administration of Oral Suspension
FYCOMPA oral suspension, 0.5 mg/mL, should be shaken well before every administration. The provided adapter and graduated oral dosing syringe should be used to administer the oral suspension. A household teaspoon or tablespoon is not an adequate measuring device. The adapter, 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 dosing syringe should be inserted into the adapter and the dose withdrawn from the inverted bottle. The cap should be replaced after each use. The cap fits properly when the adapter is in place *[see Instructions for Use]*.

Discard any unused FYCOMPA oral suspension remaining 90 days after first opening the bottle.

3 DOSAGE FORMS AND STRENGTHS
Tablets
- 2 mg tablets: orange, round, debossed with "2" on one side and "Є 275" on the other.
- 4 mg tablets: red, round, debossed with "4" on one side and "Є 277" on the other.
- 6 mg tablets: pink, round, debossed with "6" on one side and "Є 294" on the other.
- 8 mg tablets: purple, round, debossed with "8" on one side and "Є 295" on the other.
- 10 mg tablets: green, round, debossed with "10" on one side and "Є 296" on the other.
- 12 mg tablets: blue, round, debossed with "12" on one side and "Є 297" on the other.

Oral Suspension
0.5 mg/mL white to off-white opaque liquid suspension for oral administration.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Psychiatric and Behavioral Reactions

In the controlled partial-onset seizure clinical trials, hostility- and aggression-related adverse reactions occurred in 12% and 20% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. FYCOMPA-treated patients experienced more hostility- and aggression-related adverse reactions that were serious, severe, and led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients.

In general, in placebo-controlled partial-onset seizure clinical trials, neuropsychiatric events were reported more frequently in patients being treated with FYCOMPA than in patients taking placebo. These events included irritability, aggression, anger, and anxiety, which occurred in 2% or greater of FYCOMPA-treated patients and twice as frequently as in placebo-treated patients. Other symptoms that occurred with FYCOMPA and were more common than with placebo included belligerence, affect lability, agitation, and physical assault. Some of these events were reported as serious and life-threatening. Homicidal ideation and/or threat were exhibited in 0.1% of 4,368 FYCOMPA-treated patients in controlled and open label trials, including non-epilepsy trials. Homicidal ideation and/or threat have also been reported postmarketing in patients treated with FYCOMPA.

In the partial-onset seizure clinical trials, these events occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression. Some patients experienced worsening of their pre-existing psychiatric conditions. Patients with active psychotic disorders and unstable recurrent affective disorders were excluded from the clinical trials. The combination of alcohol and FYCOMPA significantly worsened mood and increased anger. Patients taking FYCOMPA should avoid the use of alcohol *[see Drug Interactions (7.3)]*.

Similar serious psychiatric and behavioral events were observed in the primary generalized tonic-clonic seizure clinical trial.

In healthy volunteers taking FYCOMPA, observed psychiatric events included paranoia, euphoric mood, agitation, anger, mental status changes, and disorientation/confusional state.

In the non-epilepsy trials, psychiatric events that occurred in perampanel-treated patients more often than placebo-treated patients included disorientation, delusion, and paranoia.

In the postmarketing setting, there have been reports of psychosis (acute psychosis, hallucinations, delusions, paranoia) and delirium (delirium, confusional state, disorientation, memory impairment) in patients treated with FYCOMPA *[see Adverse Reactions (6.2)]*.

Patients, their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least 1 month after the last dose of FYCOMPA, and especially when taking higher doses and during the initial few weeks of drug therapy (titration period) or at other times of dose increases. Dose of FYCOMPA should be reduced if these symptoms occur. Permanently discontinue FYCOMPA for persistent severe or worsening psychiatric symptoms or behaviors and refer for psychiatric evaluation.

5.2 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately

one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 patients	Relative Risk: Incidence of Events in drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing FYCOMPA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.3 Neurologic Effects

Dizziness and Gait Disturbance

FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination *[see Adverse Reactions (6.1)]*. In the controlled partial-onset seizure clinical trials, dizziness and vertigo were reported in 35% and 47% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 10% of placebo-treated patients. The gait disturbance related events (including ataxia, gait disturbance, balance disorder, and abnormal coordination) were reported in 12% and 16% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 2% of placebo-treated patients. Elderly patients had an increased risk of these adverse reactions compared to younger adults and pediatric patients.

These adverse reactions occurred mostly during the titration phase and led to discontinuation in 3% of FYCOMPA-treated patients compared to 1% of placebo-treated patients.

These adverse reactions were also observed in the primary generalized tonic-clonic seizure clinical trial.

Somnolence and Fatigue

FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events (including fatigue, asthenia, and lethargy).

In the controlled partial-onset seizure clinical trials, 16% and 18% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, reported somnolence compared to 7% of placebo patients. In the controlled

partial-onset seizure clinical trials, 12% and 15% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, reported fatigue-related events compared to 5% of placebo patients. Somnolence or fatigue-related events led to discontinuation in 2% of FYCOMPA-treated patients and 0.5% of placebo-treated patients. Elderly patients had an increased risk of these adverse reactions compared to younger adults and pediatric patients.

In the controlled partial-onset seizure clinical trials, these adverse reactions occurred mostly during the titration phase.

These adverse reactions were also observed in the primary generalized tonic-clonic seizure clinical trial.

Risk Amelioration
Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known.

5.4 Falls
An increased risk of falls, in some cases leading to serious injuries including head injuries and bone fracture, occurred in patients being treated with FYCOMPA (with and without concurrent seizures). In the controlled partial-onset seizure clinical trials, falls were reported in 5% and 10% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg per day, respectively, compared to 3% of placebo-treated patients. Falls were reported as serious and led to discontinuation more frequently in FYCOMPA-treated patients than placebo-treated patients. Elderly patients had an increased risk of falls compared to younger adults and pediatric patients.

5.5 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including FYCOMPA. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. FYCOMPA should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.6 Withdrawal of Antiepileptic Drugs
There is the potential of increased seizure frequency in patients with seizure disorders when antiepileptic drugs are withdrawn abruptly. FYCOMPA has a half-life of approximately 105 hours so that even after abrupt cessation, blood levels fall gradually. In epilepsy clinical trials FYCOMPA was withdrawn without down-titration. Although a small number of patients exhibited seizures following discontinuation, the data were not sufficient to allow any recommendations regarding appropriate withdrawal regimens. A gradual withdrawal is generally recommended with antiepileptic drugs, but if withdrawal is a response to adverse events, prompt withdrawal can be considered.

6 ADVERSE REACTIONS
The following serious adverse reactions are described below and elsewhere in the labeling:

- Serious Psychiatric and Behavioral Reactions *[see Warnings and Precautions (5.1)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.2)]*
- Neurologic Effects *[see Warnings and Precautions (5.3)]*
- Falls *[see Warnings and Precautions (5.4)]*
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Partial-Onset Seizures
Adult and Adolescent Patients (12 years of age and older)

A total of 1,038 patients receiving FYCOMPA (2, 4, 8, or 12 mg once daily) constituted the safety population in the pooled analysis of the placebo-controlled trials (Studies 1, 2, and 3) in patients with partial-onset seizures. Approximately 51% of patients were female, and the mean age was 35 years.

Adverse Reactions Leading to Discontinuation
In controlled clinical trials (Studies 1, 2, and 3), the rate of discontinuation as a result of an adverse reaction was 3%, 8%, and 19% in patients randomized to receive FYCOMPA at the recommended doses of 4 mg, 8 mg, and 12 mg per day, respectively, and 5% in patients randomized to receive placebo *[see Clinical Studies (14)]*. The adverse reactions most commonly leading to discontinuation (≥1% in the 8 mg or 12 mg FYCOMPA group and greater than placebo) were dizziness, somnolence, vertigo, aggression, anger, ataxia, blurred vision, irritability, and dysarthria *[see Warnings and Precautions (5.1, 5.3)]*.

Most Common Adverse Reactions
Table 2 gives the incidence in the controlled clinical trials (Studies 1, 2, and 3) of the adverse reactions that occurred in ≥2% of patients with partial-onset seizures in the FYCOMPA 12 mg dose group and more frequent than placebo (in order of decreasing frequency for the 12 mg dose group).

The most common dose-related adverse reactions in patients receiving FYCOMPA at doses of 8 mg or 12 mg (≥4% and occurring at least 1% higher than the placebo group) included dizziness (36%), somnolence (16%), fatigue (10%), irritability (9%), falls (7%), nausea (7%), ataxia (5%), balance disorder (4%), gait disturbance (4%), vertigo (4%), and weight gain (4%). For almost every adverse reaction, rates were higher on 12 mg and more often led to dose reduction or discontinuation.

Table 2. Adverse Reactions in Pooled Placebo-Controlled Trials in Adult and Adolescent Patients with Partial-Onset Seizures (Studies 1, 2, and 3) (Reactions ≥ 2% of Patients in Highest FYCOMPA Dose (12 mg) Group and More Frequent than Placebo)

	Placebo n=442 %	FYCOMPA		
		4 mg n=172 %	8 mg n=431 %	12 mg n=255 %
Dizziness	9	16	32	43
Somnolence	7	9	16	18
Headache	11	11	11	13
Irritability	3	4	7	12
Fatigue	5	8	8	12
Falls	3	2	5	10
Ataxia	0	1	3	8
Nausea	5	3	6	8
Vertigo	1	4	3	5
Back pain	2	2	2	5
Dysarthria	0	1	3	4
Anxiety	1	2	3	4
Blurred vision	1	1	3	4
Gait disturbance	1	1	4	4
Weight gain	1	4	4	4
Cough	3	1	1	4
Upper respiratory tract infection	3	3	3	4
Vomiting	3	2	3	4
Hypersomnia	0	1	2	3
Anger	<1	0	1	3
Aggression	1	1	2	3
Balance disorder	1	0	5	3
Diplopia	1	1	1	3
Head injury	1	1	1	3

	Placebo n=442 %	FYCOMPA		
		4 mg n=172 %	8 mg n=431 %	12 mg n=255 %
Hypoaesthesia	1	0	0	3
Pain in extremity	1	0	2	3
Constipation	2	2	2	3
Myalgia	2	1	1	3
Coordination abnormal	0	1	<1	2
Euphoric mood	0	0	<1	2
Confusional state	<1	1	1	2
Hyponatremia	<1	0	0	2
Limb injury	<1	1	1	2
Mood altered	<1	1	<1	2
Arthralgia	1	0	3	2
Asthenia	1	1	2	2
Contusion	1	0	2	2
Memory impairment	1	0	1	2
Musculoskeletal pain	1	1	1	2
Oropharyngeal pain	1	2	2	2
Paraesthesia	1	0	1	2
Peripheral edema	1	1	1	2
Skin laceration	1	0	2	2

Pediatric Patients (4 to <12 years of age)
In two studies in pediatric patients 4 to <12 years of age with epilepsy, a total of 225 patients received FYCOMPA, with 110 patients exposed for at least 6 months, and 21 patients for at least 1 year. Adverse reactions in pediatric patients 4 to <12 years of age were similar to those seen in patients 12 years of age and older

Primary Generalized Tonic-Clonic Seizures
A total of 81 patients receiving FYCOMPA 8 mg once daily constituted the safety population in the placebo-controlled trial in patients with primary generalized tonic-clonic seizures (Study 4). Approximately 57% of patients were female, and the mean age was 27 years.

In the controlled primary generalized tonic-clonic seizure clinical trial (Study 4), the adverse reaction profile was similar to that noted for the controlled partial-onset seizure clinical trials (Studies 1, 2, and 3).

Table 3 gives the incidence of adverse reactions in patients receiving FYCOMPA 8 mg (≥4% and higher than in the placebo group) in Study 4. The most common adverse reactions in patients receiving FYCOMPA (≥10% and greater than placebo) were dizziness (32%), fatigue (15%), headache (12%), somnolence (11%), and irritability (11%).

The adverse reactions most commonly leading to discontinuation in patients receiving FYCOMPA 8 mg (≥2% and greater than placebo) were vomiting (2%) and dizziness (2%).

Table 3. Adverse Reactions in a Placebo-Controlled Trial in Patients with Primary Generalized Tonic-Clonic Seizures (Study 4) (Reactions ≥ 4% of Patients in FYCOMPA Group and More Frequent than Placebo)

	Placebo n=82 %	FYCOMPA 8 mg n=81 %
Dizziness	6	32
Fatigue	6	15
Headache	10	12
Somnolence	4	11
Irritability	2	11
Vertigo	2	9
Vomiting	2	9
Weight gain	4	7
Contusion	4	6
Nausea	5	6
Abdominal pain	1	5
Anxiety	4	5
Urinary tract infection	1	4
Ligament sprain	0	4
Balance disorder	1	4
Rash	1	4

Weight Gain
Weight gain has occurred with FYCOMPA.

In controlled partial-onset seizure clinical trials, FYCOMPA-treated adults gained an average of 1.1 kg (2.5 lbs) compared to an average of 0.3 kg (0.7 lbs) in placebo-treated adults with a median exposure of 19 weeks. The percentages of adults who gained at least 7% and 15% of their baseline body weight in FYCOMPA-treated patients were 9.1% and 0.9%, respectively, as compared to 4.5% and 0.2% of placebo-treated patients, respectively. Clinical monitoring of weight is recommended.

