Consensus meeting on the use of perampanel as adjunctive therapy in clinical practice: recommendations from an expert panel

Introduction
Perampanel (Fycompa®, Eisai Ltd.) is a first-in-class antiepileptic drug (AED) that was introduced into the UK in September 2012 for the adjunctive treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 12 years and older.1 By November 2014, over 7500 patients had been treated with perampanel in the UK and Ireland.2 In light of the increasing experience of using perampanel in clinical practice, a panel of epilepsy experts met in December 2014 to review their experiences of using the treatment and to develop consensus recommendations on its appropriate use in clinical practice. This report provides an overview of the latest clinical research findings with perampanel and summarises the group’s feedback and consensus recommendations.

Mode of action of perampanel
Perampanel is a selective, non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) glutamate receptor on post-synaptic neurons.3 These receptors are localised at excitatory synapses in the central nervous system, where they are essential for the generation and spread of epileptic activity.4 Perampanel selectively and potently inhibits AMPA receptors and reduces neuronal hyperexcitability, demonstrating a broad-spectrum of activity in animal models used to identify AEDs.5 The group agreed that the novel and rational mode of action of perampanel was one of the considerations when developing an individual’s treatment plan and discussing the possibility of initiating perampanel in relevant patients. For some patients, the novel mode of action of perampanel may be an attractive feature of the treatment that helps to explain the rationale for its use as an adjunctive AED.

Special Feature 2015

Summary
Perampanel has a novel mode of action based on a rational hypothesis of seizure initiation and spread. This can be considered when discussing the possibility of initiating perampanel treatment in patients with partial-onset seizures who have failed to gain control with other AEDs.

Perampanel is an easy to use antiepileptic treatment that, based on the results of phase 3 placebo-controlled studies, has an efficacy profile comparable to other recently-introduced treatments. Currently-available data demonstrate a reduction of secondarily generalised seizures with perampanel treatment. Data from “real-world” studies and clinical experience support the evidence from randomised controlled studies and confirm that perampanel is effective and generally well tolerated in clinical practice. No new safety signals or concerns have emerged to date.

All patients with refractory partial-onset seizures should be reviewed by an epilepsy specialist when possible. Perampanel may be initiated by an epilepsy specialist, appropriately-qualified epilepsy nurse specialist or general neurologist. Ongoing perampanel prescribing may be undertaken in primary care with support from a consultant neurologist or epilepsy nurse specialist if required. Perampanel can be considered a 2nd-line adjunctive therapy option in patients aged 12 years and older with partial-onset seizures.

Perampanel may be combined with other AEDs with good efficacy outcomes. A higher dose of perampanel may be required in patients taking enzyme-inducing AEDs.

Perampanel should be initiated at a dose of 2 mg/day, taken at bedtime, and titrated by increments of 2 mg every 4 weeks according to clinical need to achieve the maximum tolerated dose (MTD) (up to 12 mg/day). Consider withdrawing perampanel if there is no evidence of clinical benefit once the MTD has been reached.

For full prescribing information please refer to the summary of product characteristics.

This publication was initiated and funded by Eisai Ltd.
Fycompa-UK0174, April 2015. Prescribing information is on the last page.
The key findings from this study were as follows:

- At the time of latest reporting, 1216 patients had received perampanel for a median of 1480 patients aged ≥12 years who were receiving one, two or three AEDs and experienced a median of 10–13 partial-onset seizures per 28 days during the pre-randomisation phase of the studies, despite most individuals (86%) receiving two or three AEDs. The most common concomitant AEDs were carbamazepine, valproic acid, lamotrigine and levetiracetam. The key findings from this analysis are outlined below:

#### Efficacy and safety of perampanel

The efficacy and safety of perampanel have been evaluated in a clinical development programme that included three phase 3, double-blind, placebo-controlled studies: study 304, study 305, and study 306, and a recently-reported long-term extension study 307. A total of 1480 patients aged ≥12 years who were receiving one, two or three AEDs and experienced at least five partial-onset seizures during a 6-week baseline period were enrolled into the phase 3 studies. Perampanel doses of 2, 4, 8, and 12 mg taken once-daily were assessed. Doses were titrated up by 2 mg each week over a 6-week period, followed by a 13-week, double-blind maintenance phase. Primary efficacy endpoints were median % change from baseline in seizure frequency per 28 days and the percentage of patients achieving a ≥50% reduction in the frequency of all seizures per 28 days (50% responder rate; baseline versus maintenance).

