Original article

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One-year clinical experience of perampanel in Spain: a multicentre study of efficacy and tolerability*

Iñigo Garamendi-Ruiz [1], María Eugenia García-García [2], Vicente Bertol-Alegre [3], José Ángel Mauri-Llerda [4], Irene García-Morales [2], Vanesa Garayoa-Irigoyen [3], Marta Agúndez-Sarasola [1], María De Toledo-Heras [5], Vanessa García-Morales [6], María José García-Gomara [7], Carolina Arcos-Sánchez [8], Ana Gago-Veiga [5], Inés Escalza-Cortina [9], Eliana Rueda-Mena [6], Elena Muñoz-Fargas [10], Sonia Santos-Lasaosa [4], José Antonio Oliván-Usieto [10], Leyre Díaz de Cerio-Julián [11], Juan Carlos Gómez-Esteban [1], Ainhoa Marinas-Alejo [1]

[1] Hospital Universitario Cruces, Baracaldo
[2] Hospital Clínico San Carlos, Madrid
[3] Hospital Universitario Miguel Servet, Zaragoza
[4] Hospital Clínico Universitario Lozano Blesa, Zaragoza
[5] Hospital de la Princesa, Madrid
[6] Hospital Universitario Araba, Vitoria
[7] Hospital Royo Villanova, Zaragoza
[8] Hospital General de la Defensa, Zaragoza
[9] Hospital Galdakao Usansolo, Galdakao
[10] Hospital de Alcañiz, Alcañiz
[11] Hospital de Barbastro, Barbastro, Spain

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ABSTRACT – Perampanel, a non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors, is the most recent antiepileptic drug available in Spain, marketed in January 2014. It was initially approved by the European Medicines Agency as adjunctive treatment for partial-onset seizures in patients 12 years and older, but recently also for primary generalized tonic-clonic seizures. Although clinical trials provide essential information about the drug, they do not reflect daily clinical practice. This retrospective study shows the initial experience with perampanel in 11 Spanish hospitals during its first year post-commercialisation. All patients who started perampanel treatment were included, but efficacy and tolerability were only assessed in those patients with a

Correspondence:
Iñigo Garamendi Ruiz
Epilepsy Unit,
Department of Neurology,
Hospital Universitario Cruces,
Baracaldo, Spain
<igaramendiruiz@gmail.com>

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minimum follow-up period of six months. In total, 256 patients were treated with perampanel before September 2014, and 253 had an observational period of one year. After six months, 216/256 patients (84%) continued on perampanel and 180/253 (71.1%) completed one year of treatment. The mean number of previous antiepileptic drugs used was 6.83 and the median number of concomitant antiepileptic drugs was 2. The mean perampanel dose was 7.06 mg and 8.26 mg at six and 12 months, respectively. The responder rate was 39.5% and 35.9% at both follow-up points, respectively. Adverse events were experienced by 91/253 (35.5%) and resulted in withdrawal in 37 (14.6%). The most common adverse events were somnolence, dizziness, and irritability. We found no significant differences between concomitant use of enzyme-inducing and non-inducing antiepileptic drugs, regarding efficacy, adverse effects, or withdrawals. Irritability was not influenced by concomitant use of levetiracetam, relative to other drugs, but was more frequently observed in patients with a history of psychiatric problems or learning disabilities.

Key words: perampanel, adverse event, efficacy, AED treatment, epilepsy

Perampanel (PER) (2-[2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl] benzonitrile hydrate) is the first antiepileptic drug (AED) with a mechanism of action involving non-competitive antagonism of the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors (Rogawski and Hanada, 2013). It was approved as adjunctive treatment for partial-onset seizures for patients 12 years and older (Rektor, 2013), as it demonstrated good efficacy and tolerability versus placebo in three clinical trials (French *et al.,* 2012; Krauss *et al.,* 2012; French *et al.,* 2013; Steinhoff *et al.,* 2013). Recently, PER was proposed as an indication for adjunctive treatment of primary generalized tonic-clonic seizures (European Medicines Agency, 2015), after a multicentre, randomised, double-blind, placebo-controlled study also demonstrated efficacy and tolerability of PER for this type of seizure (French *et al.,* 2015).

