

Optimal Use of Perampanel in Asian Patients with Epilepsy: Expert Opinion

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Abstract: Perampanel is a once-daily, first-in-class AMPA receptor antagonist approved for the treatment of epilepsy and exhibits broad-spectrum efficacy in a range of seizure types when used as both monotherapy and adjunctive therapy. Clinical studies and real-world evidence have demonstrated the advantages of initiating perampanel at low doses and utilizing a slow titration strategy. Initiating perampanel at an early stage has also been shown to be associated with better patient outcomes. However, the optimal use and place of perampanel in clinical practice has not yet been clearly defined for the Asian patient population. Use of perampanel in clinical practice varies markedly across the Asia region because of variation in knowledge, attitudes, and practice. There is currently no specific guidance on best practices for prescribing perampanel in Asian patients or how to optimize treatment strategies to maximize adherence. A group of epilepsy experts attended a virtual meeting in September 2020 to discuss their experience with using perampanel in the Asian practice setting, including their views regarding appropriate patient populations, optimal starting and maintenance doses, optimal titration regimens, key barriers to adherence, and prevention and management of adverse events. This article summarizes key clinical and real-world evidence for perampanel and consolidates the experts' opinions on optimization of perampanel prescribing and adherence in real-world practice, providing practical strategies for clinicians to implement to improve outcomes for people with epilepsy in Asia.

Keywords: perampanel, epilepsy, real-world experience, Asia

Introduction

Approximately 23 million people in Asia are living with epilepsy, with prevalence varying across countries in the region from 1.5 to 14.0 per 1000 person-years.¹ Despite treatment with anti-seizure medication (ASM), however, more than one-third of patients still experience seizures that remain uncontrolled.² Drug-refractory epilepsy is associated with reduced quality of life and increased rates of hospitalization, morbidity, and mortality.³ In addition, patients whose seizures are poorly controlled face a greater burden of healthcare costs than those whose seizures are in remission.⁴ With each subsequent ASM regimen trialed, the probability of achieving seizure freedom diminishes substantially; most patients who gain seizure control do so with the first or second ASM prescribed.² Therefore, early selection of an effective ASM for initial monotherapy or as early adjunctive therapy is critical for realizing the best possible therapeutic outcomes.

Another key factor contributing to poorly controlled epilepsy is inadequate adherence to ASM therapy.⁵ Non-adherence in epilepsy is estimated to range from 30% to 50% of patients, similar to what is observed with other chronic

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illnesses.⁵ Complicated ASM regimens are believed to negatively impact patient adherence, and simplifying treatment strategies by utilizing monotherapy and/or reducing dose frequency can be of benefit.⁶ Prescribing an ASM with characteristics that promote adherence contributes to achieving seizure freedom.

Perampanel is a first-in-class AMPA receptor antagonist approved for the treatment of epilepsy and has broad-spectrum efficacy.^{7–12} Perampanel is indicated by the US Food and Drug Administration for treatment of focal onset seizures (FOS), with or without focal-to-bilateral tonic-clonic seizures (FBTCS), in patients ≥ 4 years of age (monotherapy and adjunctive therapy) and as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (GTCS) in patients with epilepsy ≥ 12 years of age.¹³ In addition, perampanel has a once-daily dosing schedule that supports patient adherence.

Perampanel is already widely indicated for adjunctive use in Asia, and monotherapy is progressively gaining approval across the region, which will foster the earlier use of perampanel to achieve improved patient outcomes. However, there are challenges in the adoption of perampanel in real-world settings in Asia because of variation in knowledge, attitudes, and practice across the region. The optimal use and place of perampanel in clinical practice has not yet been clearly defined for the Asian patient population, and it is therefore at times inaccurately perceived as an agent that should be reserved for later stages of treatment. There is currently no specific guidance on best practices for prescribing perampanel in Asian patients or how to optimize treatment strategies to maximize adherence.