#### Pooled analysis of phase 3 studies

This pooled analysis included data from 1480 patients who took part in the three phase 3 studies.9 These were treatment-refractory patients who experienced a median of 10–13 partial-onset seizures per 28 days during the pre-randomisation phase of the studies, despite most individuals (86%) receiving two or three AEDs. The most common concomitant AEDs were carbamazepine, valproic acid, lamotrigine and levetiracetam. The key findings from this analysis are outlined below:

#### Efficacy:

- Adjunctive therapy with perampanel 4, 8 and 12 mg/day significantly reduced the frequency of partial-onset seizures (Figure 1) and improved responder rates (Figure 2) compared with placebo.

- Perampanel 4, 8 and 12 mg/day also significantly reduced the frequency of secondarily generalised seizures compared with placebo (Figure 3).

- At the recommended initial maintenance doses of 4–8 mg/day, up to 17% of patients achieved ≥75% reduction in seizure frequency.

- Seizure-freedom rates during maintenance therapy were higher with perampanel 4–12 mg/day (3.5–4.4%) than with placebo (1.0%) (p<0.05 for each dose, completers analysis).

#### Safety and tolerability:

- Perampanel was generally well tolerated. The most frequently-reported treatment-emergent adverse events (TEAEs) were dizziness and somnolence (Table 1).

- Psychiatric and behavioural TEAEs (e.g. irritability, hostility, aggression) were observed more frequently in perampanel-treated patients than in placebo-treated patients – the frequency of these events increased with increasing perampanel doses.

- Serious AEs were reported by a similar proportion of patients taking placebo (5.0%) and perampanel (5.5%).

This pooled analysis augments the findings from the individual studies demonstrating the efficacy and tolerability of perampanel as an adjunctive treatment for patients with partial-onset seizures. The group agreed that, in this highly treatment-refractory study population – which is typical of the populations now entering AED clinical trials – seizure freedom is not always a realistic goal. The efficacy profile of perampanel was considered by the group to be comparable to that of other recently-introduced AEDs.

#### Long-term extension study

Study 307 was designed as the long-term, open-label extension to the three phase 3 double-blind, placebo-controlled studies of adjunctive perampanel in partial-onset seizures to validate the initial registration study findings: 96% of eligible patients who completed the phase 3 trials entered this study. The study was designed with a 16-week, blinded conversion period, during which all participants were up-titrated by 2 mg every 2 weeks to 12 mg/day or their maximum tolerated dose (MTD). This was followed by a long-term (~5 years) follow-up period during which dose adjustments of perampanel and concomitant AEDs could be made at the investigator’s discretion.

At the time of latest reporting, 1216 patients had received perampanel for a median duration of 1.5 years (range 1 week to 3.3 years), with more than 300 patients having received treatment for >2 years. The mean daily dose of perampanel achieved was 10.6 mg, with 92% of patients taking a maximum daily dose of 10 or 12 mg. Fifty-eight percent of patients were retained on perampanel treatment at the data cut-off point for this analysis. The key findings from this study were as follows:

- Long-term adjunctive perampanel was generally well tolerated, with a safety and tolerability profile consistent with that reported in phase 2 and 3 studies.

- Most AEs reported were mild or moderate in intensity; the most frequently-reported
adverse events were dizziness, somnolence, headache, fatigue, irritability and weight increase. Only dizziness and irritability led to treatment discontinuation in >1% of patients (3.9% and 1.3%, respectively).