It was licensed for commercialisation in Europe in July 2012, but in Spain it was not introduced until January 2014. The pivotal trials, 304-305-306 trials, provide essential information about the drug, such as efficacy issues and adverse effects, but they do not reflect daily clinical practice. Some issues, such as changes in the dose of the study drug or concomitant drugs, are more difficult to assess in clinical trials. Moreover, they assess the drug over a short period, so extension studies, such as the 307 trial, are performed to confirm the results over a longer period (Krauss *et al.,* 2014; Montouris *et al.,* 2015), with a specific focus on the safety profile of the drug. When a new AED is marketed, neurologists usually use it first as adjunctive treatment for patients suffering from uncontrolled partial epilepsy, mainly in specialised epilepsy clinics (Steinhoff *et al.,* 2014; Shah *et al.,* 2016). However, since the posology of PER is straightforward (one dose daily, at bedtime), it may be used also as first or second add-on.

Therefore, the objective of this study was to describe the efficacy and safety of the drug outside clinical trials, in daily clinical practice, after six and 12 months of PER treatment.

Material and methods

This was a retrospective, observational study. All patients who started treatment with PER since availability were included in this study and their medical records were analysed. As stated before, PER has been commercialised in Spain since January 2014. The data for patients were collected from 11 Spanish hospitals, from May 2013 to September 2014, comprising specialised epilepsy surgery units and epilepsy clinics. Some patients started a few months before commercialisation because in some regions of the country PER could be obtained with special permission, if the patient had previously tried all the available AEDs and no seizure control was achieved. Data inclusion was closed on September 2015, and each patient was evaluated over a one-year follow-up period. However, only those patients with a minimum follow-up period of six months were eligible. Data were analysed retrospectively. Following EMA approval, PER was used to treat partial-onset seizures, with or without generalization. However, exceptionally, clinicians prescribed the off-label drug for primary generalized seizures if they considered it appropriate. Epidemiological (age, gender, time since epilepsy onset, type of seizure, and aetiology) and seizure data (seizure type and frequency) were assessed. Adolescents were considered as those patients between the ages of 14 and 18. Elderly subjects were those aged 65 and older. Previous and concomitant AEDs were recorded. Concomitant AEDs were divided into enzyme-inducing antiepileptic drugs (EIAEDs) and non-enzyme-inducing drugs

(non-EIAEDs). Following the assessment of the European Medication Agency and some studies (European Medicines Agency, 2015; Gidal *et al.*, 2015), carbamazepine (CBZ), phenytoin (PHT) and oxcarbazepine (OXC) were considered as EIAEDs, and eslicarbazepine acetate (ESL), phenobarbital (PB) and topiramate (TPM) as non-EIAEDs. However, as recent studies (Kwan *et al.*, 2015) suggest that these latter drugs may affect PER efficacy, an analysis to address whether they should be considered as EIAEDs was also performed.

The baseline was the three-month period prior to the initiation of PER treatment. The study period started when PER was prescribed and the patient took the first dose of the drug. All patients were monitored at three, six and 12 months, although if a clinician considered it necessary, more frequent visits were performed. Titration schedule was individualised for each patient, although increasing doses of 2 mg every two weeks was administered for most. Doses of PER and other AEDs during the baseline and the study periods were not fixed, as they could have been changed at the physician's discretion. The same was applied to patients who were on active treatment with vagus nerve stimulation (VNS). None of the patients, apart from one, underwent epilepsy surgery during the study period (after six months from the start of PER treatment), and this patient was considered to be lost to follow-up regarding the 12-month analysis. The level of PER was not investigated during the study. Efficacy and tolerability data at six and 12 months were assessed as the main outcomes. Efficacy was considered as change in seizure frequency from baseline. All seizures reported by patients or carers were counted for the baseline period and for each six-month term during the study period. Patients were considered as responders if a reduction in seizure frequency of at least 50% was achieved. Seizure freedom was defined as no seizures during the previous six months. Adverse events were recorded and the reason for discontinuation was also assessed. The results of efficacy were analysed based on intention to treat, *i.e.* all patients who had taken at least one dose of PER were included. Nonetheless, losses to follow-up (not due to withdrawal) were not included in the efficacy analysis. The adverse events recorded were those reported by the patients or relatives during the visits. The retention rate at one year was considered if a patient continued on PER after the 12-month check-up.