To address these gaps, this paper provides key recommendations on perampanel use from seven epilepsy experts in four Asian countries (China [2], Japan, Taiwan [2], and Thailand [2]) who gathered at a virtual expert advisory board meeting in September 2020. The purpose of the meeting was to discuss the contemporary use of perampanel in clinical practice in Asian countries, share best practice as it relates to prescribing perampanel in Asian patients, identify key barriers to adherence, and develop recommendations that can be easily implemented by clinicians across the region.

This paper describes the consolidated guidance on and insights into optimizing perampanel prescribing and adherence generated at the expert meeting.

Key Clinical and Real-World Evidence on Perampanel

Based on clinical trial data and real-world experience, perampanel is observed to have broad-spectrum efficacy in a range of seizure types when used as both monotherapy and adjunctive therapy.^{7–12} Clinical studies and real-world evidence have demonstrated the benefits of initiating perampanel at low doses (≤ 6 mg)^{7–12} and utilizing a slow titration strategy (increasing dose by 2 mg at ≥ 2 -week intervals).^{7,14–16} Initiating perampanel at an early stage (as initial monotherapy or early adjunctive therapy) has also been shown to be associated with better patient outcomes; these data are described below.

Clinical Trial Data

Monotherapy

FREEDOM (Study 342) was a Phase III, open-label study in Japan and South Korea of the efficacy and safety of perampanel monotherapy in patients with FOS with or without FBTCS for 26 weeks (N=73). All patients were newly diagnosed with epilepsy or had experienced seizure recurrence after a period of remission at least 2 years after the cessation of the last ASM treatment.⁸ Patients were treated with perampanel 4 mg/day, which could be titrated to 8 mg/day following a seizure. Perampanel monotherapy was found to be efficacious, with a 63.0% seizure freedom rate achieved in patients who were maintained on the 4 mg/day dose and 74.0% overall (last evaluated dose, 4 or 8 mg/day). The safety profile of perampanel 4 mg/day was found to be consistent with that of Phase III studies; treatment-emergent adverse events were reported in 64.0% of patients in the low-dose cohort and were the cause of withdrawal for only eight patients (9.0%).

Early Adjunctive Therapy

FAME (Study 412) was a Phase IV, open-label study of the efficacy and safety of perampanel as the first adjunctive therapy to monotherapy in patients with FOS with or without FBTCS in Korea (N=85).⁷ Patients received perampanel 4 mg/day, up-titrated by 2 mg over ≥ 2 -week intervals to a maximum of 12 mg/day if required. During the 24-week maintenance period, perampanel was found to be an effective broad-spectrum, first-line adjunctive therapy in patients for whom ASM monotherapy was insufficient. A 50% responder rate ($\geq 50\%$ reduction in total seizure frequency) was observed in 80% of patients during the maintenance period, with seizure improvements seen at both low (4 and 6 mg/day) and high (8, 10, and 12 mg/

day) doses. In addition, post hoc analyses suggested that when stratified by titration speed (slow: up-titration performed at ≥ 2 -week intervals; fast: up-titration performed at < 2 -week intervals), the proportions of patients in the slow titration group who achieved 50%, 75%, or 100% responder rates were numerically higher than those in the fast titration group (83.1% vs 73.1%, 72.9% vs 69.2%, and 49.2% vs 42.3%, respectively). Overall, perampanel was well tolerated, with most treatment-emergent adverse events characterized as mild. Furthermore, post hoc analyses demonstrated that when stratified by titration speed, the incidence of treatment-emergent adverse events was 82.9% for the fast titration group compared with 70.5% for the slow titration group, suggesting that slower up-titration may be a useful strategy to reduce the overall incidence of adverse events with perampanel.

In a pooled Phase III analysis, efficacy and safety of low-dose (4 mg/day) perampanel as first adjunctive or later adjunctive therapy in patients with FOS with or without FBTCS was assessed (N=979).¹¹ Compared with placebo, perampanel 4 mg/day conferred significantly greater median percentage reductions in the frequency of all focal seizures per 28 days (21.1% vs 12.6%, $P=0.0004$). Patients who received perampanel 4 mg/day also experienced a significant reduction in FBTC seizures compared with placebo (49.8% vs 17.4%, $P=0.0001$). Seizure freedom rates were also significantly higher with perampanel 4 mg/day than with placebo for all focal seizures (3.6% vs 0.8%, $P=0.0018$) and for FBTCS (18.7% vs 11.1%, $P=0.0424$). The rate of reported adverse events with adjunctive perampanel 4 mg/day in patients with focal seizures was 30.5% overall, with the most frequently reported events being dizziness (7.3%), somnolence (3.6%), and headache (3.1%). Treatment-emergent adverse events led to discontinuation in only 2% of patients receiving perampanel 4 mg/day.