- No new safety signals were observed with over 1803 patient-years of exposure to perampanel.
- Treatment efficacy in terms of seizure response was maintained over 2 years of perampanel treatment, indicating sustained benefits.
- Responder rates consistently remained above 40% after titration and reached 58% in the 337 patients treated for 2 years.
- In patients with secondarily generalised seizures at baseline, the frequency of these seizures was reduced by 77% at 9 months (n=422) and by 90% at 2 years (n=141).
- Long-term seizure freedom was achieved in some of these highly treatment-refractory patients (5% of patients treated for 1 year (n=694) and 3% of patients treated for 2 years (n=141)).

Consensus statement 2: Perampanel is an easy to use antiepileptic treatment that, based on the results of phase 3 placebo-controlled studies, has an efficacy profile comparable to other recently-introduced treatments. Currently-available data demonstrate a reduction of secondarily generalised seizures with perampanel treatment.

Perampanel in the ‘real-world’: results from European and UK studies

Data are now emerging from ‘real-world’ observational studies conducted in clinical practice. One recently-reported study involved 281 ‘difficult-to-treat’ patients with partial epilepsy being managed in epilepsy centres and neurology departments in Austria and Germany. Data from consecutively-treated patients receiving adjunctive perampanel were collected for a minimum of 6 months. The mean dose of perampanel in this study was 7.7 mg/day.

After 6 months of follow-up, 169 patients (60%) were still receiving perampanel treatment and 43 patients (15%) had been seizure-free during the preceding 3 months at a mean dose of 8.7 mg/day (Figure 4). Half the patients had experienced at least a 50% reduction in their seizure frequency (all seizure types) (Figure 4). As in the phase 3 clinical trials, the most commonly reported AEs were somnolence and dizziness. Other AEs reported were ataxia, aggression, nausea and irritability.

The results from a number of other ‘real-world’ studies conducted in Spain, the UK and Ireland have also been published or presented. These observational studies involving almost 500 patients who had taken adjunctive perampanel for up to 14 months in clinical practice confirm relatively high rates of treatment retention and good seizure response rates – typically at lower doses than were used in the controlled clinical trials. A seizure freedom rate of 17% was reported in one study. In the view of the group the tolerability profile of perampanel in these ‘real-world’ studies reflected that observed in clinical trials, with dizziness, somnolence and irritability the most commonly-reported AEs.

The group reviewed their own experiences of using perampanel in clinical practice, reporting that the treatment is easy to use in a broad range of patients; it has a manageable tolerability profile and has been very effective in some patients. Cases were presented demonstrating sustained seizure-freedom in some previously intractable patients, early responses to perampanel treatment, frequent improvements in seizure severity, more rapid post-ictal recovery and improved quality of life. Members of the group reported that, in some patients, it had been possible to reduce or withdraw other AEDs after initiation of perampanel treatment. Other cases were presented in which patients had a less favourable response, with an increase in irritability/aggression and/or mood disturbances leading to treatment withdrawal.

Consensus statement 2: Perampanel is an easy to use antiepileptic treatment that, based on the results of phase 3 placebo-controlled studies, has an efficacy profile comparable to other recently-introduced treatments. Currently-available data demonstrate a reduction of secondarily generalised seizures with perampanel treatment.

Perampanel in the ‘real-world’: results from European and UK studies

Data are now emerging from ‘real-world’ observational studies conducted in clinical practice. One recently-reported study involved 281 ‘difficult-to-treat’ patients with partial epilepsy being managed in epilepsy centres and neurology departments in Austria and Germany. Data from consecutively-treated patients receiving adjunctive perampanel were collected for a minimum of 6 months. The mean dose of perampanel in this study was 7.7 mg/day.

After 6 months of follow-up, 169 patients (60%) were still receiving perampanel treatment and 43 patients (15%) had been seizure-free during the preceding 3 months at a mean dose of 8.7 mg/day (Figure 4). Half the patients had experienced at least a 50% reduction in their seizure frequency (all seizure types) (Figure 4). As in the phase 3 clinical trials, the most commonly reported AEs were somnolence and dizziness. Other AEs reported were ataxia, aggression, nausea and irritability.

