25 July 2013  
EMA/470045/2013  
Committee for Medicinal Products for Human Use (CHMP)

Zonegran
(zonisamide)

Procedure No. EMEA/H/C/000577/II/0065
Marketing authorisation holder: Eisai Ltd

Assessment report for an extension of indication

Assessment report as adopted by the CHMP with all commercially confidential information deleted
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## 1. Scientific discussion

### 1.1. Introduction

Epilepsies are among the most common neurologic disorders affecting individuals of all ages. Seizures and epilepsy affect children more than any other age group (Moshé SL, 2000) and are approximately twice as common in children as in adults (about 700 per 100,000 in children < 16 years compared with 330 per 100,000 in adults). Partial epilepsies (focal or localization related) are frequent, accounting for > 60% of all epilepsies (Rauchenzauner M and Luef G, 2010).

Zonegran (zonisamide) is a sulphonamide with weak carbonic anhydrase activity, chemically unrelated to other anti-epileptic medication. The active ingredient is 1,2-benzisoxazole-3-methanesulfonamide.

Although the precise mechanism of action is unknown, Zonegran is thought to exert its actions by blockade of the voltage-sensitive sodium and calcium channels, thereby disrupting synchronized neuronal firing, reducing the spread of seizure discharges, and disturbing subsequent epileptic activities. Zonegran also has some effects on the synthesis, release, and degradation of a number of different neurotransmitters, including glutamate, gamma-aminobutyric acid, dopamine, serotonin, and acetylcholine, which may lead to enhancement of synaptic inhibition. Zonisamide is a benzisoxazole derivative unrelated to other AEDs.

Zonisamide is currently indicated for the adjunctive therapy of partial seizures with or without secondary generalization in adult patients. This application seeks to extend this indication to include adjunctive therapy of partial seizures with or without secondary generalization in children and adolescents aged 6 years and above. Since July 2012 the indication monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy has also been authorized.

The proposed dosing schedule for children and adolescents is to initiate treatment at 1 mg/kg/day (once-daily). Further dose increases in increments of 1 mg/kg are to be made at weekly intervals for patients receiving concomitant cytochrome P450-inducing agents, or at fortnightly intervals for those not receiving such agents. The dose may be increased up to a target maintenance dose of 8 mg/kg/day (once-daily) for patients weighing 20 to 55 kg or 500 mg day for patients > 55 kg.

Currently approved adjunctive treatments for partial onset seizures in paediatric patients in the European Union (EU) include: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate. Despite the availability of a number of AEDs that are approved for paediatric use, not all patients achieve satisfactory seizure control, hence the need for additional AEDs that are effective and well tolerated in paediatric patients with partial onset seizures.

### 1.2. Non-clinical aspects

#### 1.2.1. Introduction

The non-clinical pharmacologic, pharmacokinetic, and toxicity profile of zonisamide has been well characterized.

To support the paediatric indication the MAH has resubmitted the juvenile toxicity studies in rats previously evaluated as part of a follow-up measure FUM002 (Study No.901092 and Study No. 901093).
To support the fertility information in section 4.6 and 5.3 of the SmPC the MAH also submitted two fertility and early embryonic development studies conducted in rats submitted with the original Marketing Authorisation Application (Study Nos. RR 745-00843 and RR 745-00993) and a recently conducted juvenile rat study (Study No. 901093).

1.2.2. Juvenile Toxicity

Dose-range finding juvenile animal toxicity study (3 weeks) – Study No. 901092

In a dose-range finding study, zonisamide was administered orally by gavage to 7-day old rat pups at doses of 100, 200, and 300 mg/kg for up to 3 consecutive weeks. A dose of 300 mg/kg resulted in excessive toxicity (mortality and adverse effects on clinical condition and lower body weight gain) in juvenile rats. Therefore, treatment at this dose level was terminated on Day 8 or 9 postpartum (pp). A decrease in body weight was also evident at 200 mg/kg. Based on these results, 200 mg/kg was considered to be the maximum tolerated dose (MTD) for a subsequent definitive toxicity study in juvenile rats.