Descriptive data were expressed using the mean and standard deviation for the quantitative variables (with normal distribution) and median (without normal distribution), and percentages for the qualitative variables. For between-group comparisons of dichotomous variables, the chi-squared test was used. The Student's t-test parametric test was used to compare the mean. Normality was initially confirmed using the Kolmogorov-Smirnov test. All the analyses were carried out using the statistical software package SPSS 13 for Windows (SPSS, Chicago, IL).

This study was approved by the local ethics committee.

Results

In total, 256 patients were included in the analysis, and 216 patients (84.4%) completed six months of PER exposure. At the 12-month visit, 180/253 (71.1%) patients remained on PER treatment. Two patients who were on active therapy after six months, were lost before the 12-month follow-up review, therefore no data were available for these patients during this period. One patient underwent surgery after six months, and he was excluded from the one-year analysis. Epidemiological data are listed in *table 1*. Age ranged from 14 to 86 years, and seven adolescents and nine elderly patients received PER. The majority suffered from partial-onset seizures and fulfilled the criteria for drug-resistant epilepsy, with a mean of 6.84 previous AEDs. Only six patients were on monotherapy when they started PER. The mean number of concomitant AEDs was 2.56 (median: 2). The most frequent among these was levetiracetam (LEV), with 36.7% of patients taking treatment at baseline. One hundred and four patients were taking enzyme-inducing AEDs, and of these, the most frequently taken was carbamazepine (22.3%). When ESL, TPM and PB were also considered as EIADs, the number of patients taking these AEDs increased to 165, with CBZ still the most frequent. Twenty-seven patients were on active treatment with VNS.

Titration was increased at a rate of 2 mg every two weeks or slower in 96% of patients. Mean dose of PER at the six-month check-up was 7.06 mg and at the end of the first year was 8.26 mg. In both cases, the median was 8 mg. The doses used are detailed in *figure 1*.

The global responder rate at six months was 39.5% and at 12 months was 35.9% (*table 2*). About 13% of patients experienced a noticeable reduction in seizure frequency at both follow-up visits, but they did not achieve 50% reduction. The response rate was higher in patients with partial-onset seizures (40%) versus those with primary generalized seizures (two out of 10 patients; 20%). Patients from this latter group could be considered to be more difficult to treat, as they had previously taken more AEDs (all had tried at least six AEDs prior to PER treatment), were taking a median number of three concomitant AEDs, and had a longer history of epilepsy (mean: 29 years). We have to consider that the number of patients with primary generalized seizures was low in this study. However, in patients with partial-onset seizures, better control was achieved for secondary generalized seizures (with a responder rate of 45% and 41% at six months and

Table 1. Epidemiological and epilepsy data.

	n **(%)**	**Mean (standard deviation)**	**Median (range)**
Age (yrs)		39.1 (12.75)	
Adolescents	7 (2.8%)		
Adults	240 (93.7%)		
Elderly	9 (3.5%)		
Gender (women/men)	143/113		
Time since epilepsy onset (yrs)		24.56 (13.92)	
Seizure type			
Focal	157 (61.4%)		
Focal secondarily generalized	89 (34.8%)		
Primary generalized	10 (3.9%)		
Aetiology			
Mesial sclerosis	24 (9.4%)		
Malformations of cortical development	34 (13.3%)		
Trauma	21 (8.2%)		
Cryptogenic	133 (52%)		
Others	44 (16.3%)		
Seizure frequency			9 (0.5-90)
Previous AEDs		6.3 (2.92)	7 (2-14)
Concomitant AEDs		2.54 (0.4)	2 (1-5)
Vagus nerve stimulation	27 (10.5%)		
Enzyme-inducing AEDs			
Only CBZ, PHT, OXC	104 (40.6%)		
Including ESL, PB, TPM	165 (64.4%)		
Neuropsychiatric profile			
Learning disabilities	79 (30.9%)		
Psychiatric history	54 (21.1%)		
Both	25 (9.8%)		

CBZ: carbamazepine; PHT: phenytoin; OXC: oxcarbazepine; ESL: eslicarbazepine acetate; PB: phenobarbital; TPM: topiramate.