Similar increases in weight were also observed in adult and adolescent patients treated with FYCOMPA in the primary generalized tonic-clonic seizure clinical trial.

Elevated triglycerides
Increases in triglycerides have occurred with FYCOMPA use.

Comparison of Sex and Race
No significant sex differences were noted in the incidence of adverse reactions.

Although there were few non-Caucasian patients, no differences in the incidence of adverse reactions compared to Caucasian patients were observed.

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

Dermatologic: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.5)]*
Psychiatric: Acute psychosis, hallucinations, delusions, paranoia, delirium, confusional state, disorientation, memory impairment *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Contraceptives

With concomitant use, FYCOMPA at a dose of 12 mg per day reduced levonorgestrel exposure by approximately 40% *[see Clinical Pharmacology (12.3)]*. Use of FYCOMPA with contraceptives containing levonorgestrel may render them less effective. Additional non-hormonal forms of contraception are recommended *[see Use in Specific Populations (8.3)]*.

7.2 Moderate and Strong CYP3A4 Inducers

The concomitant use of known moderate and strong CYP3A4 inducers including carbamazepine, phenytoin, or oxcarbazepine with FYCOMPA decreased the plasma levels of perampanel by approximately 50-67% *[see Clinical Pharmacology (12.3)]*. The starting doses for FYCOMPA should be increased in the presence of moderate or strong CYP3A4 inducers *[see Dosage and Administration (2.3)]*.

When these moderate or strong CYP3A4 inducers are introduced or withdrawn from a patient's treatment regimen, the patient should be closely monitored for clinical response and tolerability. Dose adjustment of FYCOMPA may be necessary *[see Dosage and Administration (2.3)]*.

7.3 Alcohol and Other CNS Depressants

The concomitant use of FYCOMPA and CNS depressants including alcohol may increase CNS depression. A pharmacodynamic interaction study in healthy subjects found that the effects of FYCOMPA on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol *[see Clinical Pharmacology (12.3)]*. Multiple dosing of FYCOMPA 12 mg per day also enhanced the effects of alcohol to interfere with vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when FYCOMPA is used in combination with other CNS depressants. Care should be taken when administering FYCOMPA with these agents. Patients should limit activity until they have experience with concomitant use of CNS depressants (e.g., benzodiazepines, narcotics, barbiturates, sedating antihistamines). Advise patients not to drive or operate machinery until they have gained sufficient experience on FYCOMPA to gauge whether it adversely affects these activities.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as FYCOMPA, during pregnancy. Encourage women who are taking FYCOMPA during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org.

Risk Summary

There are no adequate data on the developmental risk associated with use in pregnant women. In animal studies, perampanel induced developmental toxicity in pregnant rat and rabbit at clinically relevant doses *[see Data]*. In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Oral administration of perampanel (1, 3, or 10 mg/kg/day) to pregnant rats throughout organogenesis resulted in an increase in visceral abnormalities (diverticulum of the intestine) at all doses tested; maternal toxicity was observed at the mid and high doses. In a dose-ranging study at higher oral doses (10, 30, or 60 mg/kg/day), embryo lethality and reduced fetal body weight were observed at the mid and high doses tested. The lowest dose tested (1 mg/kg/day) is similar to a human dose of 8 mg/day based on body surface area (mg/m^2).

Upon oral administration of perampanel (1, 3, or 10 mg/kg/day) to pregnant rabbits throughout organogenesis, embryo lethality and maternal toxicity were observed at the mid and high doses tested; the no-effect dose for embryo-fetal developmental toxicity in rabbit (1 mg/kg/day) is approximately 2 times a human dose of 8 mg/day based on body surface area (mg/m^2).

Oral administration of perampanel (1, 3, or 10 mg/kg/day) to rats throughout gestation and lactation resulted in fetal and pup deaths at the mid and high doses (associated with maternal toxicity) and delayed sexual maturation in males and females at the highest dose tested. No effects were observed on measures of neurobehavioral or reproductive function in the offspring. The no-effect dose for pre- and postnatal developmental toxicity in rat (1 mg/kg/day) is similar to a human dose of 8 mg/day based on body surface area (mg/m^2).

8.2 Lactation

Risk Summary

There are no data on the presence of perampanel in human milk, the effects on the breastfed child, or the effects of the drug on milk production. Perampanel and/or its metabolites are present in rat milk, and are detected at concentrations higher than that in maternal plasma.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FYCOMPA and any potential adverse effects on the breastfed child from FYCOMPA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Use of FYCOMPA may reduce the efficacy of hormonal contraceptives containing levonorgestrel. Advise women taking FYCOMPA who are using a levonorgestrel-containing contraceptive to use an additional non-hormonal form of contraception while using FYCOMPA and for a month after discontinuation *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

8.4 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 *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*. 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 *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

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 *[see Clinical Studies (14.2)]*.

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.

Juvenile Animal Data

Oral administration of perampanel (1, 3, 3/10/30 mg/kg/day; high dose increased on postnatal days [PND] 28 and 56) to young rats for 12 weeks starting on PND 7 resulted in reduced body weight, reduced growth, neurobehavioral impairment (water maze performance and auditory startle habituation) at the mid and high doses, and delayed sexual maturation at the high doses. CNS signs (reduced activity, incoordination, excessive grooming/scratching), pup death, decreased hindlimb

splay, and decreased hindlimb grip strength were observed at all doses. Effects on pup body weight, pup growth, hindlimb splay, impairment in the water maze performance, and auditory startle persisted after dosing was stopped. A no-effect dose for postnatal developmental toxicity was not identified in this study.

Oral administration of perampanel (1, 5, 5/10 mg/kg/day; high dose increased on PND 56) to juvenile dogs for 33 weeks, starting on PND 42, resulted in CNS signs (incoordination, excessive grooming/licking/scratching, spatial disorientation, and/or ataxic gait) at all doses tested.

8.5 Geriatric Use
Clinical studies of FYCOMPA did not include sufficient numbers of patients aged 65 and over to determine the safety and efficacy of FYCOMPA in the elderly population. Because of increased likelihood for adverse reactions in the elderly, dosing titration should proceed slowly in patients aged 65 years and older *[see Dosage and Administration (2.5)]*.

8.6 Hepatic Impairment
Use of FYCOMPA in patients with severe hepatic impairment is not recommended, and dosage adjustments are recommended in patients with mild or moderate hepatic impairment *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment
Dose adjustment is not required in patients with mild renal impairment. FYCOMPA should be used with caution in patients with moderate renal impairment, and slower titration may be considered. Use in patients with severe renal impairment or patients undergoing hemodialysis is not recommended *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
FYCOMPA contains perampanel and is listed as a Schedule III controlled substance.

9.2 Abuse
Prescription drug abuse is the intentional non-therapeutic use of a drug, even once, for its rewarding psychological or physiological effects. Drug addiction, which develops after repeated drug abuse, is characterized by a strong desire to take a drug despite harmful consequences, difficulty in controlling its use, giving a higher priority to drug use than to obligations, increased tolerance, and sometimes physical withdrawal. Drug abuse and drug addiction are separate and distinct from physical dependence (for example, abuse may not be accompanied by physical dependence) *[see Drug Abuse and Dependence (9.3)]*.

Studies of human abuse potential were performed to evaluate the abuse potential of FYCOMPA (8 mg, 24 mg, and 36 mg) as compared to alprazolam C-IV (1.5 mg and 3 mg), and oral ketamine C-III (100 mg) in recreational polydrug users. Supra-therapeutic doses of FYCOMPA 24 and 36 mg produced responses for “Euphoria” that were similar to ketamine 100 mg and alprazolam 3 mg. For “High,” FYCOMPA 24 mg and 36 mg produced responses comparable to ketamine 100 mg and significantly higher than both doses of alprazolam on a visual analog scale (VAS). “Drug Liking,” “Overall Drug Liking,” and “Take Drug Again” for FYCOMPA were each statistically lower than ketamine 100 mg. In addition, for “Bad Drug Effects,” FYCOMPA 24 mg and 36 mg produced responses significantly higher than ketamine 100 mg.
For “Sedation,” FYCOMPA 24 and 36 mg produced responses similar to alprazolam 3 mg and higher than ketamine 100 mg.

Additionally, on VAS measures related to dissociative phenomena such as “Floating,” “Spaced Out,” and “Detached,” FYCOMPA at supra-therapeutic doses produced responses similar to ketamine 100 mg and greater than both doses of alprazolam tested. Of note, due to somnolence a number of subjects had missing data around T_{max} of FYCOMPA. The above described data might represent an underestimate of FYCOMPA’s effects. The duration of effects of higher doses of FYCOMPA on the majority of measures was much greater than alprazolam 3 mg and ketamine 100 mg.

In this study, the incidence of euphoria following FYCOMPA administration 8 mg, 24 mg, and 36 mg was 37%, 46%, 46%, respectively, which was higher than alprazolam 3 mg (13%) but lower than ketamine 100 mg (89%).

9.3 Dependence
Physical dependence is characterized by withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug.

A nonclinical dependence study in rats demonstrated withdrawal symptoms, including hyperreactivity to handling, muscle rigidity, and decreases in food consumption and body weights.

FYCOMPA may cause dependence and withdrawal symptoms that may include anxiety, nervousness, irritability, fatigue, lethargy, asthenia, mood swings, and insomnia.

10 OVERDOSAGE

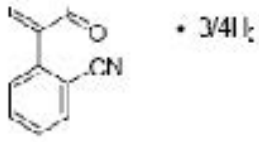
There is limited clinical experience with FYCOMPA overdose. The highest reported overdose (approximately 264 mg) was intentional. This patient experienced serious adverse reactions of altered mental status, agitation, and aggressive behavior and recovered without sequelae. In general, the adverse reactions associated with overdoses were similar to the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae.

There is no available specific antidote to the overdose reactions of FYCOMPA. In the event of overdose, standard medical practice for the management of any overdose should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital sign measurement is recommended. A certified poison control center should be contacted for updated information on the management of overdose with FYCOMPA. Due to its long half-life, the reactions caused by FYCOMPA could be prolonged.

11 DESCRIPTION
FYCOMPA tablets and oral suspension contain perampanel a non-competitive AMPA receptor antagonist as a 4:3 hydrate.

The chemical name of the active ingredient is 2-(1′,6′-dihydro-6′-oxo-1′-phenyl[2,3′-bipyridin]-5′-yl)-benzonitrile, hydrate (4:3).

The molecular formula is $C_{23}H_{15}N_3O \cdot ¾H_2O$ and the molecular weight is 362.90 (349.39 for anhydrous perampanel). It is a white to yellowish white powder. It is freely soluble in 1-methyl-2-pyrrolidinone, sparingly soluble in acetonitrile and acetone, slightly soluble in methanol, ethanol and ethyl acetate, very slightly soluble in 1-octanol and diethyl ether, and practically insoluble in heptane and water. The chemical structure is:



・3/4H2

Tablets
FYCOMPA tablets are round, bi-convex, film-coated tablets containing 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg of perampanel. Tablets contain the following inactive ingredients: lactose monohydrate, low substituted hydroxypropyl cellulose, povidone, microcrystalline cellulose, magnesium stearate, hypromellose, polyethylene glycol, talc, and titanium dioxide. Tablets of different strengths may contain yellow ferric oxide (10 mg and 2 mg), red ferric oxide (2 mg, 4 mg, 6 mg, 8 mg), black ferric oxide (8 mg), and FD&C Blue No. 2 (indigo carmine) aluminum lake (10 mg and 12 mg).

Oral Suspension
FYCOMPA oral suspension is a white to off-white opaque liquid providing perampanel in a concentration of 0.5 mg/mL. The oral suspension contains the following inactive ingredients: sorbitol, microcrystalline cellulose, carboxymethylcellulose sodium, poloxamer, simethicone, citric acid, sodium benzoate and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Perampanel is a non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal over excitation.

The precise mechanism by which FYCOMPA exerts its antiepileptic effects in humans is unknown.

12.2 Pharmacodynamics

Psychomotor Performance

In a healthy volunteer study to assess the effects of FYCOMPA tablets on psychomotor performance using a standard battery of assessments including simulated driving, single and multiple daily doses of FYCOMPA 4 mg did not impair simple psychomotor tasks, driving performance, or sensorimotor coordination. Single and multiple doses of 8 mg and 12 mg impaired psychomotor performance in a dose-related manner. Car handling ability was impaired after dosing of FYCOMPA 12 mg, but postural stability was not significantly impaired. Performance testing returned to baseline within 2 weeks of cessation of FYCOMPA dosing.

Interactions with Alcohol

In the above study (*see Psychomotor Performance*), when administered to healthy subjects receiving alcohol to achieve a blood concentration of 80-100 mg/100 mL, FYCOMPA consistently impaired simple psychomotor performance after single doses of 4 to 12 mg, and after 21 days of multiple 12 mg/day doses. The effects of FYCOMPA on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol. FYCOMPA enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion, and depression.