Study 311 was a global, multicenter, open-label, single-arm study that evaluated the safety and efficacy of perampanel in children aged 4 to < 12 years of age with FOS or GTCS (N=180).¹⁷ Perampanel was demonstrated to be well tolerated, with safety and efficacy outcomes consistent with those seen in adult studies.

Real-World Data

Monotherapy

A retrospective, multicenter, registry study assessed the efficacy and tolerability of perampanel for routine clinical treatment of FOS and GTCS in Spain (N=98). Patients

were initiated on primary perampanel monotherapy or switched to monotherapy by removal of all concomitant ASMs and treated for a median of 14 months (range: 1–57). The median maintenance dose of perampanel used was 4 mg/day (interquartile range: 4–6).¹⁰ At 3, 6, and 12 months since initiation of perampanel treatment, respectively, retention rates were 93.8%, 89.3%, and 80.9%, responder rates were 79.6%, 70.1%, and 52.8%, and seizure freedom rates were 62.7%, 56.1%, and 41.5%. Regardless of whether perampanel monotherapy was given as the primary or secondary treatment, retention rates did not vary ($P=0.57$). While not reaching statistical significance, seizure freedom rates during the whole observation period were higher in the primary monotherapy group than in the converted monotherapy group (71.4% vs 51.2% at 6 months and 58.3% vs 37.5% at 12 months). Perampanel monotherapy was generally well tolerated, with most reported adverse events being mild in nature.

A retrospective, multicenter, non-interventional study evaluated patient retention on perampanel as primary or secondary monotherapy for FOS at specialist epilepsy centers in Russia and Europe (N=60).⁹ The primary monotherapy cohort received perampanel in the absence of any other ASM, and the secondary monotherapy group were converted from adjunctive therapy by withdrawing all concomitant ASMs. Overall, perampanel retention rates at 3 and 6 months were 95% and 74%, respectively. At study cut-off at 24 months, 68% of patients were continuing to take perampanel treatment as primary or secondary monotherapy.

Early Adjunctive Therapy

A prospective, observational study investigated the efficacy and safety of perampanel as early adjunctive treatment in patients with non-controlled FOS with or without FBTCS in Spain (N=113).³ The median dose of perampanel prescribed was 6 mg/day (range: 4–12). Patients achieved significantly higher rates of seizure freedom at 12 months when perampanel was initiated as a first versus second adjunctive treatment (38.1% vs 19.7%, respectively; $P=0.033$). The treatment retention rate was high, with 83.2% and 80.5% of patients still receiving perampanel at 6 and 12 months, respectively. Overall, treatment-emergent adverse events were reported in 30.1% (34/113) of patients, and psychiatric adverse events occurred in 20.4% (23/113); most events were mild to moderate in severity. The percentage of patients who experienced adverse events (36.6% vs 19%, $P=0.049$)

and psychiatric adverse events (28.2% vs 7.1%, $P=0.008$) was significantly higher when perampanel was added as second adjunctive treatment than when it was used as first adjunctive treatment.

The FYDATA study was a retrospective, multicenter, observational study investigating the safety and efficacy of perampanel as an early adjunctive in patients with FOS ($N=464$).¹⁴ A large proportion of patients were highly treatment refractory, with an average (range) of 7.8 (1–18) prior and 2.8 (1–5) concurrent ASMs prescribed. At 1 year, the perampanel retention rate was 60.6%. Seizure reduction, safety, and tolerability were similar to those seen in clinical trials. The effect of titration schedule was also investigated; significantly fewer patients on slow titration schemes (2 mg increase every 3–4 weeks) experienced treatment-emergent adverse events than patients on fast titration schemes (2 mg increase every week; $P=0.006$). In addition, fewer patients on slow titration schemes experienced psychiatric adverse events compared with patients on fast titration, although this was not significant ($P=0.152$).