The results from a number of other ‘real-world’ studies conducted in Spain, the UK and Ireland have also been published or presented. These observational studies involving almost 500 patients who had taken adjunctive perampanel for up to 14 months in clinical practice confirm relatively high rates of treatment retention and good seizure response rates – typically at lower doses than were used in the controlled clinical trials. A seizure freedom rate of 17% was reported in one study. In the view of the group the tolerability profile of perampanel in these ‘real-world’ studies reflected that observed in clinical trials, with dizziness, somnolence and irritability the most commonly-reported AEs.

The group reviewed their own experiences of using perampanel in clinical practice, reporting that the treatment is easy to use in a broad range of patients; it has a manageable tolerability profile and has been very effective in some patients. Cases were presented demonstrating sustained seizure-freedom in some previously intractable patients, early responses to perampanel treatment, frequent improvements in seizure severity, more rapid post-ictal recovery and improved quality of life. Members of the group reported that, in some patients, it had been possible to reduce or withdraw other AEDs after initiation of perampanel treatment. Other cases were presented in which patients had a less favourable response, with an increase in irritability/aggression and/or mood disturbances leading to treatment withdrawal.

Consensus statement 2: Perampanel is an easy to use antiepileptic treatment that, based on the results of phase 3 placebo-controlled studies, has an efficacy profile comparable to other recently-introduced treatments. Currently-available data demonstrate a reduction of secondarily generalised seizures with perampanel treatment.

Perampanel in the ‘real-world’: results from European and UK studies

Data are now emerging from ‘real-world’ observational studies conducted in clinical practice. One recently-reported study involved 281 ‘difficult-to-treat’ patients with partial epilepsy being managed in epilepsy centres and neurology departments in Austria and Germany. Data from consecutively-treated patients receiving adjunctive perampanel were collected for a minimum of 6 months. The mean dose of perampanel in this study was 7.7 mg/day.

After 6 months of follow-up, 169 patients (60%) were still receiving perampanel treatment and 43 patients (15%) had been seizure-free during the preceding 3 months at a mean dose of 8.7 mg/day (Figure 4). Half the patients had experienced at least a 50% reduction in their seizure frequency (all seizure types) (Figure 4). As in the phase 3 clinical trials, the most commonly reported AEs were somnolence and dizziness. Other AEs reported were ataxia, aggression, nausea and irritability.

The results from a number of other ‘real-world’ studies conducted in Spain, the UK and Ireland have also been published or presented. These observational studies involving almost 500 patients who had taken adjunctive perampanel for up to 14 months in clinical practice confirm relatively high rates of treatment retention and good seizure response rates – typically at lower doses than were used in the controlled clinical trials. A seizure freedom rate of 17% was reported in one study. In the view of the group the tolerability profile of perampanel in these ‘real-world’ studies reflected that observed in clinical trials, with dizziness, somnolence and irritability the most commonly-reported AEs.

The group reviewed their own experiences of using perampanel in clinical practice, reporting that the treatment is easy to use in a broad range of patients; it has a manageable tolerability profile and has been very effective in some patients. Cases were presented demonstrating sustained seizure-freedom in some previously intractable patients, early responses to perampanel treatment, frequent improvements in seizure severity, more rapid post-ictal recovery and improved quality of life. Members of the group reported that, in some patients, it had been possible to reduce or withdraw other AEDs after initiation of perampanel treatment. Other cases were presented in which patients had a less favourable response, with an increase in irritability/aggression and/or mood disturbances leading to treatment withdrawal.
The panel members agreed that, in their experience, perampanel was generally well tolerated by most patients, with predictable early side-effects (e.g., dizziness), an acceptable neurocognitive profile, and manageable levels of headache and irritability. Treatment retention rates were reported to be generally high.

**Consensus statement 3:** Data from ‘real-world’ studies and clinical experience support the evidence from randomized controlled studies and confirm that perampanel is effective and generally well tolerated in clinical practice. No new safety signals or concerns have emerged to date.