Potential to Prolong QT Interval

In a placebo-controlled thorough QT study of perampanel in healthy subjects, there was no evidence that perampanel caused QT interval prolongation of clinical significance at doses of 6 or 12 mg (i.e., the upper bound of the 95% confidence interval for the largest placebo-adjusted baseline-corrected QTc was below 10 msec). The exposures observed with the 12 mg dose in this study will not cover the exposures expected in patients with hepatic impairment taking doses over 6 mg/day. At the highest recommended dose (12 mg), perampanel did not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Pharmacokinetics of perampanel are similar in healthy subjects, patients with partial-onset seizures, and patients with primary generalized tonic-clonic seizures. The half-life of perampanel is about 105 hours, so that steady state is reached in about 2-3 weeks. AUC of perampanel increased in a dose-proportional manner after single-dose administration of 0.2-12 mg tablets and after multiple-dose administration of 1-12 mg tablets once daily.

FYCOMPA oral suspension has comparable bioavailability to FYCOMPA tablets under steady state. Both formulations may be used interchangeably.

The pharmacokinetics of perampanel are similar when used as monotherapy or as adjunctive therapy for the treatment of partial-onset seizures (in the absence of concomitant moderate or strong CYP3A4 inducers).

Absorption

Perampanel is rapidly and completely absorbed after oral administration with negligible first-pass metabolism. Median time to reach peak concentration (t_{max}) ranged from 0.5 to 2.5 hours under fasted condition. Co-administration of FYCOMPA tablet with a high fat meal had no impact on the total exposure (AUC_{0-inf}) of perampanel and reduced the peak plasma concentration (C_{max}) of perampanel by 11%-40%. The t_{max} was delayed by approximately 1-3 hours in fed state compared to that under fasted conditions.

Distribution

Data from *in vitro* studies indicate that, in the concentration range of 20 to 2000 ng/mL, perampanel is approximately 95-96% bound to plasma proteins, mainly bound to albumin and α1-acid glycoprotein. Blood to plasma ratio of perampanel is 0.55-0.59.

Metabolism

Perampanel is extensively metabolized via primary oxidation and sequential glucuronidation. Oxidative metabolism is primarily mediated by CYP3A4/5 and to a lesser extent by CYP1A2 and CYP2B6, based on results of *in vitro* studies using recombinant human CYPs and human liver microsomes. Other CYP enzymes may also be involved.

Following administration of radiolabeled perampanel, unchanged perampanel accounted for 74-80% of total radioactivity in systemic circulation, whereas only trace amounts of individual perampanel metabolites were detected in plasma.

Elimination

Following administration of a radiolabeled perampanel tablet dose to 8 healthy elderly subjects, 22% of administered radioactivity was recovered in the urine and 48% in the feces. In urine and feces, recovered radioactivity was primarily composed of a mixture of oxidative and conjugated metabolites. Population pharmacokinetic analysis of pooled data from 19 Phase 1 studies reported that $t_{1/2}$ of perampanel was 105 hours on average. Apparent clearance of perampanel in healthy subjects and patients was approximately 12 mL/min.

Specific Populations

Hepatic Impairment

The pharmacokinetics of perampanel following a single 1 mg tablet dose were evaluated in 12 subjects with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 demographically matched healthy subjects. The total (free and protein bound) exposure ($AUC_{0\text{-}inf}$) of perampanel was 50% greater in subjects with mild hepatic impairment and more than doubled (2.55-fold) in subjects with moderate hepatic impairment compared to their healthy controls. The $AUC_{0\text{-}inf}$ of free perampanel in subjects with mild and moderate hepatic impairment was 1.8-fold and 3.3-fold, respectively, of those in matched healthy controls. The $t_{1/2}$ was prolonged in subjects with mild impairment (306 vs. 125 hours) and moderate impairment (295 vs. 139 hours). Perampanel has not been studied in subjects with severe hepatic impairment *[see Dosage and Administration (2.4), Use in Specific Populations (8.6)]*.

Renal Impairment

A dedicated study has not been conducted to evaluate the pharmacokinetics of perampanel in patients with renal impairment. Population pharmacokinetic analysis was performed on pooled data from patients with partial-onset seizures and receiving FYCOMPA tablets up to 12 mg/day in placebo-controlled clinical trials. Results showed that perampanel apparent clearance was decreased by 27% in patients with mild renal impairment (creatinine clearance 50-80 mL/min) compared to patients with normal renal function (creatinine clearance >80 mL/min), with a corresponding 37% increase in AUC. Considering the substantial overlap in the exposure between normal and mildly impaired patients, no dosage adjustment is necessary for patients with mild renal impairment. Perampanel has not been studied in patients with severe renal impairment and patients undergoing hemodialysis *[see Dosage and Administration (2.5), Use in Specific Populations (8.7)]*.

Sex

In a population pharmacokinetic analysis of patients with partial-onset and primary generalized tonic-clonic seizures receiving FYCOMPA tablets in placebo-controlled clinical trials, perampanel apparent clearance in females (0.54 L/hr) was 18% lower than in males (0.66 L/hr). No dosage adjustment is necessary based on sex.

Pediatrics

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.

Geriatrics

In a population pharmacokinetic analysis of patients with partial-onset seizures and primary generalized tonic-clonic seizures ranging in age from 12 to 74 years receiving FYCOMPA tablets in placebo-controlled trials, no significant effect of age on perampanel apparent clearance was found *[see Dosage and Administration (2.6), Use in Specific Populations (8.5)]*.

Race

In a population pharmacokinetic analysis of patients with partial-onset seizures and primary generalized tonic-clonic seizures, which included 614 Caucasians, 15 Blacks, 4 Japanese, 4 American Indians/Alaska Natives, 79 Chinese and 108

other Asians receiving FYCOMPA tablets in placebo-controlled trials, no significant effect of race on perampanel apparent clearance was found. No dosage adjustment is necessary.

Drug Interaction Studies

***In Vitro* Assessment of Drug Interactions**

Drug Metabolizing Enzymes

In human liver microsomes, perampanel at a concentration of 30 µmol/L, about 10 fold the steady state C_{max} at a 12 mg dose, had a weak inhibitory effect on CYP2C8, CYP3A4, UGT1A9, and UGT2B7. Perampanel did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, UGT1A1, UGT1A4, and UGT1A6 up to a concentration of 30 µmol/L.

Compared with positive controls (including phenobarbital and rifampin), perampanel was found to weakly induce CYP2B6 (30 µmol/L) and CYP3A4/5 (≥3 µmol/L) in cultured human hepatocytes. Perampanel also induced UGT1A1 (≥3 µmol/L) and UGT1A4 (30 µmol/L). Perampanel did not induce CYP1A2 at concentrations up to 30 µmol/L.

Transporters

In vitro studies showed that perampanel is not a substrate or significant inhibitor of the following: organic anion transporting polypeptides 1B1 and 1B3; organic anion transporters 1, 2, 3, and 4; organic cation transporters 1, 2, and 3; efflux transporters P-glycoprotein and Breast Cancer Resistance Protein.

***In Vivo* Assessment of Drug Interactions**

Drug Interactions with AEDs

Effect of Concomitant AEDs on FYCOMPA:

Carbamazepine. As an inducer of CYP enzymes, carbamazepine increases perampanel clearance. Steady state administration of carbamazepine at 300 mg BID in healthy subjects reduced the C_{max} and $AUC_{0\text{-}inf}$ of a single 2 mg tablet dose of perampanel by 26% and 67%, respectively. The $t_{1/2}$ of perampanel was shortened from 56.8 hours to 25 hours. In clinical studies examining partial-onset and primary generalized tonic-clonic seizures, a population pharmacokinetic analysis showed that perampanel AUC was reduced by 64% in patients on carbamazepine compared to the AUC in patients not on enzyme-inducing AEDs *[see Dosage and Administration (2.3), Drug Interactions (7.2)]*.

Oxcarbazepine. In clinical studies examining partial-onset and primary generalized tonic-clonic seizures, a population pharmacokinetic analysis showed that perampanel AUC was reduced by 48% in patients on oxcarbazepine compared to patients not on enzyme-inducing AEDs *[see Dosage and Administration (2.3), Drug Interactions (7.2)]*.

Eslicarbazepine. Eslicarbazepine is structurally similar to oxcarbazepine and thus may also reduce perampanel plasma concentrations when used concomitantly.

Phenytoin. In clinical studies examining partial-onset and primary generalized tonic-clonic seizures, a population pharmacokinetic analysis showed that perampanel AUC was reduced by 43% in patients on phenytoin compared to patients not on enzyme-inducing AEDs *[see Dosage and Administration (2.3), Drug Interactions (7.2)]*.

Phenobarbital and Primidone: In a population pharmacokinetic analysis of patients with partial-onset and primary generalized tonic-clonic seizures in clinical trials (40 patients co-administered phenobarbital and 9 patients co-administered primidone), no significant effect on perampanel AUC was found. A modest effect of phenobarbital and primidone on perampanel concentrations cannot be excluded.

Topiramate: Population pharmacokinetic analysis of patients with partial-onset and primary generalized tonic-clonic seizures in clinical trials showed that perampanel AUC was reduced by approximately 19% in patients on topiramate compared to patients not on enzyme-inducing AEDs.

Other AEDs: Population pharmacokinetic analysis of patients with partial-onset and primary generalized tonic-clonic seizures in clinical trials showed that clobazam, clonazepam, lamotrigine, levetiracetam, valproate, and zonisamide did not have an effect on perampanel clearance.

Other strong CYP3A inducers (e.g., rifampin, St. John's wort) may also greatly increase clearance of perampanel and reduce perampanel plasma concentrations *[see Drug Interactions (7.2)]*.

Effect of FYCOMPA on Concomitant AEDs:
FYCOMPA tablets up to 12 mg/day did not significantly affect the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide based on a population pharmacokinetic analysis of patients with partial-onset seizures in clinical trials. FYCOMPA had a statistically significant effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid, but the increases in clearance of these drugs were each less than 10% at the highest perampanel dose evaluated (12 mg/day). FYCOMPA co-administration resulted in a 26% decrease in oxcarbazepine clearance and increased its concentrations. The concentrations of 10-monohydroxy metabolite (MHD), the active metabolite of oxcarbazepine, were not measured.

Drug-drug Interaction Studies with Other Drugs

Effect of Other Drugs on FYCOMPA

Ketoconazole. Co-administration of single 1-mg dose of perampanel tablet with 400 mg once daily doses of ketoconazole, a strong CYP3A4 inhibitor, for 8 days in healthy subjects prolonged perampanel $t_{1/2}$ by 15% (67.8 vs. 58.4 hours) and increased $AUC_{0\text{-}inf}$ by 20%.

Contraceptives. Perampanel C_{max} and $AUC_{0\text{-}72h}$ were not altered when a single 6-mg dose of perampanel tablet was administered to healthy female subjects following a 21-day course of oral contraceptives containing ethinylestradiol 30 µg and levonorgestrel 150 µg.

Effect of FYCOMPA on Other Drugs
Midazolam. Perampanel administered as 6 mg tablet once daily doses for 20 days decreased $AUC_{0\text{-}inf}$ and C_{max} of midazolam (a CYP3A4 substrate) by 13% and 15%, respectively, in healthy subjects.

Contraceptives. Co-administration of perampanel 4 mg tablet once daily with an oral contraceptive containing ethinylestradiol 30 µg and levonorgestrel 150 µg for 21 days did not alter C_{max} or $AUC_{0\text{-}24h}$ of either ethinylestradiol or levonorgestrel in healthy female subjects. In another study, a single dose of the oral contraceptive was administered following 21-day once daily dosing of FYCOMPA 12 mg or 8 mg tablets in healthy females. FYCOMPA at 12 mg did not alter $AUC_{0\text{-}24h}$ of ethinylestradiol but decreased its C_{max} by 18%, and also decreased C_{max} and $AUC_{0\text{-}24h}$ of levonorgestrel by 42% and 40%, respectively. FYCOMPA at 8 mg did not have significant effect on C_{max} or $AUC_{0\text{-}24h}$ of either ethinylestradiol or levonorgestrel, with a decrease in $AUC_{0\text{-}24h}$ of levonorgestrel (9% on average) *[see Drug Interactions (7.1), Use in Specific Populations (8.3)]*.

Levodopa. Perampanel tablets administered as 4 mg once daily doses for 19 days had no effect on C_{max} and $AUC_{0\text{-}inf}$ of levodopa in healthy subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis
Perampanel was administered orally to mice (1, 3, 10, or 30 mg/kg/day) and rats (10, 30, or 100 mg/kg/day in males; 3, 10, or 30 mg/kg/day in females) for up to 104 weeks. There was no evidence of drug-related tumors in either species. Plasma perampanel exposures (AUC) at the highest doses tested were less than that in humans dosed at 8 mg/day.

Mutagenesis
Perampanel was negative in the *in vitro* Ames and mouse lymphoma *tk* assays, and in the *in vivo* rat micronucleus assay.