A retrospective, observational, two-center study analyzed the efficacy of perampanel as early adjunctive treatment in patients with FOS in Japan ($N=51$).¹⁸ The seizure-freedom rates at 6 and 12 months were 29% and 28%, respectively. In the 30 patients who received perampanel continuously for 6 months, the seizure-freedom rates were significantly higher in those who used perampanel as a first adjunctive treatment (75%) compared with those who used it later (31.8%). The most frequently prescribed perampanel dose among patients who achieved seizure freedom was 2 mg/day.

A multicenter, retrospective, observational study evaluated the efficacy and safety of perampanel as early adjunctive treatment in patients with idiopathic generalized epilepsy (IGE), including myoclonic and absence seizures.¹² The median dose of perampanel prescribed was 6 mg/day. Rates of retention and seizure freedom were significantly higher when perampanel was used as early (≤ 2 prior ASMs) versus late (> 2 prior ASMs) adjunctive therapy.

The effect of perampanel in the treatment of myoclonic and absence seizures was also evaluated in a post hoc analysis of a Phase III study ($N=163$).¹⁹ Myoclonic seizure freedom was achieved in 16.7% of perampanel-treated patients compared with 13.0% of those treated with placebo, and absence seizure freedom was achieved in 22.2% versus 12.1%, respectively (P values not reported).

A multicenter, retrospective, observational study determined the 12-month efficacy and tolerability of perampanel as an adjunctive treatment in children ≥ 4 years of age with epilepsy in Korea ($N=220$).²⁰ Response and seizure freedom rates were 43.6% and 17.7%, respectively, with no significant differences across age groups. Adverse events were reported in 40% of patients, but most were of mild severity.

Special Populations

A retrospective, observational study evaluated the efficacy and safety of perampanel as an adjunctive treatment in patients with refractory status epilepticus (SE) in Taiwan ($N=81$).²¹ Clinical improvement and EEG resolution ≤ 72 hours after perampanel administration was achieved in 27 (33.3%) patients, with a median response time of 40 hours (1–69 hours). The median dose of perampanel initially prescribed was 4 mg/day (2–36 mg/day). Perampanel was well tolerated with no cardiorespiratory events or laboratory changes recorded. Larger clinical studies are required to fully assess the value of perampanel for status epilepticus.²²

Perampanel has shown efficacy and safety in elderly patients with epilepsy; the once-daily dosing schedule has been highlighted as a particular advantage in this cohort.²³ As with younger patients, utilizing a slow titration approach and a low starting dose help to minimize adverse events.

There are currently only preliminary data regarding the use of perampanel in women with epilepsy; further outcome data are required to estimate the prevalence of adverse pregnancy outcomes with perampanel exposure.²⁴

Best Practice Expert Recommendations

Initiation of Perampanel in Asian Populations

Consistent with the published data, the expert group recommend early initiation of perampanel as initial monotherapy or early adjunctive therapy. In their clinical experience, they have found that patients tend to achieve better outcomes with early use than when perampanel is initiated later in their treatment journey.

The following patient groups were also highlighted by the expert group as those who could most benefit from treatment with perampanel in the following settings.

Perampanel as Initial Monotherapy

- FOS with or without FBTCs in adolescents (>12 years of age), adults, and the elderly.⁸

Perampanel is also likely to be of particular benefit when used as initial monotherapy in the following specific groups of patients with epilepsy; however, further studies are needed to fully evaluate its effectiveness in these settings:

- FOS or generalized onset seizures (GOS) in pediatric patients
- Myoclonic epilepsy (eg progressive myoclonic epilepsy [PME], juvenile myoclonic epilepsy)

Perampanel as Early Adjunctive Therapy

Perampanel is likely to be of particular benefit when used as early adjunctive therapy in the following specific groups of patients with epilepsy; however, further studies are needed to fully evaluate its effectiveness in these settings:

- Patients with focal lesions²⁵ (eg focal cortical dysplasia, tuberous sclerosis complex)
- Tonic-clonic seizures in IGE¹²
- PME²⁶
- Brain-tumor-related epilepsy²⁷

Dose Optimization in Asian Populations

Starting Dose

The expert group advise that the optimal perampanel starting dose in Asian patients is 2 mg/day, consistent with the approved prescribing information. However, if adverse events are observed at the 2 mg/day starting dose and perampanel suspension/granule formulations are available, a reduction to a 1 mg/day starting dose may be considered.