### Optimising use of perampanel in clinical practice

Clinical guidelines from the National Institute for Health and Clinical Excellence (NICE) relating to the diagnosis and treatment of epilepsy were published in January 2012 and do not, therefore, include recommendations for the adjunctive use of perampanel in partial-onset seizures. The guidelines currently recommend that all patients with newly diagnosed partial-onset seizures are offered monotherapy with carbamazepine or lamotrigine as a first-line treatment (Table 1). Alternative monotherapies for patients in whom these treatments are unsuitable or not tolerated are levetiracetam, oxcarbazepine and sodium valproate. NICE-recommended adjunctive treatments are shown in Table 1. The NICE guidelines recommend that if standard adjunctive treatment is ineffective or not tolerated, advice should be sought from a tertiary epilepsy specialist.

When to consider initiating perampanel

There are currently no clear-cut, evidence-based guidelines to assist in the selection and sequencing of AED treatment. Treatment decisions are made empirically based on the seizure type and/or syndrome, the patient’s age and gender, comorbidities and learning status, the side-effect profile of the drug, personal preferences, cost and affordability. The group agreed that, based on its ease of use and efficacy and tolerability profile, perampanel could be considered a 2nd-line adjunctive therapy option in patients with partial-onset seizures (Table 1). The group recommended that perampanel may be considered before pregabalin, gabapentin, tiagabine, phenytoin, phenobarbital, vigabatrin and retigabine in most patients. There are currently no specific predictive factors for the efficacy and tolerability of perampanel treatment – patients aged 12 years and older whose partial seizures are uncontrolled on monotherapy could therefore be potential candidates to receive adjunctive perampanel.

In-line with NICE guidance, the meeting participants concurred that all patients with refractory partial-onset seizures should be reviewed by an epilepsy specialist when possible. They agreed that perampanel may be initiated by an epilepsy specialist, appropriately-qualified epilepsy nurse specialist or general neurologist. Ongoing perampanel prescribing may be undertaken in primary care with support from a consultant neurologist or epilepsy nurse specialist if required.

**Consensus statement 4:** All patients with refractory partial-onset seizures should be reviewed by an epilepsy specialist when possible. Perampanel may be initiated by an epilepsy specialist, appropriately-qualified epilepsy nurse specialist or general neurologist. Ongoing perampanel prescribing may be undertaken in primary care with support from a consultant neurologist or epilepsy nurse specialist if required. Perampanel can be considered a 2nd-line adjunctive therapy option in patients aged 12 years and older with partial-onset seizures.

### Perampanel

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo (n=442)</th>
<th>2 mg/day (n=180)</th>
<th>4 mg/day (n=172)</th>
<th>8 mg/day (n=431)</th>
<th>12 mg/day (n=255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>294 (67%)</td>
<td>111 (62%)</td>
<td>111 (65%)</td>
<td>350 (81%)</td>
<td>227 (89%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>40 (9%)</td>
<td>18 (10%)</td>
<td>28 (16%)</td>
<td>137 (32%)</td>
<td>109 (43%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>32 (7%)</td>
<td>22 (12%)</td>
<td>16 (9%)</td>
<td>67 (16%)</td>
<td>45 (18%)</td>
</tr>
<tr>
<td>Headache</td>
<td>50 (11%)</td>
<td>16 (9%)</td>
<td>19 (11%)</td>
<td>49 (11%)</td>
<td>34 (13%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (5%)</td>
<td>8 (4%)</td>
<td>13 (8%)</td>
<td>36 (8%)</td>
<td>31 (12%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>13 (3%)</td>
<td>7 (4%)</td>
<td>7 (4%)</td>
<td>29 (7%)</td>
<td>30 (12%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (5%)</td>
<td>4 (2%)</td>
<td>5 (3%)</td>
<td>25 (6%)</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>Fall</td>
<td>15 (3%)</td>
<td>2 (1%)</td>
<td>3 (2%)</td>
<td>22 (5%)</td>
<td>26 (10%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>18 (4%)</td>
<td>7 (4%)</td>
<td>9 (5%)</td>
<td>23 (5%)</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Upper RTI</td>
<td>12 (3%)</td>
<td>11 (6%)</td>
<td>6 (4%)</td>
<td>14 (3%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>14 (3%)</td>
<td>21 (8%)</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>2 (&lt;1%)</td>
<td>0</td>
<td>0</td>
<td>22 (5%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