Impairment of Fertility
In male and female rats administered perampanel (oral doses of 1, 10, or 30 mg/kg/day) prior to and throughout mating and continuing in females to gestation day 6, there were no clear effects on fertility. Prolonged and/or irregular estrus cycles were observed at all doses but particularly at the highest dose tested. Plasma perampanel exposures (AUC) at all doses were lower than that in humans dosed at 8 mg/day.

14 CLINICAL STUDIES

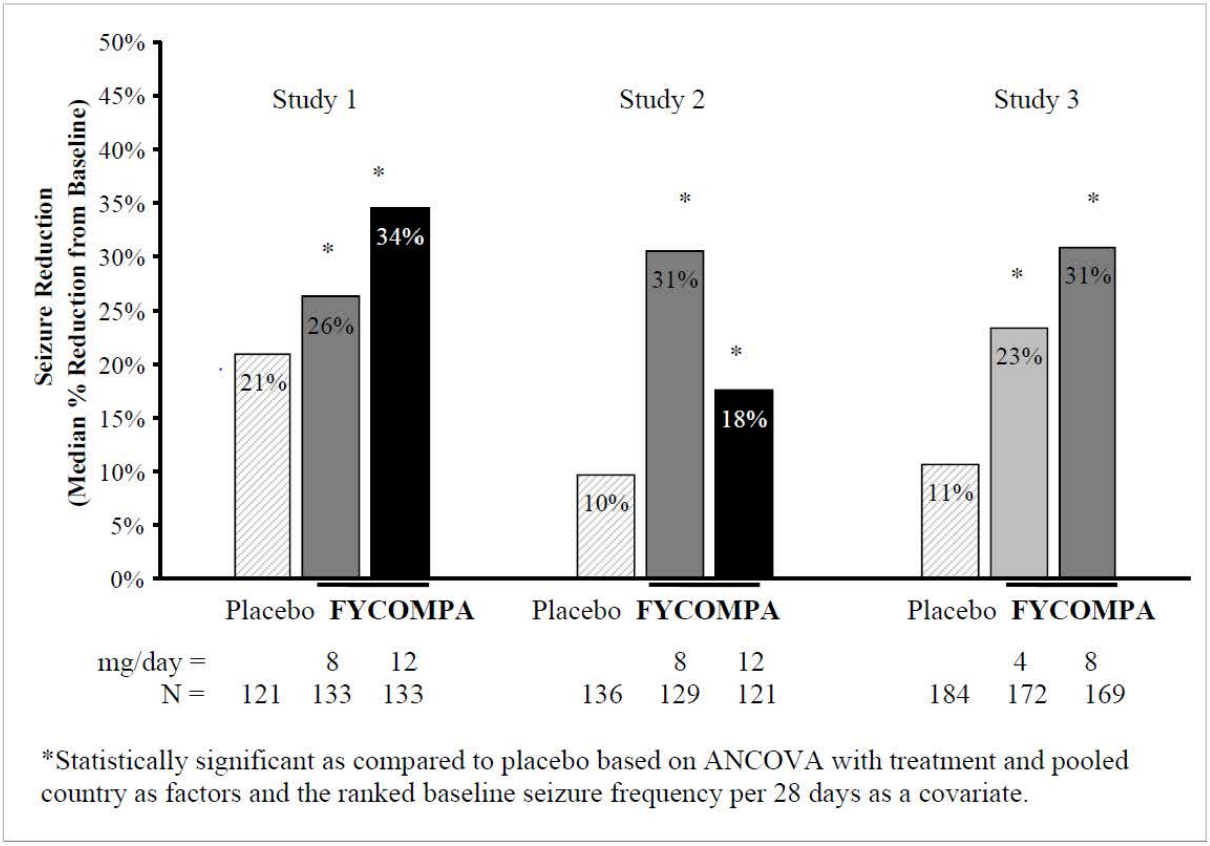
14.1 Partial-Onset Seizures

The efficacy of FYCOMPA in partial-onset seizures, with or without secondary generalization, was studied in patients who were not adequately controlled with 1 to 3 concomitant AEDs in 3 randomized, double-blind, placebo-controlled, multicenter trials (Studies 1, 2, and 3) in adult and pediatric patients (12 years of age and older). All trials had an initial 6-week Baseline Period, during which patients were required to have more than five seizures in order to be randomized. The Baseline Period was followed by a 19-week Treatment Period consisting of a 6-week Titration Phase and a 13-week Maintenance Phase. Patients in these 3 trials had a mean duration of epilepsy of approximately 21 years and a median baseline seizure frequency ranging from 9 to 14 seizures per 28 days. During the trials, more than 85% of patients were taking 2 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation, and approximately 50% were on at least one AED known to induce CYP3A4, an enzyme critical to the metabolism of FYCOMPA (i.e., carbamazepine, oxcarbazepine, or phenytoin), resulting in a significant reduction in FYCOMPA's serum concentration *[see Drug Interactions (7.2), Clinical Pharmacology (12.3)]*.

Each study evaluated placebo and multiple FYCOMPA dosages (see Figure 1). During the Titration period in all 3 trials, patients on FYCOMPA received an initial 2 mg once daily dose, which was subsequently increased in weekly increments of 2 mg per day to the final dose. Patients experiencing intolerable adverse reactions were permitted to have their dose reduced to the previously tolerated dose.

The primary endpoint in Studies 1, 2, and 3 was the percent change in seizure frequency per 28 days during the Treatment Period as compared to the Baseline Period. The criterion for statistical significance was $p<0.05$. A statistically significant decrease in seizure rate was observed at doses of 4 to 12 mg per day. Dose response was apparent at 4 to 8 mg with little additional reduction in frequency at 12 mg per day.

Figure 1. Median Percent Reduction in Seizure Frequency per 28 Days from Baseline to Treatment Period



Tables 4 and 5 present an analysis combining data from all 3 studies, grouping patients based upon whether or not concomitant enzyme-inducing AEDs (carbamazepine, oxcarbazepine, or phenytoin) were used. The analysis revealed a substantially reduced effect in the presence of inducers.

Table 4. Median Percent Reduction for Combined Studies (Study 1, 2 and 3) Based on the Presence or Absence of Concomitant Enzyme-Inducing AEDs (carbamazepine, oxcarbazepine, phenytoin)[a]

	Without Enzyme-Inducing AEDs		With Enzyme-Inducing AEDs	
	Placebo %	FYCOMPA %	Placebo %	FYCOMPA %
2 mg/day	16	23	14	16
4 mg/day	16	22	14	33
8 mg/day	19	45	12	24
12 mg/day	19	54	9	22

[a]Patients from Latin American region are excluded because of a significant treatment-by-region interaction due to high placebo response

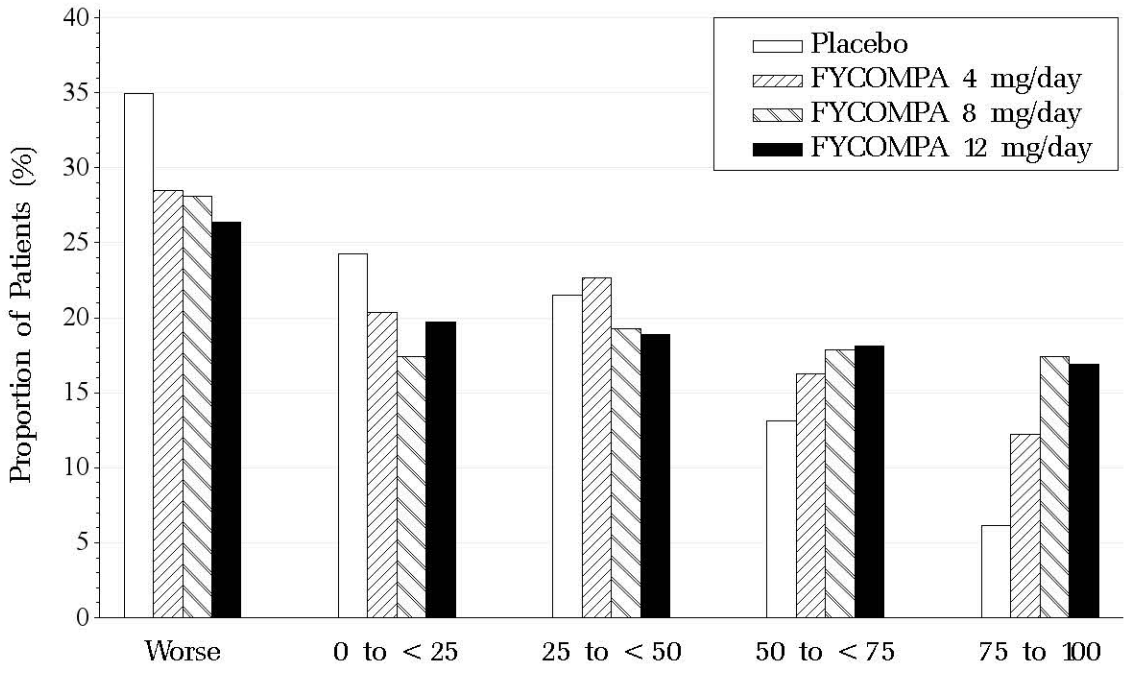
Table 5. Responder Rate for Combined Studies (Study 1, 2 and 3) Based on the Presence or Absence of Concomitant Enzyme-Inducing AEDs (carbamazepine, oxcarbazepine, phenytoin)[a,b]

	Without Enzyme-Inducing AEDs		With Enzyme-Inducing AEDs	
	Placebo %	FYCOMPA %	Placebo %	FYCOMPA %
2 mg/day	19	26	18	20
4 mg/day	19	35	18	26
8 mg/day	17	45	19	32
12 mg/day	15	54	21	33

[a] Patients from Latin American region are excluded because of a significant treatment-by-region interaction due to high placebo response
[b] The proportion of patients with at least a 50% decrease in seizure frequency

Figure 2 shows the proportion of patients with different percent reductions during the maintenance phase over baseline across all three trials. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in the remaining four categories.

Figure 2. Proportion of Patients Exhibiting Different Percent Reductions During the Maintenance Phase Over Baseline Across All Three Trials.



The percentages of patients with a 50% or greater reduction in seizure frequency were 19%, 29%, 35%, 35% for placebo, 4, 8, and 12 mg, respectively.

14.2 Primary Generalized Tonic-Clonic (PGTC) Seizures

The efficacy of FYCOMPA as adjunctive therapy in patients 12 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic seizures was established in one multicenter, randomized, double-blind, placebo-controlled study (Study 4), conducted at 78 sites in 16 countries. Eligible patients on a stable dose of 1 to 3 AEDs experiencing at least 3 primary generalized tonic-clonic seizures during the 8-week baseline period were randomized to either FYCOMPA or placebo. Efficacy was analyzed in 162 patients (FYCOMPA N=81, placebo N=81) who received medication and at least one post-treatment seizure assessment. Patients were titrated over 4 weeks up to a dose of 8 mg per day or the highest tolerated dose and treated for an additional 13 weeks on the last dose level achieved at the end of the titration period. The total treatment period was 17 weeks. Study drug was given once per day.

The primary endpoint was the percent change from baseline in primary generalized tonic-clonic seizure frequency per 28 days during the treatment period as compared to the baseline period. The criterion for statistical significance was $p<0.05$. Table 6 shows the results of this study. A statistically significant decrease in seizure rate was observed with FYCOMPA compared to placebo.

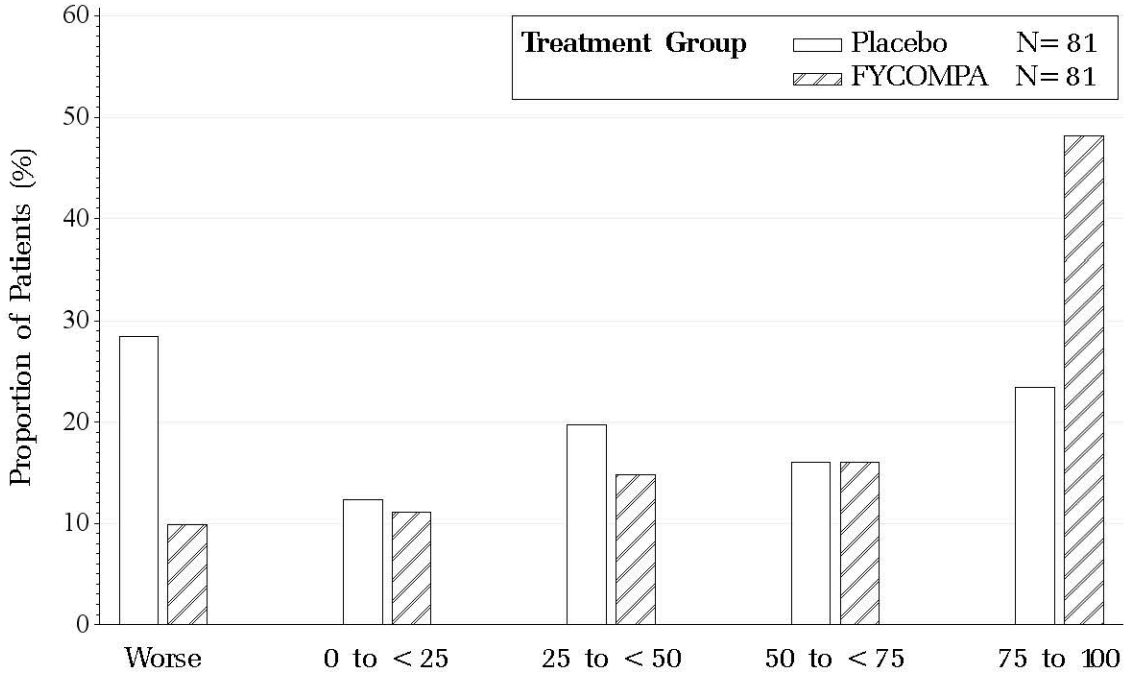
Table 6. Median Percent Reduction from Baseline in Primary Generalized Tonic-Clonic Seizure Frequency in Study 4

	Placebo (N=81)	FYCOMPA 8 mg (N=81)
Percent Reduction During Treatment	38	76[a]

[a] P-value compared to placebo: <0.0001. Statistically significant as compared to placebo based on ANCOVA with treatment and pooled country as factors and the ranked baseline seizure frequency per 28 days as a covariate.

