MANAGEMENT OF CHILDHOOD EPILEPSY

ARE WE ON THE RIGHT TRACK?

Highlights of a satellite symposium held at the
10th European Paediatric Neurology Society Congress,
25–28 September 2013, Brussels, Belgium

Key points:

- Challenges of managing childhood epilepsy are heightened by the need to focus on the development of the child, as well as their epilepsy; in particular, by the potential effects of both seizures and AED treatment on the child's neurodevelopment
- There is a need to increase the knowledge base to inform treatment decisions through well-designed clinical trials of AEDs and real-world data in the paediatric population
- Zonisamide is the latest AED to have gained a paediatric license for the adjunctive treatment of partial seizures, approval being based on a randomised controlled trial that followed stringent regulatory requirements
- Since many paediatric patients are refractory to treatment, there continues to be a need for further AEDs, particularly those with novel mechanisms of action
- Perampanel▼ – a first-in-class, selective, non-competitive AMPA receptor antagonist – is the latest approved AED. This has been shown to be efficacious and generally well tolerated as adjunctive therapy in adolescent patients with refractory partial seizures

Management of childhood epilepsy is particularly challenging, since treatment decisions may not only affect a child's current health status, but also their longer-term development. Key issues affecting the management of children with epilepsy were the focus of the Eisai-sponsored symposium at the recent 10th European Paediatric Neurology Society Congress in Belgium, which was entitled '*Management of childhood epilepsy – are we on the right track?*' and chaired by Professor Lieven Lagae (University of Leuven, Belgium).

Professor Helen Cross (UCL Institute of Child Health and Great Ormond Street Hospital, London, UK) began by discussing the challenges associated with diagnosing epilepsy in children, highlighting the complexity of accurate diagnosis among the plethora of childhood syndromes. She stressed the importance of getting the patient's diagnosis correct, since inappropriate treatment may exacerbate the child's seizures. Professor Cross highlighted that children with epilepsy are at an increased risk of cognitive and behavioural problems, the reasons for which are complex and multifactorial. Seizure activity can itself have damaging effects on a child's neurodevelopment, which may already be impaired by their underlying pathology. In addition, antiepileptic drugs (AEDs) may have adverse cognitive and behavioural side effects. Treatment decisions must therefore weigh the potential risks and benefits for each individual child – seizures are not the only consideration. Professor Cross also discussed the challenges involved in providing appropriate management and support to paediatric patients and their families throughout a child's development, including the transition of care from paediatric to adult services.

Dr Stéphane Auvin (Inserm and Hôpital Robert Debré, Paris, France) then focussed on the need for clinical evidence to inform treatment decisions; in particular, the need for different types of evidence – from clinical trials and clinical practice – to provide an overall picture of the likely risks and benefits of a particular treatment approach. He began by highlighting that regulatory requirements for paediatric epilepsy have become increasingly stringent, an important aspect of this being the assessment of an AED's long-term impact on cognition, growth and development. Despite the need for well-designed clinical trials, relatively few have been conducted in the paediatric population to date. The most recent of these was a Phase III trial assessing the safety and efficacy of adjunctive zonisamide for the treatment of partial seizures in children, results of which formed the basis for zonisamide gaining its paediatric license in this setting.[1] In this trial, zonisamide was shown to be well tolerated and significantly more effective than placebo in reducing partial seizure frequency, the proportion of children experiencing ≥50% seizure frequency reduction over the 12-week maintenance period being 50% with zonisamide versus 31% with placebo (p=0.0044).[1] Importantly, an extension study demonstrated that long-term treatment with zonisamide was associated with no consistent detrimental effects on long-term growth and development; overall, no new or unexpected safety signals emerged and the efficacy of zonisamide was maintained over a treatment period of at least 1 year.[2,3] Dr Auvin went on to reiterate that, since clinical trials are conducted under tightly controlled conditions, there is a need for 'real-world' evidence from clinical practice to complement data from clinical trials, illustrating this with a case study of the use of zonisamide in his practice. Dr Auvin also highlighted that clinical trials are difficult to conduct in patients with rare conditions, a problem that has been addressed by the Orphan Drug Law, which lessened the statistical burden for proof of efficacy in Phase III trials, in recognition of low patient numbers. Conditions for which AEDs have been granted orphan drug status include Dravet syndrome and Lennox-Gastaut syndrome. Dr Auvin stressed that there is a particular need for long-term safety surveillance for drugs developed in this way, including the use of registries and evidence from clinical practice, underlining the importance of real-world data.