Titration Strategy

The expert group recommend following a slow titration strategy for perampanel in Asian patients by increasing the daily dose by 2 mg every 2 weeks or at even longer intervals. Where perampanel suspension/granule formulations are available, an alternative strategy is to increase the perampanel dose by 1 mg every 2 weeks.

The expert group suggest that rapid titration (increasing the dose more frequently than every 2 weeks) may be considered in patients with concomitant enzyme-inducing ASMs, status epilepticus and other emergencies, severe epilepsy, frequent seizures, or brain-tumor-related epilepsy.

Maintenance Dose

Based on their clinical experience, the expert group recommend that the optimal maintenance dose for perampanel for most patients is either 4 mg/day or 6 mg/day; these doses offer

effective seizure reduction while minimizing adverse events in most patients. In some cases, a maintenance dose of 8 mg/day or higher may be required for optimal effect, but this is not a frequent occurrence in the experience of the expert group.

Key Considerations When Initiating Perampanel in Asian Populations

Age

ASM options are limited in elderly patients because of safety concerns, but perampanel, particularly when administered early, has a favorable efficacy and safety profile in the experience of the expert group.

The group recommend consideration of a lower starting dose (≤ 1 mg/day) for elderly and pediatric populations, with slow up-titration of perampanel dose at >2 -week intervals when feasible.

Comorbidities

The expert group advise that treatment with perampanel may offer specific benefits to patients with certain comorbidities.

Owing to its neutral effect on cognitive function,²⁸ perampanel treatment may be advantageous for patients with existing mild cognitive abnormalities. Cognitive impairment such as memory loss, mental slowness, and attention deficits are commonly associated with epilepsy.²⁹ Approximately a quarter of people with epilepsy have an intellectual disability,³⁰ and these impairments can significantly impact patients' quality of life.³ Cognitive impairment can also be an adverse effect associated with ASM, so early management is important if this does occur.²⁹ Based on the experts' clinical experience, perampanel appears to exert no negative impact on cognitive function and therefore is a rational option for these patients.

Another group of patients identified as likely to benefit markedly from treatment with perampanel are those who suffer from insomnia. Problems with sleep are common in people with epilepsy, with prevalence estimates ranging from 24% to 55%.³¹ Insomnia exerts a negative effect on seizure control and quality of life in this patient group.³¹ The expert group advise that perampanel may contribute to improved sleep quality, which would be highly advantageous for these patients.

Concomitant Medications

Enzyme-inducing ASMs have been shown to promote the metabolism of concomitant ASMs, which may result in serum concentrations of the ASM being reduced and

seizure control being adversely affected.³² Given its extensive metabolism, systemic exposure to perampanel may be reduced when administered in conjunction with an enzyme-inducing ASM.³³

In the experts' experience, a higher maintenance dose (>6 mg/day) of perampanel may be required in cases where patients are taking concomitant enzyme-inducing ASMs. Utilizing a more rapid titration approach may also be of benefit.

Optimizing Perampanel Adherence in Asian Populations

ASM non-adherence is associated with a wide range of negative consequences.^{5,6,34} It is one of the key contributors to uncontrolled seizures and has been linked with a >3-fold increased risk of mortality compared with patients who are adherent to therapy.⁶ ASM non-adherence has also been correlated with higher rates of hospital admissions, increased healthcare costs, and reduced quality of life.⁶ However, as patients are often unaware of the serious consequences of non-adherence, they may choose to discontinue treatment.²⁹

There are multiple barriers to good ASM adherence and long-term treatment retention, including frequent ASM dosing schedules and treatment-emergent adverse events; addressing these factors is therefore critical for optimal perampanel adherence and treatment outcomes.³⁴ Newer ASMs such as perampanel tend to have a more favorable safety profile than first-generation ASMs;²⁹ however, early and frequent follow-up after initiation of perampanel is critical to identify and effectively manage adverse events before they result in patient discontinuation.