Figure 3 shows the proportion of patients with different percent reductions during the maintenance phase over baseline in primary generalized tonic-clonic seizure frequency. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in the remaining four categories.

Figure 3. Proportion of Patients Exhibiting Different Percent Reductions During the Maintenance Phase Over Baseline in Primary Generalized Tonic-Clonic Seizure Frequency.



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FYCOMPA Tablets

- 2 mg are orange, round, biconvex, film-coated tablets debossed with "2" on one side and "Ɛ 275" on the other. They are supplied as follows:
  Bottles of 30　NDC 62856-272-30
  Bottles of 90　NDC 62856-272-90

- 4 mg are red, round, biconvex, film-coated tablets debossed with "4" on one side and "Є 277" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-274-30
  Bottles of 90 NDC 62856-274-90

- 6 mg are pink, round, biconvex, film-coated tablets debossed with "6" on one side and "Є 294" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-276-30
  Bottles of 90 NDC 62856-276-90

- 8 mg are purple, round, biconvex, film-coated tablets debossed with "8" on one side and "Є 295" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-278-30
  Bottles of 90 NDC 62856-278-90

- 10 mg are green, round, biconvex, film-coated tablets debossed with "10" on one side and "Є 296" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-280-30
  Bottles of 90 NDC 62856-280-90

- 12 mg are blue, round, biconvex, film-coated tablets debossed with "12" on one side and "Є 297" on the other. They are supplied as follows:
  Bottles of 30 NDC 62856-282-30
  Bottles of 90 NDC 62856-282-90

FYCOMPA Oral Suspension

- 0.5 mg/mL is a white to off-white opaque liquid. It is supplied in a round amber PET bottle with a child-resistant closure. It is packaged with a dispenser set that provides two 20-mL graduated oral dosing syringes and a push-in bottle adapter.
  Bottle containing 340 mL NDC 62856-290-38

16.2 Storage

Tablets: store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]

Oral Suspension: Do not store above 30°C (86°F). Do not freeze. Use within 90 days after the first opening of the bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration of Oral Suspension

Advise patients who are prescribed the oral suspension to shake the bottle well before every administration and to use the adaptor and oral dosing syringe provided. Advise patients that a household teaspoon or tablespoon is not an adequate measuring device. Instruct patients to discard any unused FYCOMPA oral suspension remaining 90 days after first opening the bottle *[see Dosage and Administration (2.7)]*.

Serious Psychiatric and Behavioral Reactions

Counsel patients, families, and caregivers of patients of the need to monitor for the emergence of anger, aggression, hostility, hallucinations, delusions, confusion, unusual changes in mood, personality, or behavior, and other behavioral symptoms. Advise them to report any such symptoms immediately to their healthcare providers *[see Warnings and Precautions (5.1)]*.

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and families that AEDs, including FYCOMPA, may increase the risk of suicidal thinking and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression,

any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Instruct patients, caregivers, and families to report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.2)]*.

Neurologic Effects: Dizziness, Gait Disturbance, Somnolence, and Fatigue

Counsel patients that FYCOMPA may cause dizziness, gait disturbance, somnolence, and fatigue. Advise patients taking FYCOMPA not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with FYCOMPA *[see Warnings and Precautions (5.3)]*.

Falls

Counsel patients that FYCOMPA may cause falls and injuries *[see Warnings and Precautions (5.4)]*.

DRESS/Multi-organ Hypersensitivity

Instruct patients that a fever associated with signs of other organ system involvement (e.g., rash, lymphadenopathy, hepatic dysfunction) may be drug-related and should be reported to their healthcare provider immediately *[see Warnings and Precautions (5.5)]*.

Withdrawal of Antiepileptic Drugs

Counsel patients that abrupt discontinuation of FYCOMPA may increase seizure frequency *[see Warnings and Precautions (5.6)]*.

Contraceptives

Counsel females of reproductive potential that FYCOMPA may decrease efficacy of contraceptives containing levonorgestrel, and advise them to use an additional non-hormonal form of contraception while using FYCOMPA and for a month after discontinuation *[see Drug Interactions (7.1), Use in Specific Populations (8.3)]*.

Alcohol and Other CNS Depressants

Counsel patients that FYCOMPA may enhance the impairment effects of alcohol. These effects may also be seen if FYCOMPA is taken with other CNS depressants *[see Drug Interactions (7.3)]*.

Missed Doses

Counsel patients that if they miss a dose, they should resume dosing the following day at their prescribed daily dose. Instruct patients to contact their physician if more than one day of dosing is missed.

Controlled Substance

Counsel patients that FYCOMPA is a controlled substance that can be misused and abused *[see Drug Abuse and Dependence (9.1)]*.

Pregnancy Registry

Advise women who are exposed to FYCOMPA during pregnancy that there is a pregnancy exposure registry that monitors pregnancy outcomes. Encourage these patients to enroll in the NAAED Pregnancy Registry *[see Use in Specific Populations (8.1)]*.

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MEDICATION GUIDE

FYCOMPA® (fi-COM-puh)
(perampanel)
tablets, for oral use, CIII

FYCOMPA® (fi-COM-puh)
(perampanel)
oral suspension, CIII

What is the most important information I should know about FYCOMPA?

1. **FYCOMPA may cause mental (psychiatric) problems, including:**
   - new or worse aggressive behavior (including homicidal behavior), hostility, anger, anxiety, or irritability
   - being suspicious or distrustful (believing things that are not true)
   - seeing objects or hearing things that are not there
   - confusion
   - difficulty with memory
   - other unusual or extreme changes in behavior or mood

   Tell your healthcare provider right away if you have any new or worsening mental problems while taking FYCOMPA.
2. **Like other antiepileptic drugs, FYCOMPA may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**
   Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
   - thoughts about suicide or dying
   - new or worse depression
   - feeling agitated or restless
   - trouble sleeping (insomnia)
   - acting aggressive, being angry, or violent
   - an extreme increase in activity and talking (mania)
   - attempt to commit suicide
   - new or worse anxiety
   - panic attacks
   - new or worse irritability
   - acting on dangerous impulses
   - other unusual changes in behavior or mood

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop FYCOMPA without first talking with a healthcare provider. Stopping FYCOMPA suddenly can cause serious problems. Stopping FYCOMPA suddenly can cause you to have seizures more often.

What is FYCOMPA?

FYCOMPA is a prescription medicine used:

- to treat partial-onset seizures with or without secondarily generalized seizures in people with epilepsy who are 4 years of age and older
- with other medicines to treat primary generalized tonic-clonic seizures in people with epilepsy who are 12 years of age and older

FYCOMPA is a controlled substance (CIII) because it can be abused or lead to drug dependence. Keep your FYCOMPA in a safe place to protect it from theft. Never give your FYCOMPA to anyone else because it may harm them. Selling or giving away this medicine is against the law.

It is not known if FYCOMPA is safe and effective for partial onset seizures in children under 4 years of age or for primary generalized tonic clonic seizures in patients under 12 years of age.

Before taking FYCOMPA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems, aggressive or hostile behavior (for example, homicidal behavior), suicidal thoughts or behavior, or other psychiatric problems.
- have liver or kidney problems
- drink alcohol
- have abused prescription medicines, street drugs, or alcohol in the past
- are pregnant or plan to become pregnant. It is not known if FYCOMPA will harm your unborn baby.
  - If you become pregnant while taking FYCOMPA, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334 or go to http://www.aedpregnancyregistry.org. The purpose of this registry is to collect information about the safety of FYCOMPA and other antiepileptic medicine during pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if FYCOMPA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take FYCOMPA. You and your healthcare provider should decide if you will take FYCOMPA or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines,

vitamins, and herbal supplements.
Taking FYCOMPA with certain other medicines can cause side effects or reduce the benefit of either drug. **Especially tell your healthcare provider if you take:**

- contraceptives (birth control). FYCOMPA may lower your contraceptive's ability to prevent pregnancy if your contraceptive contains levonorgestrel. Use an additional non-hormonal form of contraception (like condoms or a diaphragm and spermicide) while using FYCOMPA and for 1 month after you have stopped taking FYCOMPA.
- carbamazepine (CARBATROL®, TEGRETOL®, TEGRETOL-XR®, EQUETRO®, EPITOL®)
- phenytoin (DILANTIN®, PHENYTEK®)
- oxcarbazepine (TRILEPTAL®)
- rifampin (RIFADIN®, RIMACTANE®)
- St. John's Wort

How should I take FYCOMPA?

- See the complete Instructions for Use below for information on how to use the dosing syringes and measure your dose of FYCOMPA Oral Suspension.
- Take FYCOMPA exactly as your healthcare provider tells you. Your healthcare provider will tell you how much FYCOMPA to take and when to take it. FYCOMPA is usually taken 1 time a day at bedtime.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- If you take FYCOMPA Oral Suspension, shake the bottle well before you take each dose.
- Measure your dose of FYCOMPA Oral Suspension using the bottle adapter and dosing syringes provided. **Do not** use a household teaspoon.
- Talk to your healthcare provider about what to do if you miss 1 or more doses of FYCOMPA.
- If you take too much FYCOMPA, call your local Poison Control Center or go to the nearest hospital emergency room right away.

What should I avoid while taking FYCOMPA?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how FYCOMPA affects you. FYCOMPA may make you dizzy, sleepy, or tired.
- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking FYCOMPA until you talk to your healthcare provider. FYCOMPA taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse. FYCOMPA when taken with alcohol may also make your mood worse, increase anger, confusion, and depression.

What are the possible side effects of FYCOMPA?
See **"What is the most important information I should know about FYCOMPA?"**
FYCOMPA may cause other serious side effects, including:

- **Dizziness, vertigo (sense of spinning), and problems walking normally.** You may have problems walking normally if you are unsteady because you feel dizzy. These symptoms can increase when your dose of FYCOMPA is increased. Your risk of feeling dizzy and having problems walking normally may be higher if you are elderly.
- **Sleepiness and tiredness.** See "**What should I avoid while taking FYCOMPA?"**
- **Increased risk of falls.** Taking FYCOMPA can increase your chance of falling. These falls can cause serious injuries. Your risk of falling may be higher if you are elderly.
- **A serious allergic reaction that may affect your skin or other parts of your body such as your liver, kidneys, heart, or blood cells.** This allergic reaction can be life-threatening and can cause death. Call your healthcare provider right away if you have:
  - a skin rash, hives
  - fever or swollen glands that do not go away
  - swelling of your face
  - shortness of breath, swelling of the legs, yellowing of the skin or whites of the eyes, or dark urine.

The most common side effects of FYCOMPA include:

- dizziness
- sleepiness
- tiredness
- irritability
- falls
- nausea and vomiting
- weight gain
- vertigo (sense of spinning)
- problems walking normally
- problems with muscle coordination
- headache
- bruising
- abdominal pain
- anxiety

These are not all of the possible side effects of FYCOMPA. For more information ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FYCOMPA?

- Store FYCOMPA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Store FYCOMPA oral suspension below 86°F (30°C). **Do not** freeze.
- Replace the cap tightly after opening.
- Use FYCOMPA oral suspension within 90 days after the bottle is first opened.

Keep FYCOMPA and all medicines out of the reach of children.

General information about the safe and effective use of FYCOMPA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FYCOMPA for a condition for which it was not prescribed. Do not give FYCOMPA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about FYCOMPA that is written for health professionals.

What are the ingredients in FYCOMPA?

Active ingredient: perampanel

Inactive ingredients (tablets): lactose monohydrate, low substituted hydroxypropyl cellulose, povidone, microcrystalline cellulose, magnesium stearate, hypromellose, polyethylene glycol, talc, and titanium dioxide. Tablets of different strengths also may contain yellow ferric oxide (10 mg and 2 mg), red ferric oxide (2 mg, 4 mg, 6 mg, 8 mg), black ferric oxide (8 mg), and FD&C blue # 2 (indigo carmine) aluminum lake (10 mg and 12 mg).

Inactive ingredients (oral suspension): sorbitol, microcrystalline cellulose, carboxymethylcellulose sodium, poloxamer, simethicone, citric acid, sodium benzoate, and purified water.