Professor Elena Belousova (Moscow Institute of Pediatrics and Pediatric Surgery, Russia) discussed the need for further treatment options, particularly those with novel mechanisms of action. She pointed out that, despite the availability of a wide range of AEDs, 20–40% of children fail to respond to their first AED therapy.[4] However, other data have shown that almost one in five patients become seizure free with the addition of an alternative AED after failure of two to five agents,[5] so it is still worth persisting with alternative treatment options in refractory patients. Professor Belousova went on to focus on the latest AED to have gained a license – perampanel – a first-in-class, selective, non-competitive AMPA receptor antagonist. Professor Belousova presented pooled data from three Phase III trials demonstrating that adjunctive perampanel treatment was generally well tolerated and provided improvements in seizure outcomes in adolescent patients (n=143; age 12–17 years) with refractory partial epilepsy over a treatment period of 19 weeks, as per the overall population.[6,7] An extension study demonstrated that adjunctive perampanel continued to be generally well tolerated over a treatment period of up to 12 months, and that its efficacy was maintained throughout treatment, the proportion of patients demonstrating ≥50% seizure frequency reduction ranging from 40–60% during weeks 27–52.[8] Professor Belousova supported these findings with a case study of her personal experience of using perampanel in clinical practice. She concluded by remarking that more recent AEDs are aiming to advance the concept of efficacy (antiepileptic potency) to efficiency (effectiveness plus tolerability), which may translate into improved quality of life for patients.

Despite the considerable difficulties associated with managing childhood epilepsy, an expanding evidence base and advances in drug development are helping to tackle some of these key challenges.

References

1. Guerrini R, et al. Epilepsia 2013;54:1473–80.
2. Guerrini R, et al. Poster presented at 10th European Paediatric Neurology Society Congress, 2013.
3. Rosati A, et al. Poster presented at 10th European Paediatric Neurology Society Congress, 2013.
4. Chu-Shore CJ & Thiele EA. Semin Pediatr Neurol 2010;17:214–23.
5. Schiller Y & Najjar Y. Neurology 2008;70:54–65.
6. Steinhoff BJ, et al. Epilepsia 2013;54:1481–9.
7. Eisai Europe Ltd Data on File PER039.
8. Conry J, et al. Poster presented at 41st Annual Meeting of the Child Neurology Society, 2012.

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Prescribing information is available for perampanel and zonisamide on the page overleaf

PRESCRIBING INFORMATION

Fycompa®* (perampanel)
Please refer to the SPC before prescribing.
Presentation: Film-coated tablets: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg perampanel. ***Indication:*** Adjunctive treatment of partial-onset seizures with or without secondarily generalised 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 4mg/day to 12mg/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 8mg. 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 from Fycompa therapy taking into account the benefit of breastfeeding for the child and the benefit of 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, levetiracetam, phenobarbital, phenytoin, topiramate, zonisamide, carbamazepine, clobazam, lamotrigine and valproic acid. The effect of perampanel on monohydroxycarbazepine 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. Ketoconazole, 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, dysathria, 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 10mg 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