TEAE, treatment-emergent adverse event; RTI, respiratory tract infection

<table>
<thead>
<tr>
<th>1st-line monotherapy (NICE guidelines)</th>
<th>2nd-line monotherapy (NICE guidelines)</th>
<th>1st-line adjunctive therapy (NICE guidelines)</th>
<th>2nd-line adjunctive therapy (Consensus meeting participants)</th>
<th>3rd-line adjunctive therapy (Consensus meeting participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Carbamazepine Lamotrigine</td>
<td>Carbamazepine Clobazam Lamotrigine</td>
<td>Eslicarbazepine acetate Lacosamide Perampanel Zonisamide</td>
<td>Gabapentin Phenobarbital Phenytoin Pregabalin Retigabine Tiagabine Vigabatin</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Levetiracetam Oxcarbazepine Sodium valproate</td>
<td>Levetiracetam Oxcarbazepine Sodium valproate Topiramate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Recommended place of perampanel in the pharmacological management of partial-onset seizures based on the NICE guidelines and the experience of the consensus meeting participants.
Perampanel should be initiated at a dose of 2 mg/day and titrated in 1- to 2-weekly intervals, however, ‘real-world’ data and experience in clinical practice suggests that perampanel should be titrated slowly to the MTD (up to 12 mg/day). If there is no evidence of clinical benefit once the MTD has been reached, treatment withdrawal should be considered.

Consensus statement 6: Perampanel should be initiated at a dose of 2 mg/day, taken at bedtime, and titrated by increments of 2 mg every 4 weeks according to clinical need to achieve the MTD (up to a maximum dose of 12 mg/day). If there is no evidence of clinical benefit once the MTD has been reached, treatment withdrawal should be considered.

Summary and conclusions
Perampanel is a valuable addition to the armamentarium for treating partial-onset seizures and preventing secondary generalisation. Its unique mode of action, ease of use, and good efficacy and tolerability profile make it potentially suitable for use as an adjunctive therapy in most treatment-refractory patients aged 12 years and older with partial epilepsy. Clinicians should consider perampanel as a 2nd-line adjunctive therapy option in patients who have not responded adequately to other AEDs.

Perampanel treatment may be initiated by an epilepsy specialist, appropriately-qualified epilepsy nurse specialist or general neurologist. Experience in clinical practice suggests that perampanel should be titrated slowly to the MTD (up to 12 mg/day) to enhance tolerability and treatment retention. Ongoing prescribing of perampanel may be undertaken in primary care with support from a consultant neurologist or epilepsy specialist nurse if required.

Acknowledgements
This report was initiated, supported and funded by Eisai Ltd. Medical writing support was provided by Ali Jordan and Innervate Ltd, and funded by Eisai Ltd.

References
PRESENTATION: Film-coated tablets: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg per panem. INDICATION: Adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

DOSE AND ADMINISTRATION: Adults and Adolescents: Starting dose is 2 mg daily. Dose should be titrated based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of between 4 mg/day to 12 mg/day. Dose should be taken orally once daily before bedtime. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel 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 should be titrated no more frequently than at 1-week intervals. Withdraw gradually. Elderly and patients with renal or hepatic impairment: Dosage adjustments not required in elderly patients. Dosage adjustments not required in mild renal impairment, not recommended in patients with moderate or severe renal impairment or patients undergoing haemodialysis. Caution in mild or moderate hepatic impairment, titration should not be faster than every 2 weeks and maximum daily dosage not exceeding 8 mg. Not recommended in severe hepatic impairment. Children and adolescents under 12 years: No data available.

CONTRA-INDICATIONS: Hypersensitivity to perampanel or any excipient.

PREGNANCY: Not recommended.