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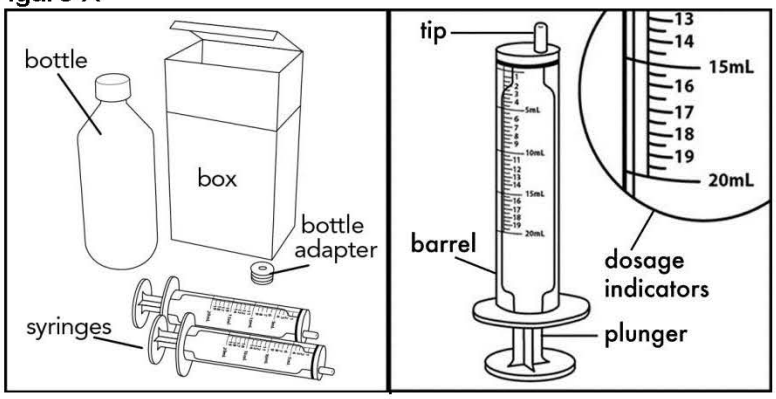
This Medication Guide has been approved by the U.S. Food and Drug Administration　　Revised 9/2018

Instructions for Use
FYCOMPA® (fi-COM-puh)
(perampanel)
Oral Suspension

Read this Instructions for Use before you start using FYCOMPA Oral Suspension and each time you get a refill. There may be new information. This leaflet does not take the place of ta king to your healthcare provider about your medical condition or treatment.

Prepare the FYCOMPA Oral Suspension dose
You will need the following supplies: **See Figure A**
• FYCOMPA Oral Suspension bottle
• Bottle adapter
• Dosing syringe (2 dosing syringes are included in the FYCOMPA Oral Suspension box)

Figure A



Step 1. Remove the FYCOMPA Oral Suspension bottle, bottle adapter, and 2 syringes from the box. **See Figure A**

Step 2. Shake the bottle well before each use. **See Figure B**

Figure B



Step 3. Uncap the bottle and insert the bottle adapter into the bottle by pressing downward. **See Figure C and Figure D**

Figure C

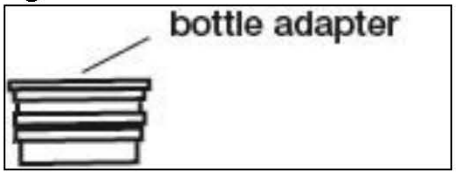


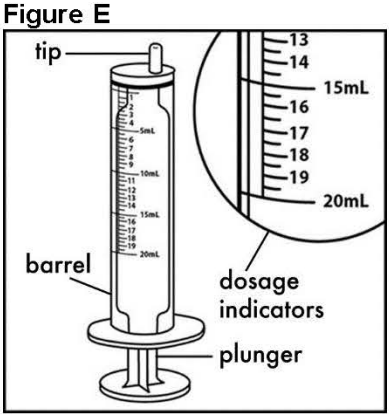
Figure D



After the bottle adapter is in place, it cannot be removed.

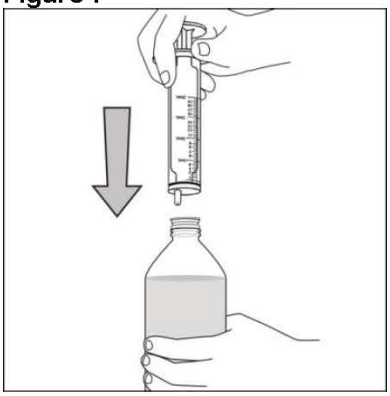
Step 4. Check the dose in milliliters (mL) as prescribed by your healthcare provider. Find this number on the syringe. **See Figure E**

Figure E



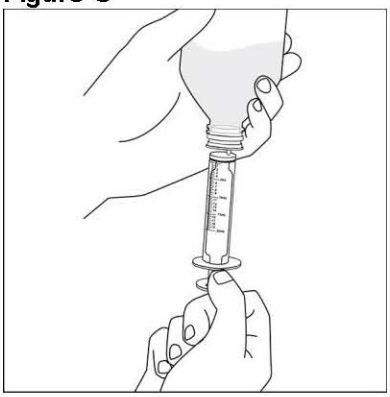
Step 5. Push the plunger of the syringe all the way down then insert the syringe into the upright bottle through the opening in the bottle adapter. **See Figure F**

Figure F



Step 6. With the syringe in place, turn the bottle upside down. Pull the plunger to withdraw the dose prescribed by your healthcare provider (the amount of liquid medicine in Step 4). If you see air bubbles in the oral syringe, fully push in the plunger so that the oral solution flows back into the bottle. Then, withdraw your prescribed dose of oral suspension. **See Figure G**

Figure G



Measure the mLs of medicine from the **white** layer at the end of the plunger, not the black layer.

Step 7. If the dose is more than 20 mL, you can use:
• 2 syringes

or

• 1 syringe, taking 2 steps to draw up the medicine in that same syringe

For example:
If your dose is 24 mL, draw up 20 mL in the first syringe and the remaining 4 mL in the second syringe.

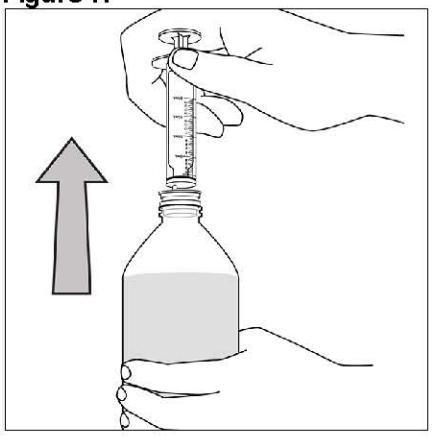
or

If your dose is 24 mL, draw up 20 mL in the single syringe and squirt the medicine into your mouth, then draw up the remaining 4 mL in that same syringe.

"If your dose is more than 20 mL, repeat Steps 4 through 6 when drawing up the remaining dose of medicine."

Step 8. Turn the bottle right-side up and remove the syringe from the bottle adapter**. See Figure H**

Figure H



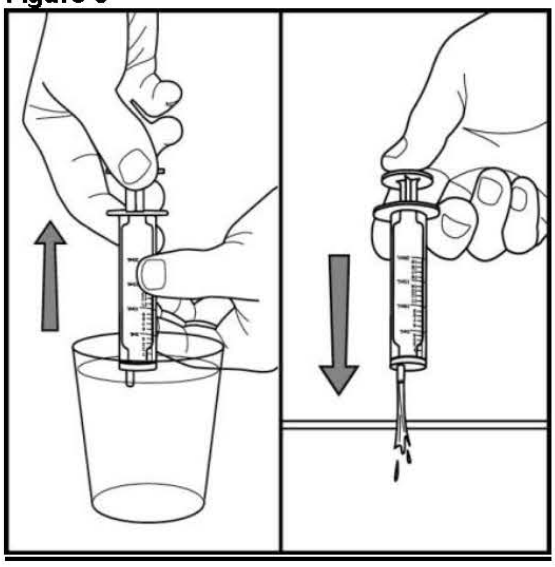
Step 9. Slowly squirt the FYCOMPA oral suspension directly into the corner of your mouth until all of the liquid medicine is given. If you need 2 syringes for your dose, slowly squirt the medicine from the first syringe into your mouth, then slowly squirt the medicine from the second syringe into your mouth. **See Figure I**

Figure I



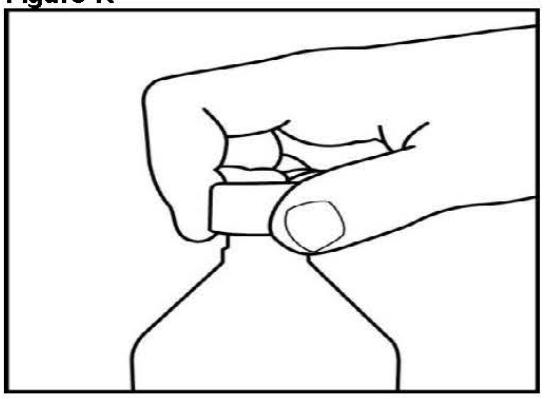
Step 10. Rinse the syringe (or syringes) with tap water after each use. **See Figure J**
• Fill a cup with water
• Pull back on the plunger and draw the water from the cup into the syringe
• Push down on the plunger to release the water into the sink

Figure J



Step 11. Cap the bottle tightly. The cap will fit over the bottle adapter. **See Figure K**

Figure K



How should I store FYCOMPA Oral Suspension?

- Store FYCOMPA oral suspension below 86°F (30°C). **Do not** freeze.
- Replace the cap tightly after opening.

- Use FYCOMPA oral suspension within 90 days after the bottle is first opened.
- After 90 days safely throw away any FYCOMPA Oral Suspension that has not been used.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Approved: April 2016

ANNEX I

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

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

Film-coated tablet (tablet)

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 adult and adolescent patients from 12 years of age with epilepsy.

Fycompa is indicated for the adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy (see section 5.1).

4.2 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.

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. 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.

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.

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS)

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), 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. If signs and symptoms suggestive of these reactions appear, perampanel should be withdrawn immediately and an alternative treatment considered (as appropriate).

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).

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

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

1) Active metabolite monohydroxycarbazepine was not assessed.

Some anti-epileptic drugs known as CYP450 3A enzyme inducers (carbamazepine, phenytoin, oxcarbazepine) have been shown to increase perampanel clearance and consequently to decrease plasma concentrations of perampanel. Conversely, withdrawal of a concomitant CYP450 3A enzyme inducer can be expected to increase plasma concentrations of perampanel and dose reduction may be required.

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.

Effect of perampanel on CYP3A substrates

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

Effect of cytochrome P450 inducers on perampanel pharmacokinetics

Strong inducers of cytochrome P450, such as rifampicin and hypericum, are expected to decrease perampanel concentrations and the potential for higher plasma concentrations of 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 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.

Breast-feeding

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 breast-feeding or to discontinue/abstain from Fycompa therapy taking into account the benefit of breast--feeding for the child and the benefit of therapy for the woman.

Fertility

In the fertility study in rats, prolonged and irregular oestrous cycles were observed at high-dose (30 mg/kg) in females; however, these changes did not affect the fertility and early embryonic development. There were no effects on male fertility (see section 5.3). The effect of 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%, 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 randomised to receive perampanel 8 mg, and 1.2% in patients randomised 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 Anxiety Confusional state	Suicidal ideation Suicide attempt	
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)*
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 generalised tonic-clonic seizures, the overall safety profile in adolescents was similar to that of adults, except for aggression, which was observed more frequently in adolescents than in adults.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal overexcitation. 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).

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 perampanel 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 perampanel 8 and 12 mg/day with placebo and the third study (study 306) compared doses of perampanel 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 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.

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, randomised, double-blind, placebo-controlled study (Study 332). Eligible patients on a stable dose of 1 to 3 AEDs experiencing at least 3 primary generalised tonic-clonic seizures during the 8-week baseline period were randomised to either 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 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 Prerandomisation 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 generalised 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
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 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.

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

Distribution

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 $t_{½}$ of perampanel was 105 hours. When dosed in combination with the strong CYP3A inducer carbamazepine, the average $t_{½}$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 $t_{½}$ 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) was 18% lower than in males (0.66 l/h).

Elderly (65 years of age and above)
In a population pharmacokinetic analysis of patients with partial-onset seizures (age range 12 to 74 years) and primary generalised tonic-clonic seizures (age range 12 to 58 years), and receiving perampanel up to 8 or 12 mg/day in placebo-controlled clinical trials, 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 pooled from the Phase 2 and 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

Fycompa 2 mg, 4 mg film-coated tablets

Core
Lactose monohydrate
Low-substituted hydroxypropyl cellulose
Povidone K-29/32
Magnesium stearate (E470b)

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

Core
Lactose monohydrate
Low-substituted hydroxypropyl cellulose
Povidone K-29/32
Microcrystalline cellulose
Magnesium stearate (E470b)

Fycompa 2 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
Ferric oxide, yellow (E172)
Ferric oxide, red (E172)

Fycompa 4 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
Ferric oxide, red (E172)

Fycompa 6 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
Ferric oxide, red (E172)

Fycompa 8 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)

Ferric oxide, red (E172)
Ferric oxide, black (E172)

Fycompa 10 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
Ferric oxide, yellow (E172)
FD&C Blue #2 Indigo carmine aluminium lake (E132)

Fycompa 12 mg film-coated tablets

Film coating
Hypromellose 2910
Talc
Macrogol 8000
Titanium dioxide (E171)
FD&C Blue #2 Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blisters

Fycompa 2 mg film-coated tablets
Pack of 7 only for first week of dosing, 28 and 98

Fycompa 4 mg film-coated tablets
4 mg – packs of 7, 28, 84 and 98

Fycompa 6 mg film-coated tablets
6 mg – packs of 7, 28, 84 and 98

Fycompa 8 mg film-coated tablets
8 mg – packs of 7, 28, 84 and 98

Fycompa 10 mg film-coated tablets
10 mg – packs of 7, 28, 84 and 98

Fycompa 12 mg film-coated tablets
12 mg – packs of 7, 28, 84 and 98

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Eisai Europe Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom
tel: +44 (0)208 600 1400
fax: +44 (0)208 600 1401
e-mail: EUmedinfo@eisai.net

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/001-023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23/07/2012
Date of latest renewal: 6 April 2017

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 0.5 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

3. PHARMACEUTICAL FORM

Oral suspension
White to off-white suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Fycompa is indicated for the adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy (see section 5.1).