Definitive juvenile animal toxicity study (10 weeks followed by a 4-week recovery period) – Study No. 901093

In a definitive juvenile animal toxicity study, zonisamide (20, 60, and 200 mg/kg) was administered to a total of 324 male and 324 female Sprague-Dawley (Crl:CD[SD]) rat pups by oral gavage for 10 weeks (dosing commencing on Day 7 pp, followed by a 4-week recovery period). A control group received an equivalent volume of vehicle (0.5% Tragacanth, 10 mL/kg). Mortality and signs of ill health or reaction to treatment, detailed examination, body weight, food consumption, growth measurements, physical (sexual) development assessment, behavioural performance assessments (qualitative and quantitative observational assessments in a functional observation battery, grip strength and hind limb splay) motor activity, auditory startle habituation, learning and memory (Cincinnati water maze), body temperature, ophthalmology, reproductive function, laboratory investigations (haematology, clinical biochemistry, urinalysis), toxicokinetics, gross and histopathological examinations including neuropathology, organ weights, and brain and bone measurements were recorded and evaluated for the pups during the study.

There was no treatment-related mortality and no effects upon clinical signs, with the exception of salivation observed during the post-weaning treatment period on occasion at 60 mg/kg and for the majority of animals at 200 mg/kg. Decreases in body weight and food intake were observed at doses ≥ 60 mg/kg. In addition, a transient effect on crown-rump length and a delay in male physical (preputial separation) development was observed at 200 mg/kg, which was likely related to the decreased body weight. Effects on some behavioural endpoints (functional observation battery, grip strength, hind limb splay activity, auditory startle habituation, learning and memory) observed at 200 mg/kg were considered related to the exaggerated pharmacologic effects of zonisamide and were in most instances reversible. Changes in clinical pathology parameters and histopathologic changes in the liver and/or kidneys were noted at ≥ 60 mg/kg, and were considered to be related to adaptive change by hepatic enzyme induction and/or carbonic anhydrase inhibition by zonisamide. Increase incidence of cortical vacuolation in the adrenal glands was noted in males at 200 mg/kg and prolonged diestrous and lower mating and fertility indices were observed in females.

At the end of treatment, increased white blood cell count associated with increases in neutrophil and lymphocyte counts were noted in males and females at 200 mg/kg. Slight increases in alanine aminotransferase (ALT) and blood urea nitrogen were observed at ≥ 60 mg/kg. Increases in urine volume, pH, and excretion of sodium and chloride, and decreased excretion of potassium, were noted at 200 mg/kg. At the end of the recovery period, changes in the haematology, blood chemistry and
urinalysis parameters were no longer apparent. The effects, where assessed, typically showed reversibility over a 4-week period, except for histopathological changes in kidneys at 200 mg/kg, which only showed partial reversibility, and some behavioural changes at 200 mg/kg when assessed after 1 to 2 weeks of recovery. Based on the results, the no observed adverse effect level (NOAEL) for zonisamide in this study was 20 mg/kg.

At the end of the treatment period, the maximum drug concentration (Cmax) at 20 mg/kg was 15.5 and 17.5 μg/mL in males and females, respectively, and the area under the concentration × time curve (AUC(0−24h)) was 205 μg·h/mL in both sexes. The mean Cmax and AUC(0−24h) values were 16.5 μg/mL, and 205 μg·h/mL, respectively. When compared with the human PK data in 12 to 15 year-old paediatric subjects (Study AN46046-225), the exposure at the NOAEL was 0.51 (Cmax) and 0.29 (AUC) times than the human exposure.

### 1.2.3. Developmental and Reproductive Toxicity

In the reproductive and development toxicity program conducted and assessed with the initial MAA, two fertility and early embryonic development studies were conducted in rats; the first study was a dietary study up to 100 mg/kg, and the second study was an oral gavage study conducted at doses up to 200 mg/kg.

In the first fertility study (Study No. RR 745-00843), zonisamide was administered to sexually mature male and female rats as a dietary admixture at daily doses of 25, 50, or 100 mg/kg. Treatment began in the males at least 60 days prior to mating and continued until sacrifice (on Week 15). For females, treatment began 14 days prior to mating and continued until sacrifice. F0 females were mated with a male from the same group. Up to 100 mg/kg of zonisamide by dietary administration showed no adverse effects on reproductive or litter parameters. Pregnancy rate, parturition, and maternal behaviour were not adversely affected by treatment with zonisamide.