LACTATION: Unknown if excreted into breast milk. A decision whether to discontinue breastfeeding or to discontinue/abstain fromFYcompa therapy taking into account the benefit of breastfeeding for the child and benefit for the therapy for the woman.

WARNINGS AND PRECAUTIONS: Monitor for signs of suicidal ideation and behaviours and consider appropriate treatment. Perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. At doses of 12 mg/day FYcompa may decrease the effectiveness of progestative-containing hormonal contraceptives. There appears to be an increased risk of falls, particularly in the elderly. Aggressive and hostile behaviour has been reported; 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. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of perampanel abuse. Patients should be closely monitored for tolerability and clinical response when adding or removing cytochrome P450 inducers or inhibitors, or switching from concomitant non-inducer anti-epileptic medicinal products to enzyme inducing medicinal products and vice versa, since perampanel plasma levels can be decreased or increased; the dose of perampanel may need to be adjusted accordingly. There are no data regarding the effects of withdrawal of concomitant anti-epileptic medicinal products to achieve monotherapy with perampanel. 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.

DRUG INTERACTIONS: 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. Carbamazepine, phenytoin, oxcarbazepine and topiramate have been shown to increase perampanel clearance and consequently to decrease plasma concentrations of perampanel. FYcompa did not affect in a clinically relevant manner the clearance of clonazepam, lorazepam, phenobarbital, phenytoin, topiramate, zonisamide, carbamazepine, clobazam, lamotrigine and valproic acid. The effect of perampanel on monohydroxyoxcarbazepine concentrations is not known. FYcompa (6 mg once daily for 20 days) decreased midazolam AUC by 13% in healthy subjects. Strong inducers of cytochrome P450 such as rifampicin and hypericum are expected to decrease perampanel concentrations. Felbamate has been shown to decrease the concentrations of some drugs and may also reduce perampanel concentrations. Ketocazole, a CYP3A4 inhibitor, increased perampanel AUC by 20% and prolonged perampanel half-life by 15%. Strong inhibitors of other cytochrome P450 isoforms could potentially also increase perampanel concentrations. FYcompa used in combination with other central nervous system (CNS) depressants such as alcohol can increase levels of anger, confusion, and depression. The effects of perampanel on tasks involving alertness and vigilance such as driving ability were additive or supra-additive to the effects of alcohol.

SIDE EFFECTS: Adverse reactions most commonly lead to discontinuation of perampanel were dizziness and somnolence. Refer to SPC for all side effects. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10): decreased appetite, increased appetite, aggression, anger, anxiety, confusional state, ataxia, dysaesthesia, balance disorder, irritability, diplopia, vision blurred, vertigo, nausea, back pain, gait disturbance, fatigue, weight increased, falls. Based on the clinical trial database of 143 adolescents, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults.

LEGAL CATEGORY: POM

BASIC UK NHS COST: FYcompa 2 mg: packs of 7 £35.00, FYcompa 4 mg: packs of 28 £140.00, FYcompa 6 mg: packs of 28 £140.00, FYcompa 8 mg: packs of 28 £140.00, FYcompa 10 mg: packs of 28 £140.00, FYcompa 12 mg: packs of 28 £140.00.

IRISH PRICE TO WHOLESALER: FYcompa 2 mg: packs of 7 €40.95, FYcompa 4 mg: packs of 28 €163.80, FYcompa 6 mg: packs of 28 €163.80, FYcompa 8 mg: packs of 28 €163.80, FYcompa 10 mg: packs of 28 €163.80, FYcompa 12 mg: packs of 28 €163.80.

Marketing authorisation numbers: FYcompa 2 mg 7 tablets: EU/1/12/776/001, FYcompa 4 mg 28 tablets: EU/1/12/776/003, FYcompa 6 mg 28 tablets: EU/1/12/776/006, FYcompa 8 mg 28 tablets: EU/1/12/776/009, FYcompa 10 mg 28 tablets: EU/1/12/776/012, FYcompa 12 mg 28 tablets: EU/1/12/776/015.

Marketing authorisation holder: Eisai Ltd.

Further information from/Marketed by: Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN

Date of preparation: November 2013