For UK healthcare professionals:
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Zebinix® (eslicarbazepine acetate)
Please refer to the SPC before prescribing. ***Presentation:*** Tablets containing 800 mg eslicarbazepine acetate. ***Indication:*** Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation ***Dose and administration:*** May be taken with or without food. Starting dose is 400 mg once daily, increased to 800 mg once daily after one or two weeks. Dose may be increased to 1200 mg once daily. Withdraw gradually to minimise the potential of increased seizure frequency. ***Elderly patients***: Caution. ***Children and adolescents <18years of age:*** Not recommended. **Patients with renal impairment:** Adjust dose according to creatinine clearance (CL_{cr}). Not recommended in severe impairment. ***Patients with hepatic impairment:*** No dose adjustment in mild to moderate impairment. Not recommended in severe impairment. ***Contra-Indications:*** Hypersensitivity to the active substance, other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or any excipients. Known second or third degree AV block. ***Pregnancy:*** No data on the use of Zebinix in pregnant women. Carefully re-evaluate treatment if women become pregnant or plan to become pregnant, and use minimum effective doses. Interacts with oral contraceptives. Use an alternative method of contraception during treatment and up to the end of the current menstrual cycle after treatment has been stopped. ***Lactation:*** Excretion in human breast milk is unknown. Breastfeeding should be discontinued during treatment. ***Warnings and precautions:*** May cause some CNS reactions such as dizziness and somnolence. Do not use with oxcarbazepine. Rash has been reported. Discontinue if signs or symptoms of hypersensitivity develop. Screen for allele HLA-B*1502 in individuals of Han Chinese and Thai origin as this has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Allele HLA-A*3101 has been shown to increase the risk of developing carbamazepine induced cutaneous adverse reactions including Stevens Johnson syndrome (SJS), TEN, Drug rash with eosinophilia (DRESS) or less severe acute generalised exanthematous pustulosis (AGEP) and maculopapular rash in patients of European descent and Japanese populations. Examine serum sodium levels in patients with pre-existing renal disease or who are treated with medicinal products which may lead to hyponatraemia or if clinical signs of hyponatraemia occur. Discontinue if clinically relevant hyponatraemia develops. Do not use in primary generalised seizures. Prolongations in PR interval have been observed. Caution in patients with medical conditions or when taking concomitant medicinal products associated with PR prolongation. Monitor for signs of suicidal ideation and behaviours. ***Drug interactions:*** Has an inducing effect on the metabolism of medicinal products mainly eliminated by CYP3A4 or UDP-glucuronyl transferases, therefore the dose of these products may need to be increased when used concomitantly with Zebinix. May take 2 to 3 weeks to reach the new level of enzyme activity when initiating, discontinuing or changing dose, therefore take time delay into account when using with other medicines that require dose adjustment. Interactions can arise when co-administering high doses with medicinal products that are mainly metabolised by CYP2C19. Carbamazepine: Zebinix dose may need to be increased if used concomitantly with carbamazepine. Concomitant treatment with carbamazepine increased the risk of the diplopia, abnormal coordination and dizziness. An increase in other adverse reactions cannot be excluded. Phenytoin: An increase of Zebinix dose and a decrease of phenytoin dose may be required. Lamotrigine and topiramate: No dose adjustments are required. Valproate and levetiracetam: Concomitant administration appeared not to affect the exposure to eslicarbazepine but has not been verified by conventional interaction studies. Oral contraceptives: Interacts with the oral contraceptive. Simvastatin: An increase of the simvastatin dose may be required when used concomitantly with Zebinix. Rosuvastatin: concomitant administration reduced exposure to rosuvastatin. Monitor response to therapy (e.g., cholesterol levels). Warfarin: Can decrease exposure to S-warfarin. No effects on R-warfarin or coagulation. Monitoring of INR should be performed in the first weeks after initiation or ending concomitant treatment. Digoxin: no effect. MAOIs: an interaction between eslicarbazepine acetate and MAOIs is theoretically possible. ***Side effects:*** Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with Zebinix. Refer to SPC for all side effects. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10): Headache, abnormal coordination, disturbance in attention, tremor, diplopia, vision blurred, vertigo, nausea, vomiting, diarrhoea, rash, fatigue, gait disturbance. Serious side effects: hypersensitivity, hyponatraemia, dehydration, grand mal convulsion, ocular hyperaemia, palpitations, bradycardia, hypertension, hypotension, chest pain, epistaxis, liver disorder, drug toxicity, poisoning, Some rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during clinical studies. However, they have been reported with oxcarbazepine and their occurrence during treatment with Zebinix cannot be excluded. ***Legal Category:*** POM. ***Basic UK NHS cost:*** Zebinix 800mg: pack of 30 £136.00. ***Irish price to wholesaler:*** Zebinix 800mg: pack of 30 €143.19. ***Marketing authorisation numbers:*** EU/1/09/514/012-020. ***Marketing authorisation holder:*** Bial-Portela & Cª., S.A. À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado – Portugal. ***Further Information from:*** Eisai Limited, European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, UK. **Date of preparation**: January 2013