In the second fertility study (Study No. RR 745-00993), zonisamide was administered daily to male and female rats by oral gavage at dose levels of 20, 60, and 200 mg/kg. Males were treated for 63 days prior to mating with treatment continuing throughout cohabitation and until necropsy for a total of 100 or 101 days. Treatment of females began 14 days prior to mating and continued up to gestation Day 7. At the end of the respective pre-mating treatment periods, females and males were cohabitated in a 1:1 ratio within treatment groups for a maximum of 14 days. Major parental toxicity observed was dose-related decrease in body weight with decreased food consumption at 60 mg/kg and higher. A decrease in the number of live foetuses at 200 mg/kg and decreases in corpora lutea and implantation sites at ≥ 60 mg/kg were observed, and irregular estrus cycles were also noted in females at 200 mg/kg. No drug-related effects on fertility and early embryonic development were found at any dose.

In a recently conducted pivotal juvenile rat study (Study No. 901093), effects on reproductive performance were examined and there was a slightly higher incidence of females in prolonged diestrous at 200 mg/kg as compared with the control. The mating and fertility indices were also lower at 200 mg/kg, although the conception rate (number pregnant/number mated) was not affected. At 200 mg/kg the mean day to mating was also longer than that seen in control animals.

It is difficult to compare the results of these studies and conclude the effect of zonisamide on fertility and early embryonic development precisely, since the first and second fertility studies were very old and conducted in different periods, using different study designs and regimens and in different facilities. But taking a conservative approach, NOAEL for fertility in rats is considered to be 20 mg/kg based on the second study. When the exposure at 20 mg/kg in the fertility and early embryonic development study (Study No. RR 745-00993), which was extrapolated from a juvenile rat study [Study No. 901093], is compared with that at a dose of 8 mg/kg in adolescent subjects in the clinical
study (Study AN46046-225), the margin of safety is below one-fold for AUC or Cmax. A margin of safety at 60 mg/kg, although a dose at which decreases in corpora lutea and implantation sites in female rats were observed, is one-fold for AUC, or two-fold for Cmax.

The CHMP noted that when Zonegran was tested in rats at systemic exposure similar to therapeutic exposure, reductions in corpora lutea and implantation sites were observed.

Irregular estrus cycles were also noted in females at 200 mg/kg. Extrapolated from the juvenile toxicity study, exposure at this dose was approximately 2-3 fold human therapeutic exposure.

When adult rats were tested for fertility and early embryonic effects no adverse effects were observed. However, when juvenile rats were exposed, even if the mating and fertility indices were lower at 200 mg/kg, the conception rate (number pregnant/number mated) was not affected.

**Ecotoxicity/environmental risk assessment**

An updated environmental risk assessment was submitted with variation II/59 (extension to the indication to monotherapy use, concluded in May 2012), encompassing an update of the environmental exposure due to the already authorised indication and the environmental exposure due to the planned extensions to the indication to include adjunctive use in paediatric patients (aged 6 years and above) and monotherapy in newly diagnosed adult patients.

The MAH provided a revised ERA including a Phase I with calculation of a PEC_{surfacewater} and additional studies for a Phase II assessment, and the ERA concluded that the increase in the overall environmental exposure was not thought to impact on the environmental risk. However, a final conclusion on the environmental risk cannot be drawn due to the absence of a valid algae growth inhibition test and a sediment organism toxicity test. The MAH was requested to provide a valid algae growth inhibition test and a study on sediment dwelling organisms. Further justification by the MAH as to why the provided algae growth inhibition test and sediment organism toxicity test can be considered valid was not accepted by the CHMP. The alga test previously submitted for procedure EMEA/H/C/0577/II/59 is not valid due to irregular testing within the first 24 hours. Within this time there was no illumination resulting in a missing exponential growth. This is a formal aspect of the OECD 201 guideline which cannot be waived by the argumentation of the applicant.

Additionally, the MAH’s rationale for waiving a sediment dwelling organism toxicity study cannot be accepted. The data used to substantiate the rationale such as DT50 values from the water/sediment system study, information on human metabolites, the potential for bioaccumulation, and NOEC values derived from testing with other organisms are not relevant for the assessment of the toxicity for sediment organisms. The CHMP concluded that a sediment dwelling organism toxicity study is required if more than 10% of the active ingredient shifted to the sediment at the end of the study thus the MAH is asked to submit a sediment organism toxicity test.