12 months, respectively) than partial seizures (with a responder rate of 37% and 34% at six and 12 months, respectively). All the subjects who achieved a reduction in seizure frequency of at least 50% were taking a dose of PER between 4 and 12 mg (median: 8 mg). Fifteen (5.9%) patients were seizure-free during the first six-month period, and 11 (4.3%) during the second period. Ten (3.9%) patients remained seizure-free during the entire 12-month study period. The median dose in this group was 6 mg. Considering the number of AEDs taken previously, those subjects who had tried four or less AEDs responded better (43% responder rate at one year) compared to those treated with five or more AEDs prior to PER (33.5% responder rate at one year). All but one patient, who remained seizure-free during the entire period, had taken less than five AEDs. Withdrawals were similar in both groups. The best response was obtained when PER was used as bitherapy, as 9/20 (45%) patients achieved a reduction in seizure frequency of 50% or more at 12 months, of whom three were seizure-free. Efficacy was not increased with any concomitant drugs or combination of AEDs; few patients were on monotherapy at baseline, and many different combinations of AEDs were used. By comparing specific age groups, such as adolescents and elderly patients, no differences were found concerning efficacy; in all groups, the responder rate was around 30% after 12 months.

Adverse effects were reported in 91 (35.5%) patients (*table 3*). The most frequent adverse events were dizziness (9.9%), somnolence (9.5%), and irritability (9.1%). Patients taking concomitant LEV developed irritability

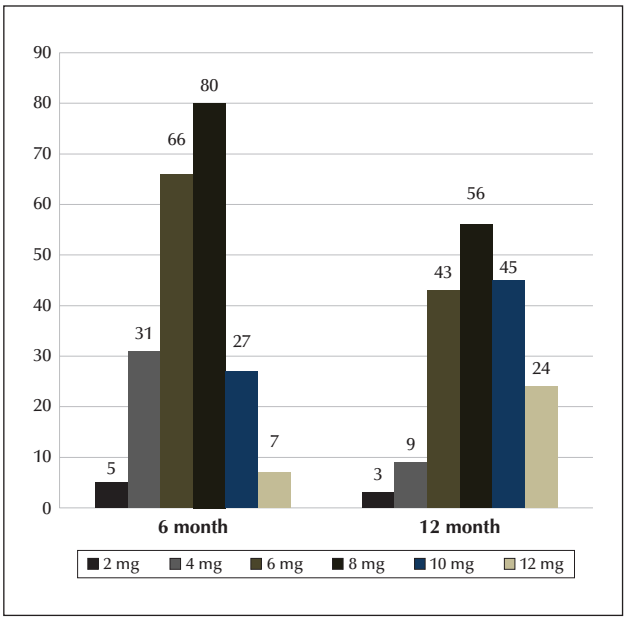

Figure 1. Doses of PERAMPANEL at 6 and 12 months.

Table 2. Response with PER at 6 and 12 months.

	6 months (*n* = 256)	**12 months (*n* = 253)**
Worsening	5 (2.0%)	2 (0.8%)
No response	108 (42.2%)	86 (34%)
Response	86 (33.6%)	81 (32%)
Seizure freedom	15(5.9%)	11 (4.3%)
Withdrawal	42 (16.4%)	73 (28.9%)

(9/92), but with no significant difference in frequency compared to those without LEV (9.8% and 9.3%, respectively; p = 0.983). However, subjects with a history of psychiatric problems or learning disabilities developed irritability more frequently (15.9%) than others (4.8%, p = 0.004), especially those with learning disabilities (22.6%). More adverse effects were reported in adolescents (57.1%) and the elderly (55.6%), than in adults (34.2%). The most frequent adverse effects in adolescents were behavioural disturbances (2/7; 29%) and in elderly subjects, somnolence and dizziness (22.2% for each). However, the number of patients in these specific age groups was small. PER was discontinued due to adverse effects in 37 (14.6%) patients, and among them, irritability was the most frequent (5.1%). Falls were reported in three patients, but no specific condition was found to be related (mean age: 41 years; range: 33-54; mainly with partial-onset cryptogenic seizures). No life-threatening adverse events were reported. One patient committed suicide

Table 3. Adverse events reported by patients or carers during the study period (253 patients).