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Zebinix®: Pregnancy Registry
To provide information regarding the effects of in utero exposure to Zebinix® physicians are advised to enrol pregnant patients taking Zebinix® in the International Registry of Antiepileptic Drugs and Pregnancy (EURAP). More information can be found at the website http://www.eurapinternational.org/. BIAL-Portela and Ca S.A. Sponsors the EURAP Pregnancy Registry to advance scientific knowledge about safety and outcomes in pregnant women being treated with antiepilpetic drugs including eslicarbazepine acetate (Zebinix®) and to respond to a requirement of the Committee for Medicinal Products for Human Use (CHMP) to address missing information on safety in pregnancy.

Zonegran® (zonisamide)
Please refer to the SPC before prescribing. ***Presentation:*** Hard capsules: 25 mg, 50 mg, 100 mg zonisamide. ***Indication:*** Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy. Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.
Dose and administration: Adults: Monotherapy: Starting dose is 100 mg once a day. After two weeks, increase to 200 mg once a day. Then increase at two-weekly intervals in 100 mg increments. Withdraw gradually. ***Adjunctive therapy:*** Starting dose is 50 mg in two divided doses. After one week, increase to 100 mg daily. Then increase at one weekly intervals in 100 mg increments. Can be taken once or twice daily after titration. In renal or hepatic impairment and patients not receiving CYP3A4-inducing agents consider two weekly intervals. ***Paediatric population (aged 6 years and above):*** **Adjunctive therapy:** starting dose is 1 mg/kg once a day. After one week, increase at weekly intervals in increments of 1 mg/kg. In patients not receiving CYP3A4-inducing agents consider two weekly intervals in increments of 1 mg/kg. For patients weighing 20 to 55 kg a maintenance dose of 6 to 8 mg/kg once a day is recommended. For patients weighing above 55 kg a maintenance dose of 300 to 500 mg once a day is recommended. Withdraw gradually**.** ***Elderly and patients with renal or hepatic impairment:*** Caution. Not recommended in severe hepatic impairment. ***Contra-Indications:*** Hypersensitivity to zonisamide, sulphonamide or any excipient. ***Pregnancy:*** Do not use during pregnancy unless potential benefits justify the risks. Women of childbearing potential must use contraception during treatment and for one month after discontinuation. ***Lactation:*** Excreted into breast milk. Either discontinue Zonegran or stop breast-feeding. ***Warnings and Precautions:*** Serious rashes occur, including cases of Stevens-Johnson syndrome. Closely supervise and consider discontinuation in patients with unexplained rash. Zonegran contains a sulphonamide group which is associated with serious immune based adverse reactions. Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. Monitor for signs of suicidal ideation and behaviours and consider appropriate treatment. Use with caution in patients with risk factors for nephrolithiasis, including prior stone formation, family history of nephrolithiasis and hypercalcuria. In the event kidney stones occur in paediatric patients, Zonegran should be discontinued. If a hepatic event is suspected, liver function should be evaluated and discontinuation should be considered. Evaluate and monitor serum bicarbonate levels in patients who are at risk of metabolic acidosis. If metabolic acidosis develops and persists, consider reducing Zonegran dose, discontinuing Zonegran treatment or adding alkali treatment with Zonegran as osteopenia may develop. Use with caution in adult patients treated with carbonic anhydrase inhibitors, e.g. topiramate or acetazolamide. Not recommended for use in paediatric patients with other carbonic anhydrase inhibitors. Monitoring of serum bicarbonate levels should be carried out in the paediatric population. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration; avoid excessive temperatures and strenuous physical exercise. Prescribers should draw the attention of patients and their carer to the advice in the PIL (patient information leaflet) on preventing heatstroke and overheating. Discontinuation should be considered in the event of signs or symptoms of dehydration, oligohydrosis, or elevated body temperature. Co-medication in paediatric patients with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity are not recommended. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, consider discontinuation. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage and consider discontinuation. Not recommended in paediatric patients who are underweight or have decreased appetite. Weight should be monitored in paediatric patients. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore children aged 6 years and above with a body weight of less than 20 kg should be treated with caution. The long term effect of weight loss in the paediatric population on growth and development is unknown. Zonegran 100 mg capsules contain E110. ***Drug Interactions:*** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate or acetazolamide. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. Interaction studies have only been performed in adults.***Side effects:*** The most common adverse reactions in a randomised, controlled monotherapy trial comparing zonisamide with carbamazepine prolonged release were decreased bicarbonate, decreased appetite, and decreased weight. Very common effects (≥1/10): decreased bicarbonate. Common effects (≥1/100, <1/10): decreased appetite, agitation, depression, insomnia, mood swings, anxiety, ataxia, dizziness, memory impairment, somnolence, bradyphrenia, disturbance in attention, paraesthesia, diplopia, constipation, diarrhoea, dyspepsia, nausea, vomiting, rash, fatigue, pyrexia, irritability, weight decreased, blood creatinine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). A pooled analysis of safety data on 95 elderly subjects has shown a relatively higher reporting frequency of oedema peripheral and pruritus compared to the adult population. Post-marketing data suggests patients aged ≥65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. Most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Refer to SPC for all side effects. Very common effects (≥1/10): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diplopia, decreased bicarbonate. Common effects (≥1/100, <1/10): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, pruritis, alopecia, nephrolithiasis, fatigue, influenza-like illness, pyrexia, oedema peripheral, weight decreased. Serious effects: pneumonia, suicidal attempt, convulsion, cholecystitis, calculus urinary, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms, hypersensitivity-type pneumonitis. The adverse event profile of zonisamide in paediatric patients aged 6 to 17 years in placebo-controlled clinical studies was consistent with that of adults. A pooled analysis of safety data on 420 paediatric subjects has shown a relatively higher reporting frequency of pneumonia, dehydration, decreased sweating, abnormal liver function tests, otitis media, pharyngitis, sinusitis and upper respiratory tract infection, cough, epistaxis and rhinitis, abdominal pain, vomiting, rash and eczema, and fever compared to the adult population (particularly in subjects aged below 12 years) and, at a low incidence, amnesia, creatinine increased, lymphadenopathy, and thrombocytopenia**.** The incidence of a decrease in body weight of 10% or more was 10.7%. In some cases of weight decrease there was a delay in transition to the next Tanner stage and in bone maturation. ***Legal Category:*** POM ***Basic UK NHS cost:*** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. ***Irish price to wholesaler:*** Zonegran 25 mg: packs of 14 €9.20, Zonegran 50 mg: packs of 56 €48.78, Zonegran 100 mg: packs of 56 €65.18. ***Marketing authorisation numbers:*** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. ***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.

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