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 suspension should be taken orally once daily at bedtime.
It may be taken with or without food, but preferably always under the same conditions. 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.

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.

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 (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
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 is for oral use.

Preparation: 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.

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.

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS)

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), 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. If signs and symptoms suggestive of these reactions appear, perampanel should be withdrawn immediately and an alternative treatment considered (as appropriate).

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).

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

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.

Sorbitol

Fycompa contains sorbitol (E420); therefore patients with rare hereditary problems of fructose intolerance 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.

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

2) Active metabolite monohydroxycarbazepine was not assessed.

Some anti-epileptic drugs known as CYP450 3A enzyme inducers (carbamazepine, phenytoin, oxcarbazepine) have been shown to increase perampanel clearance and consequently to decrease plasma concentrations of perampanel. Conversely, withdrawal of a concomitant CYP450 3A enzyme inducer can be expected to increase plasma concentrations of perampanel and dose reduction may be required.

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.

Effect of perampanel on CYP3A substrates

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

Effect of cytochrome P450 inducers on perampanel pharmacokinetics

Strong inducers of cytochrome P450, such as rifampicin and hypericum, are expected to decrease perampanel concentrations and the potential for higher plasma concentrations of 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 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.

Breast-feeding

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 breast-feeding or to discontinue/abstain from Fycompa therapy taking into account the benefit of breast--feeding for the child and the benefit of therapy for the woman.

Fertility

In the fertility study in rats, prolonged and irregular oestrous cycles were observed at high-dose (30 mg/kg) in females; however, these changes did not affect the fertility and early embryonic development. There were no effects on male fertility (see section 5.3). The effect of 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%, 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 randomised to receive perampanel 8 mg, and 1.2% in patients randomised 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 Anxiety Confusional state	Suicidal ideation Suicide attempt	
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)*
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 generalised tonic-clonic seizures, the overall safety profile in adolescents was similar to that of adults, except for aggression, which was observed more frequently in adolescents than in adults.

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. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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-isoxazolepopionic 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).

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 perampanel 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 perampanel 8 and 12 mg/day with placebo and the third study (study 306) compared doses of perampanel 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 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.

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, randomised, double-blind, placebo-controlled study (Study 332). Eligible patients on a stable dose of 1 to 3 AEDs experiencing at least 3 primary generalised tonic-clonic seizures during the 8-week baseline period were randomised to either 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 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 Prerandomisation 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 generalised 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
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 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.

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 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.

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, 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 $t_{½}$ of perampanel was 105 hours. When dosed in combination with the strong CYP3A inducer carbamazepine, the average $t_{½}$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 $t_{½}$ 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) was 18% lower than in males (0.66 l/h).

Elderly (65 years of age and above)
In a population pharmacokinetic analysis of patients with partial-onset seizures (age range 12 to 74 years) and primary generalised tonic-clonic seizures (age range 12 to 58 years), and receiving perampanel up to 8 or 12 mg/day in placebo-controlled clinical trials, 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 pooled from the Phase 2 and 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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After first opening: 90 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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.

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. MARKETING AUTHORISATION HOLDER

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e-mail: EUmedinfo@eisai.net

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23/07/2012
Date of latest renewal: 6 April 2017

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eisai Manufacturing Ltd.
European Knowledge Centre
Mosquito Way
Hatfield, Herts AL10 9SN
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton of 7, 28 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 2 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/001
EU/1/12/776/017
EU/1/12/776/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fycompa 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack (PVC/Aluminium blister)

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 2 mg tablets
Perampanel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cartons of 7, 28, 84 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 4 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
84 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/002
EU/1/12/776/003
EU/1/12/776/004
EU/1/12/776/019

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fycompa 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack (PVC/Aluminium blister)

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 4 mg tablets
Perampanel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cartons of 7, 28,84 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 6 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 6 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
84 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/005
EU/1/12/776/006
EU/1/12/776/007
EU/1/12/776/020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fycompa 6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack (PVC/Aluminium blister)

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 6 mg tablets
Perampanel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cartons of 7, 28,84 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 8 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 8 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
84 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/008
EU/1/12/776/009
EU/1/12/776/010
EU/1/12/776/021

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fycompa 8 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack (PVC/Aluminium blister)

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 8 mg tablets
Perampanel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cartons of 7, 28, 84 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 10 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
84 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/011
EU/1/12/776/012
EU/1/12/776/013
EU/1/12/776/022

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fycompa 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack (PVC/Aluminium blister)

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 10 mg tablets
Perampanel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cartons of 7, 28,84 and 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 12 mg film-coated tablets
Perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12 mg perampanel.

3. LIST OF EXCIPIENTS

Contains lactose: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
84 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/014
EU/1/12/776/015
EU/1/12/776/016
EU/1/12/776/023

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fycompa 12 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack (PVC/Aluminium blister)

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 12 mg tablets
Perampanel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Fycompa 0.5 mg/ml oral suspension
perampanel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 0.5 mg perampanel.
1 bottle (340 ml) contains 170 mg perampanel.

3. LIST OF EXCIPIENTS

Contains sorbitol: see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension 340 ml.
1 bottle
2 oral syringes
1 press-in-bottle adapter (PIBA)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Shake for at least 5 seconds before use.

Oral use

Open date:

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8.	EXPIRY DATE

EXP
After first opening: use within 90 days.

9.	SPECIAL STORAGE CONDITIONS

10.	SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11.	NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12.	MARKETING AUTHORISATION NUMBER(S)

EU/1/12/776/024

13.	BATCH NUMBER

Lot

14.	GENERAL CLASSIFICATION FOR SUPPLY

15.	INSTRUCTIONS ON USE

16.	INFORMATION IN BRAILLE

Fycompa 0.5 mg/ml

17.	UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

Fycompa 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg film-coated tablets
Perampanel

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Fycompa is and what it is used for
2. What you need to know before you take Fycompa
3. How to take Fycompa
4. Possible side effects
5. How to store Fycompa
6. Contents of the pack and other information

1. What Fycompa is and what it is used for

Fycompa contains a medicine called perampanel. It belongs to a group of medicines called anti epileptics. These medicines are used to treat epilepsy - where someone has repeated fits (seizures). It has been given to you by your doctor to reduce the number of fits that you have.

Fycompa is used in association with other antiepileptic drugs to treat certain forms of epilepsy in people aged 12 years and older.
- It is used to treat fits that affect one part of your brain (called a “partial seizure”).
- These partial seizures may or may not then be followed by a fit affecting all of your brain (called a “secondary generalisation”).
- It is also used to treat certain fits that affect all of your brain from the start (called “generalised seizures”) and cause convulsions or staring spells.

2. What you need to know before you take Fycompa

DO NOT TAKE Fycompa:
- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking perampanel.
- If you are allergic to perampanel or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Fycompa if you have liver problems or moderate or severe kidney problems.
You should not take Fycompa if you have serious liver problems or moderate or serious kidney problems.
Before taking this medicine you should tell your doctor if you have a history of alcoholism or drug dependence.

- Fycompa may make you feel dizzy or sleepy, particularly at the beginning of treatment.

- Fycompa may make you more likely to fall over, particularly if you are an older person; this might be due to your illness.
- Fycompa may make you aggressive, angry or violent. It may also cause you to have unusual or extreme changes in behaviour or mood.

If any of these happens, talk to your doctor or pharmacist.

A small number of people being treated with anti-epileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, contact your doctor straight away.

Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of perampanel.

- DRESS typically, although not exclusively, appears as flu-like symptoms and a rash with a high body temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.

If you experience any of the above after taking Fycompa (or you are not sure) talk to your doctor or pharmacist.

Children

Fycompa is not recommended for children aged under 12. The safety and effectiveness are not yet known in this age group.

Other medicines and Fycompa

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. Taking Fycompa with certain other medicines may cause side effects or affect how they work. Do not start or stop other medicines without talking to your doctor or pharmacist.

- Other anti-epileptic medicines, such as carbamazepine, oxcarbazepine, and phenytoin that are used to treat fits may affect Fycompa. Tell your doctor if you are taking or have recently taken these medicines as your dose may need to be adjusted.
- Felbamate (a medicine used to treat epilepsy) may also affect Fycompa. Tell your doctor if you are taking or have recently taken this medicine as your dose may need to be adjusted.
- Midazolam (a medicine used to stop prolonged, acute (sudden) convulsive seizures, for sedation and sleep problem) may be affected by Fycompa. Tell your doctor if you are taking midazolam as your dose may need to be adjusted.
- Some other medicines such as rifampicin (a medicine used to treat bacterial infections), hypericum (St. John's Wort) (a medicine used to treat mild anxiety) and ketoconazole (a medicine used to treat fungal infections) may affect Fycompa. Tell your doctor if you are taking or have recently taken these medicines as your dose may need to be adjusted.
- Oral contraceptives (also called "hormonal contraceptives").

Tell your doctor if you are taking hormonal contraceptives. Fycompa may make certain hormonal contraceptives such as levonorgestrel less effective. You should use other forms of safe and effective contraception (such as a condom or coil) when taking Fycompa. You should continue doing this for one month after stopping treatment. Discuss with your doctor what may be appropriate contraception for you.

Fycompa with alcohol

Speak to your doctor before drinking alcohol. Be careful about consuming alcohol with epilepsy medicines including Fycompa.

- Drinking alcohol while taking Fycompa can make you less alert and affect your ability to drive or use tools or machines.
- Drinking alcohol while taking Fycompa can also make any feelings of anger, confusion or sadness worse.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. Do not stop treatment without first discussing it with your doctor.
- Fycompa is not recommended in pregnancy.
- You must use a reliable method of contraception to avoid becoming pregnant while you are being treated with Fycompa. You should continue doing this for one month after stopping treatment. Tell your doctor if you are taking hormonal contraceptives. Fycompa may make certain hormonal contraceptives such as levonorgestrel less effective. You should use other forms of safe and effective contraception (such as a condom or coil) when taking Fycompa. You should also do this for one month after stopping treatment. Discuss with your doctor what may be appropriate contraception for you.

It is not known whether the ingredients of Fycompa can pass into breast milk.
The doctor will weigh up the benefit and risks to your baby of taking Fycompa while you are breast-feeding.

Driving and using machines
Do not drive or use machines until you know how Fycompa affects you.
You must talk to your doctor about the effect of your epilepsy on driving and using machines.
- Fycompa may make you feel dizzy or sleepy, particularly at the beginning of treatment. If this happens to you, do not drive or use any tools or machines.
- Drinking alcohol while taking Fycompa may make these effects worse.

Fycompa contains lactose
Fycompa contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Fycompa

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How much to take
The usual starting dose is 2 mg once a day before you go to bed.
- Your doctor may increase this in 2 mg steps to a maintenance dose between 4 mg and 12 mg - depending on your response.
- If you have mild or moderate liver problems, your dose should not be more than 8 mg each day and your dose increases should be at least 2 weeks apart.
- Don’t take more Fycompa than your doctor has recommended. It may take a few weeks to find the right dose of Fycompa for you.

How to take
Swallow the tablet whole with a glass of water. You can take Fycompa with or without food. Do not chew, crush or split the tablet. The tablets cannot be split accurately as there is no break line.

If you take more Fycompa than you should
If you have taken more Fycompa than you should contact your doctor straight away. You may experience confusion, agitation and aggressive behaviour.

If you forget to take Fycompa
- If you forget to take a tablet, wait until your next dose and then carry on as usual.
- Do not take a double dose to make up for a forgotten dose.
- If you have missed less than 7 days of treatment with Fycompa, continue taking your daily tablet as originally instructed by your doctor.

- If you have missed more than 7 days of treatment with Fycompa, talk to your doctor immediately.

If you stop taking Fycompa
Take Fycompa for as long as your doctor recommends. Do not stop unless your doctor advises you to. Your doctor may reduce your dose slowly to avoid your fits (seizures) coming back or getting worse. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

A small number of people being treated with anti-epileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, contact your doctor straight away.

Very common (may affect more than 1 user in 10) are:
- feeling dizzy
- feeling sleepy (drowsiness or somnolence)

Common (may affect more than 1 user in 100) are:
- increased or decreased appetite, weight gain
- feeling aggressive, angry, irritable, anxious or confused
- difficulty with walking or other balance problems (ataxia, gait disturbance, balance disorder)
- slow speech (dysarthria)
- blurred vision or double vision (diplopia)
- spinning sensation (vertigo)
- feeling sick (nausea)
- back pain
- feeling very tired (fatigue)
- falling down

Uncommon (may affect more than 1 user in 1000) are:
- thoughts about harming yourself or ending your own life (suicidal thoughts), tried to end your own life (attempted suicide)

Not known (the frequency of this side effect cannot be estimated from the available data) are:
- widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome).