	***n* (%)**
None	160 (63.2%)
Dizziness	25 (9.9%)
Somnolence Transient-mild Permanent-intense	24 (9.5%) 10 (4.0%) 14 (5.5%)
Irritability	23 (9.1%)
Neuropsychiatric Depression Anxiety	8 (3.2%) 5 (3%) 3(1.2%)
Falls	3 (1.2%)
Weight gain	3 (1.2%)
Others	7 (2.8%)

after 11 months of treatment, with a stable 10-mg dose of PER for longer than six months. Moreover, he suffered from severe depression and refractory epilepsy before starting PER. Thirty-six (14.2%) patients discontinued PER because of a lack of efficacy. Withdrawals were more frequent in adolescents (4/7; 57.7%) than in other age groups, mainly due to a lack of adequate seizure control (3/7; 42.8%). Retention rate at the 12-month follow-up visit was 180 (71.14%).

Regarding the use of concomitant EIAEDs, the differences are shown in *table 4A* and *B*. No significant differences were found concerning responder rate, adverse events, or withdrawals. Median dose at six months was higher in those patients taking EIAEDs, but was the same at 12 months. When ESL, PB and TPM were considered as EIAEDs, fairly similar results were obtained. The only statistically significant difference was that EIAEDs resulted in less reported adverse effects (31.3% *vs* 44.4%; EIAEDs *vs* non-EIAEDs, p = 0.026).

Discussion

The aim of this retrospective study was to reflect the use of PER in daily clinical practice during its first year of post-commercialisation in Spain. The results of this series of patients are consistent with those from clinical trials (Hsu *et al.*, 2013; Kramer *et al.*, 2014), although study conditions were not the same, possibly due to the fact that in both cases the drug was used in patients with uncontrolled epilepsy.

Comparing the patients of the present study with those of other series (Krauss *et al.*, 2014; Steinhoff *et al.*, 2014;

Table 4A. Differences between concomitant treatment with enzyme-inducing and non-enzyme-inducing AEDs (eslicarbazepine, phenobarbital and topiramate as non-EIAEDs).

	Enzyme-inducing AEDs	**Non-enzyme-inducing AEDs**	***p***
n	104 (102)	152 (151)	
Median PER dose at 6 months (mg)	8 (2-12)	7 (2-12)	
Median PER dose at 12 months (mg)	8 (2-12)	8 (2-12)	
Responder rate at 6 months	40.4%	38.8%	0.45
Responder rate at 12 months	38.2%	34.4%	0.31
Adverse events	33.3%	37.7%	0.28
Withdrawals	28.4%	36.4%	0.12

Table 4B. Differences between concomitant treatment with enzyme-inducing and non-enzyme-inducing AEDs (eslicarbazepine, phenobarbital and topiramate as EIAEDs).

	Enzyme-inducing AEDs	**Non-enzyme-inducing AEDs**	***p***
n	165 (163)	91 (90)	
Median PER dose at 6 months (mg)	8 (2-12)	6 (2-12)	
Median PER dose at 12 months (mg)	8 (2-12)	8 (4-12)	
Responder rate at 6 months	38.4%	40%	0.51
Responder rate at 12 months	37.4%	33.3%	0.46
Adverse events	31.3%	44.4%	0.026
Withdrawals	35.5%	32.2%	0.346

Montouris *et al.*, 2015), the responder rate and rate of seizure freedom are lower (about 50% and 14% in previous series and 36% and 5% in the present study, respectively). The main reasons for these differences are probably due to the fact that the dose achieved in the present series was not as high as that in previous studies, and that patients included in the present study suffered from very difficult-to-treat epilepsy, as 48.8% of patients were taking at least three AEDs at baseline, and 58.2% had previously taken at least six AEDs before starting PER. In addition, more than 10% of the subjects were on active treatment with VNS.

The occurrence of adverse events was lower in this study compared to other series (Zaccara *et al.*, 2013; Steinhoff *et al.*, 2014). This may be due to three reasons: first, the dose achieved was lower; second, the titration was slow (generally 2 mg per two weeks or even slower); and finally, the events recorded were those spontaneously reported by patients or relatives, rather than based on a systematic questionnaire. Although dizziness was the most frequent side effect, somnolence and irritability were perhaps most notable. Somnolence is dramatically reduced when PER is taken at bedtime, therefore it rarely leads to discontinuation. Thus, irritability seems to be the main adverse event to be aware of when PER is prescribed. As seen in clinical trials (Ettinger *et al.*, 2015), irritability-aggression was the most frequent neuropsychiatric adverse event. In our series, concomitant use of LEV with PER did not cause irritability relative to any other drug. Nonetheless, previous psychiatric comorbidity or learning disabilities were more frequently associated, as has been reported in some series (Coyle *et al.*, 2014), but not in others (Shah *et al.*, 2016). One patient committed suicide. Suicidal ideation with PER has been reported in patients with severe depression and refractory epilepsy (Coyle *et al.*, 2014). In our case, the event was not considered to be related to PER, because it occurred after a long period with a stable dose of PER and the patient suffered from severe depression before starting the drug.