The following types of adverse events are highlighted by the expert group as being particularly detrimental to adherence to perampanel in the Asian patient population: behavioral and psychiatric adverse events (eg aggression, irritability, depression); somnolence and dizziness; and ataxia/gait disturbance.

Owing to its long half-life, perampanel requires only once-daily dosing, which has been demonstrated to be an effective strategy for improving patient adherence and is also more forgiving in the event of missed doses.³⁵ The expert group recommend instructing patients to schedule their daily perampanel dose for the evening and to go directly to bed afterwards.

The expert group advise the following approaches when prescribing perampanel to prevent and manage

adverse events and maximize adherence and long-term retention on treatment.

Strategies for the Prevention of Adverse Events with Perampanel in Asian Patients

- At perampanel initiation, patients and/or family members should be advised on the criticality of adherence in relation to the benefits of treatment. Clinicians should also educate patients and/or family members about potential adverse effects so that they are not surprised or overly distressed should they occur and know to report them to their treating clinician as soon as practicable
- Inform patients and carers on how adverse events can be prevented and provide reassurance that they can be effectively managed if they do arise and do not necessarily mean that the patient will discontinue perampanel
- Initiate perampanel at a low dose and titrate to the maintenance dose slowly
- Inform patients and carers that adverse events frequently occur in the early phase of treatment, and patients become better able to tolerate these effects the longer they take perampanel
- Instruct patients or carers to take/administer perampanel at night, just before retiring to bed. This is a critical step to help minimize the impact of somnolence, and dizziness in particular, which are adverse events that may result in discontinuation
- Proactively monitor patients for the development of any adverse events during treatment. Ensure that the patient schedules their first follow-up appointment within 1 week of perampanel initiation, then every 2–4 weeks thereafter, depending on the patient's individual circumstances and availability
- During the titration period, clinicians must pay particular attention to emergent adverse events as it is the period of highest risk. Greater scrutiny should also be applied when a higher dose of perampanel has been prescribed for treatment maintenance
- In adolescent patients or patients with a history of any psychiatric comorbidity or family history of psychiatric disorders, prescribers may consider utilizing a slow dose-titration strategy and more intensive monitoring

Strategies for Managing Adverse Events with Perampanel in Asian Patients

Should adverse effects develop while the patient is taking perampanel, the expert group recommend the following strategies:

- The patient should not discontinue treatment abruptly but should consult their treating clinician for advice
- If the adverse effect develops during the titration period, slow the titration speed by increasing the time between dose increases to 4-week intervals. Alternatively, down-titrate to the previous tolerated dosage for a 2- to 4-week period before attempting another slow up-titration
- If the adverse effect develops during the maintenance period, then reduce the perampanel dose for a short period of time until the adverse effect resolves; the dose may be up-titrated again once the patient is better tolerating the medication
- Reiterate the importance of taking perampanel immediately before going to bed should somnolence or dizziness occur

Conclusions

Perampanel offers broad-spectrum efficacy in a range of seizure types as a once-daily dose; however, clinical data in Asian patients are limited and practical guidance has been lacking on how to optimize the use of this agent in the Asian setting. This expert group recommend several practical strategies that clinicians in the region can easily incorporate into their clinical practice when initiating perampanel for the treatment of epilepsy. Perampanel is likely to be effective in FOS with or without FBTCS across a wide range of age groups, in GOS, and in myoclonic epilepsy. Initiating perampanel early in the treatment journey can optimize efficacy. Selecting a low starting dose and utilizing a slow titration strategy is recommended to minimize the impact of adverse effects, maximize adherence, and increase patient retention. Educating patients and carers about treatment-emergent adverse events that frequently develop in the early phases of treatment is advised, as is instructing patients to take their dose at bedtime to maximize tolerance.

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version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work. Yotin Chinvarun is the lead author.

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