Stop using perampanel if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fycompa

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister. The expiry date refers to the last day of the month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Fycompa contains
The active substance is perampanel. Each film-coated tablet contains 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg perampanel.

The other ingredients are:
Tablet core (2 mg and 4 mg tablets):
Lactose monohydrate, low-substituted hydroxypropyl cellulose, povidone, magnesium stearate (E470b)

Tablet core (6 mg, 8 mg, 10 mg and 12 mg tablets)
Lactose monohydrate, low-substituted hydroxypropyl cellulose, povidone, microcrystalline cellulose, magnesium stearate (E470b)

Film coating (2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets)
Hypromellose 2910, talc, Macrogol 8000, titanium dioxide (E171), colourants*

*The colourants are:
2 mg tablet: Ferric Oxide, Yellow (E172), Ferric Oxide, Red (E172)
4 mg tablet: Ferric Oxide, Red (E172)
6 mg tablet: Ferric Oxide, Red (E172)
8 mg tablet: Ferric Oxide, Red (E172), Ferric Oxide, Black (E172)
10 mg tablet: Ferric Oxide, Yellow (E172), FD&C Blue #2 Indigo carmine aluminium lake (E132)
12 mg tablet: FD&C Blue #2 Indigo carmine aluminium lake (E132)

What Fycompa looks like and contents of the pack
All strengths of Fycompa are round, biconvex film-coated tablets
2 mg: orange, marked with E275 on one side and 2 on other side
4 mg: red, marked with E277 on one side and 4 on other side
6 mg: pink, marked with E294 on one side and 6 on other side
8 mg: purple, marked with E295 on one side and 8 on other side
10 mg: green, marked with E296 on one side and 10 on other side
12 mg: blue, marked with E297 on one side and 12 on other side

Fycompa is available in packs of:
2 mg tablet – pack of 7, 28 and 98
4 mg, 6 mg, 8 mg, 10 mg, 12 mg tablets – packs of 7, 28, 84 and 98

Not all pack sizes may be marketed

Marketing Authorisation Holder

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This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

Package leaflet: Information for the user

Fycompa 0.5 mg/ml oral suspension
Perampanel

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Fycompa is and what it is used for
2. What you need to know before you take Fycompa
3. How to take Fycompa
4. Possible side effects
5. How to store Fycompa
6. Contents of the pack and other information

1. What Fycompa is and what it is used for

Fycompa contains a medicine called perampanel. It belongs to a group of medicines called anti-epileptics. These medicines are used to treat epilepsy - where someone has repeated fits (seizures). It has been given to you by your doctor to reduce the number of fits that you have.

Fycompa is used in association with other antiepileptic drugs to treat certain forms of epilepsy in people aged 12 years and older.
- It is used to treat fits that affect one part of your brain (called a “partial seizure”).
- These partial seizures may or may not then be followed by a fit affecting all of your brain (called a “secondary generalisation”).
- It is also used to treat certain fits that affect all of your brain from the start (called “generalised seizures”) and cause convulsions or staring spells.

2. What you need to know before you take Fycompa

DO NOT TAKE Fycompa:
- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking perampanel.
- If you are allergic to perampanel or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Fycompa if you have liver problems or moderate or severe kidney problems.
You should not take Fycompa if you have serious liver problems or moderate or serious kidney problems.
Before taking this medicine you should tell your doctor if you have a history of alcoholism or drug dependence.

- Fycompa may make you feel dizzy or sleepy, particularly at the beginning of treatment.

- Fycompa may make you more likely to fall over, particularly if you are an older person; this might be due to your illness.
- Fycompa may make you aggressive, angry or violent. It may also cause you to have unusual or extreme changes in behaviour or mood.

If any of these happens, talk to your doctor or pharmacist.

A small number of people being treated with anti-epileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, contact your doctor straight away.

Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of perampanel.

- DRESS typically, although not exclusively, appears as flu-like symptoms and a rash with a high body temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.

If you experience any of the above after taking Fycompa (or you are not sure) talk to your doctor or pharmacist.

Children

Fycompa is not recommended for children aged under 12. The safety and effectiveness are not yet known in this age group.

Other medicines and Fycompa

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. Taking Fycompa with certain other medicines may cause side effects or affect how they work. Do not start or stop other medicines without talking to your doctor or pharmacist.

- Other anti-epileptic medicines, such as carbamazepine, oxcarbazepine, and phenytoin that are used to treat fits may affect Fycompa. Tell your doctor if you are taking or have recently taken these medicines as your dose may need to be adjusted.
- Felbamate (a medicine used to treat epilepsy) may also affect Fycompa. Tell your doctor if you are taking or have recently taken this medicine as your dose may need to be adjusted.
- Midazolam (a medicine used to stop prolonged, acute (sudden) convulsive seizures, for sedation and sleep problem) may be affected by Fycompa. Tell your doctor if you are taking midazolam as your dose may need to be adjusted.
- Some other medicines such as rifampicin (a medicine used to treat bacterial infections), hypericum (St. John's Wort) (a medicine used to treat mild anxiety) and ketoconazole (a medicine used to treat fungal infections) may affect Fycompa. Tell your doctor if you are taking or have recently taken these medicines as your dose may need to be adjusted.
- Oral contraceptives (also called "hormonal contraceptives").

Tell your doctor if you are taking hormonal contraceptives. Fycompa may make certain hormonal contraceptives such as levonorgestrel less effective. You should use other forms of safe and effective contraception (such as a condom or coil) when taking Fycompa. You should continue doing this for one month after stopping treatment. Discuss with your doctor what may be appropriate contraception for you.

Fycompa with alcohol

Speak to your doctor before drinking alcohol. Be careful about consuming alcohol with epilepsy medicines including Fycompa.

- Drinking alcohol while taking Fycompa can make you less alert and affect your ability to drive or use tools or machines.
- Drinking alcohol while taking Fycompa can also make any feelings of anger, confusion or sadness worse.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. Do not stop treatment without first discussing it with your doctor.
- Fycompa is not recommended in pregnancy.
- You must use a reliable method of contraception to avoid becoming pregnant while you are being treated with Fycompa. You should continue doing this for one month after stopping treatment. Tell your doctor if you are taking hormonal contraceptives. Fycompa may make certain hormonal contraceptives such as levonorgestrel less effective. You should use other forms of safe and effective contraception (such as a condom or coil) when taking Fycompa. You should also do this for one month after stopping treatment. Discuss with your doctor what may be appropriate contraception for you.

It is not known whether the ingredients of Fycompa can pass into breast milk.
The doctor will weigh up the benefit and risks to your baby of taking Fycompa while you are breast-feeding.

Driving and using machines
Do not drive or use machines until you know how Fycompa affects you.
You must talk to your doctor about the effect of your epilepsy on driving and using machines.
- Fycompa may make you feel dizzy or sleepy, particularly at the beginning of treatment. If this happens to you, do not drive or use any tools or machines.
- Drinking alcohol while taking Fycompa may make these effects worse.

Fycompa contains sorbitol
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Fycompa.

Taking Fycompa with other anti-epileptic medicine, which contains sorbitol, may affect how much they work. Tell your doctor or pharmacist if you are taking any other anti-epileptic medicine(s) with sorbitol.

3. How to use Fycompa

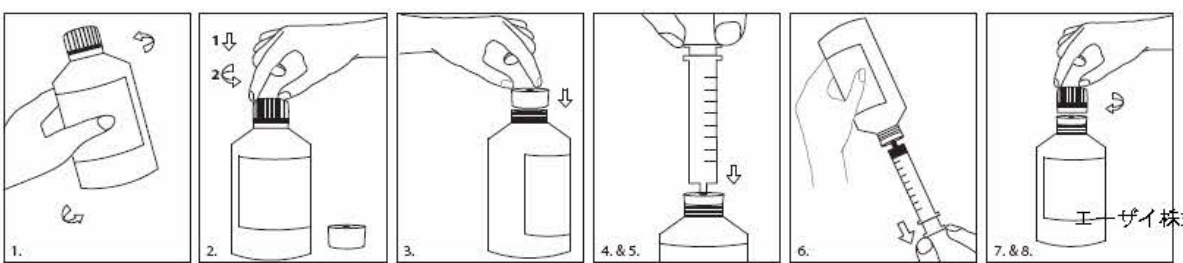
Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How much to take
The usual starting dose is 2 mg (4 ml) once a day before you go to bed.
- Your doctor may increase this in 2 mg (4 ml) steps to a maintenance dose between 4 mg (8 ml) and 12 mg (24 ml) depending on your response.
- If you have mild or moderate liver problems, your dose should not be more than 8 mg each day and your dose increases should be at least 2 weeks apart.
- Don’t take more Fycompa than your doctor has recommended. It may take a few weeks to find the right dose of Fycompa for you.

How to take
Fycompa is for oral use. You can take Fycompa with or without food and should always take it the same way. For example, if you decide to take Fycompa with food, always take it that way.

For dosing please use the oral syringe and adaptor provided.

Instructions on how to use the oral syringe and adaptor are provided below:



1. Shake for at least 5 seconds before use.
2. Push down and turn cap to open bottle.
3. Insert adaptor into the neck of the bottle until a tight seal is made.
4. Push plunger of oral syringe completely down.
5. Insert the oral syringe into the opening of the adaptor as far as possible.
6. Turn upside down and withdraw the prescribed amount of Fycompa from the bottle.
7 Turn upright and remove the oral syringe.
8 Leave the adaptor in place and replace cap on bottle. Wash the oral syringe with clean water and dry thoroughly.

If you take more Fycompa than you should
If you have taken more Fycompa than you should contact your doctor straight away. You may experience confusion, agitation and aggressive behaviour.

If you forget to take Fycompa
- If you forget to take Fycompa, wait until your next dose and then carry on as usual.
- Do not take a double dose to make up for a forgotten dose.
- If you have missed less than 7 days of treatment with Fycompa, continue taking your daily dose as originally instructed by your doctor.
- If you have missed more than 7 days of treatment with Fycompa, talk to your doctor immediately.

If you stop taking Fycompa
Take Fycompa for as long as your doctor recommends. Do not stop unless your doctor advises you to. Your doctor may reduce your dose slowly to avoid your fits (seizures) coming back or getting worse.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

A small number of people being treated with anti-epileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, contact your doctor straight away.

Very common (may affect more than 1 user in 10) are:
- feeling dizzy
- feeling sleepy (drowsiness or somnolence)

Common (may affect more than 1 user in 100) are:
- increased or decreased appetite, weight gain
- feeling aggressive, angry, irritable, anxious or confused
- difficulty with walking or other balance problems (ataxia, gait disturbance, balance disorder)
- slow speech (dysarthria)
- blurred vision or double vision (diplopia)
- spinning sensation (vertigo)
- feeling sick (nausea)
- back pain
- feeling very tired (fatigue)
- falling down.

Uncommon (may affect more than 1 user in 1000) are:
- thoughts about harming yourself or ending your own life (suicidal thoughts), tried to end your own life (attempted suicide)

Not known (the frequency of this side effect cannot be estimated from the available data) are:
- widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome).

Stop using perampanel if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fycompa

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton. The expiry date refers to the last day of the month.

This medicinal product does not require any special storage conditions.

If you have any suspension left in the bottle more than 90 days after it was first opened, you should not use it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Fycompa contains
- The active substance is perampanel. Each millilitre contains 0.5 mg of perampanel.
- The other ingredients are sorbitol (E420) liquid (crystallising), microcrystalline cellulose (E460), carmellose sodium (E466), poloxamer 188, simethicone emulsion 30% (containing purified water, silicone oil, polysorbate 65, methylcellulose, silica gel, macrogol stearate, sorbic acid, benzoic acid and sulfuric acid), citric acid, anhydrous (E330), sodium benzoate (E211) and purified water.

What Fycompa looks like and contents of the pack
Fycompa 0.5 mg/ml oral suspension is a white to off-white suspension. It comes in a bottle of 340 ml with 2 graduated oral syringes and an LDPE press-in bottle adapter (PIBA).

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Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for perampanel, the scientific conclusions of CHMP are as follows:

Drug reaction with eosinophilia and systemic symptoms (DRESS) in association with perampanel use was first reported in a PSUR in 2014. This case concerned a 13- year- old girl who presented with DRESS after increasing the dose of perampanel from 4 to 8 mg and developed acute respiratory distress and required mechanical ventilation and vasopressors, methylprednisolone and IV immunoglobulin. The patient improved after all antiepileptics were stopped. Skin biopsy confirmed DRESS. As this was the index case the issue of DRESS has been kept under close review at all subsequent PSURs. This second case of DRESS that is reported within this PSUR period in the 10 year old has several possible confounding factors but an association with perampanel exposure cannot be rule out particularly given the TWO positive rechallenges. We now have two cases of DRESS and there is already class labelling for serious cutaneous adverse reactions for antiepileptics. Taking into account the totality of data available on the association between perampanel and serious skin reactions it is concluded there is sufficient data to warrant an update of sections 4.4 and 4.8 of the SmPC and the package leaflet to reflect the risk of DRESS.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for perampanel the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing perampanel is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

Perampanel:
Company Core Data Sheet (CCDS)

August 2017