The comparison between different age groups did not show differences in efficacy but rather a difference in the occurrence of adverse effects. This may

be explained by the fact that patients or carers in these specific age groups may be more sensitive to adverse effects. The percentage of adverse events in young patients is similar to that reported in some series (Biró *et al*., 2015), but behavioural disturbances were more frequent than previously reported (Rosenfeld *et al*., 2015). In elderly patients, no falls were reported. These results also differ from other series (Leppik *et al*., 2015; Trinka *et al*., 2016), however, in our series, the number of patients in this group was low.

Comparing enzyme-inducing and non-enzyme-inducing AEDs, no differences were identified regarding most of the variables studied. Only median PER dose at six months was higher in patients who were taking CYP3A4 inducers. When ESL, PB and TPM were considered as EIADs, no other significant differences were found between the concomitant use of EIADs and non-EIADs, except for the occurrence of adverse effects. This study did not evaluate efficacy relative to the dose, as performed in clinical trials (Kwan *et al*., 2015), therefore it is difficult to draw any comparisons. However, globally, in our series, the use of EIAEDs had little influence on the outcomes.

This study is intended to reflect the use of a new drug in daily clinical practice. Typically, a new drug is used first for those patients with difficult-to-treat epilepsy. Thus, the majority of subjects in our series suffered from partial-onset seizures and many therapeutic schedules had been previously tried. Although PER was proposed as an indication for primary generalized seizures in patients 12 years and older during 2015, this study included a small number of patients with this type of seizure. Our results are less favourable than those reported in a previous clinical trial (French *et al*., 2015), however, this is probably due to the type of generalized epilepsy, because our patients with primary generalized tonic-clonic seizures suffered from symptomatic generalized epilepsy, and a mean of 7.4 AEDs had been tried with a median of three concomitant AEDs. Thus, poorer control might have been expected. Nevertheless, and consistently with other series (Montouris *et al*., 2015), better control was achieved for secondary generalized seizures relative to other types of seizures. The use of PER as early add-on treatment was not a primary focus of this study, since patients with refractory epilepsy were mainly included. However, a small number, those patients who were on bitherapy, achieved better response. The straightforward posology and favourable pharmacokinetic profile makes this drug a logical choice as an add-on AED. With future clinical experience, as more patients are treated, further evidence of efficacy will be reported.

A possible limitation of this study is the change in doses of PER or other AEDs (or VNS) during baseline and study periods, making it difficult to determine optimal doses or drug combinations. Another limitation is that serum levels of PER were not performed, therefore adjustments of doses and outcome data were based only on clinical data.

In conclusion, this PER study showed good efficacy and safety for this drug-resistant epilepsy population, in real-life conditions. It was also safe for adolescents and elderly people, although patients should be monitored for adverse effects. The concomitant use of enzyme-inducing AEDs did not appear to affect the performance of PER. Caution should be taken for patients with a history of psychiatric problems or learning disabilities. Further studies should be carried out to establish the profile of PER in other therapeutic approaches, such as early add-on treatment or the treatment of specific types of epilepsy.

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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All other authors declare no conflict of interest.

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TEST YOURSELF

(1) Is perampanel indicated for partial-onset seizures only?
A. Yes, only for partial-onset seizures (with or without secondary generalized seizures)
B. No, it is also indicated for primary generalized tonic-clonic seizures
C. No, it is indicated for all types of seizures

(2) For which of these populations perampanel is already licenced?
A. Adolescents, adults and elderly people
B. Only patients 18 years and older
C. Only adolescents and adults up to 65 years

(3) Which are the most frequently expected adverse events with perampanel?
A. Blurred vision, nausea and dizziness
B. Dizziness, somnolence and irritability
C. Somnolence, hyponatraemia and irritability

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".