The wording of section 6.6, Special precautions for disposal, was amended to “Any unused medicinal product or waste material should be disposed of in accordance with local requirements”.

**1.2.4. Conclusion on non-clinical aspects**

Overall, the findings seen in the juvenile rat studies were consistent with and comparable to the findings observed in the previously conducted oral repeated-dose studies in adult rats. Thus the MAH concludes that no unexpected toxicity is expected in young animals compared to adult animals.

The CHMP noted that at the NOAEL of 20 mg/kg the systemic exposure in animals is lower than systemic exposure in humans.
At 60 mg/kg, exposure was similar to therapeutic exposure and (exaggerated) pharmacological effects occur, consisting of decrease of body weight associated with decreased food consumption and behavioural effects, consisting of decreased incidence of rearing. The MAH states that similar effects have been observed in adult animals as well. However, a behavioural parameter such as rearing is not commonly observed in repeated dose toxicity studies. Behavioural effects such as transient mild sedation, reduced muscle tone and slight ataxia were seen in a 9-months rat study (RR745-00467) but at higher doses than in the juvenile study.

At the same dose (60 mg/kg) various effects in the kidney were seen. A dose related increase in incidence and severity of tubular hyaline droplets in treated males was observed. Similar findings were noted in control males with lower incidence and were associated with early stages of tubular degeneration and/or presence of granular casts at > 60 mg/kg. Medullary/papillary tubular mineralization, calculus/basophilic material and transitional cell hyperplasia were found at a higher incidence at 60 and 200 mg/kg. Tubular hyaline droplet accumulation was considered due to male rat specific metabolism of alpha2 globulin and was considered to be of little toxicological relevance to humans. Mineralization, calculus formation and transitional cell hyperplasia were considered possibly related to carbonic anhydrase inhibition by zonisamide. Of note, however, the exposure at the LOAEL in juvenile rats (60 mg/kg; 1 or 2-fold exposure in humans) is similar to the exposure at the NOAEL in adult rats (30-100 mg/kg; 1.4-fold expected exposure in humans, according to the EPAR for Zonegran). This indicates that juvenile rats are more susceptible to the renal effects caused by zonisamide.

At higher dosages (200 mg/kg) growth inhibitory effects were more evident (decreased crown-rump length, delay of preputial separation) and CNS effects were evident (decreased performance in water maze, increased startle response). In addition, effects on urinary system, liver and reproductive performance were observed. The latter effects were also observed in the adult rats in previous repeated-dose toxicity and/or reproductive toxicity studies and were reversible. However, renal effects at this higher dose were only partially reversible.

At the request of CHMP, the MAH presented a comparison of the adverse effects observed in juvenile and adult rats on the basis of systemic exposure. The MAH noted that juvenile animals are generally more susceptible than adult animals in terms of dose and systemic exposure. The MAH also notes that in clinical studies body weight and renal effects were observed consistent with the observations in rats. The MAH also provided additional paediatric data (5-11 and 12-15 years) to allow safety margins to be considered for the findings seen in the juvenile rat study. The systemic exposure at the no adverse effect level (NOAEL) was lower than the human exposure at the maximum recommended dose in both adults (500 mg/day) and paediatric subjects (8 mg/kg/day). The main findings seen (decreased body weights/food consumption, clinical sign and behavioural changes (due to exaggerated Zonisamide pharmacology) and effects in kidney and liver were reversible in both adult and juvenile rats or partially reversible in the case of kidney findings in juvenile rats.

Regarding the kidney findings, the effects in juvenile animals were only partially reversible. At the end of the recovery period, the incidence and severity of tubular hyaline droplets in the kidney of males at 60 and 200 mg/kg were reduced compared to the observations made at the end of the treatment period however, the incidence of minimal or slight mineralization of medullary/papillary tubules seen at 200 mg/kg remained comparable or had increased. Presence of calculus and/or mineralized basophilic material in the renal pelvis or minimal focal hyperplasia of transitional epithelium was seen in a few animals at 200 mg/kg. The lower incidence of tubular hyaline droplets, calculus/basophilic material and transitional cell hyperplasia indicates partial recovery whereas the comparable or higher incidence of medullary/papillary tubular mineralization did not suggest reversibility at the 200 mg/kg dose level.
Effects on growth, physical development (shorter crown-to-rump length, delay in prepuital separation) and on learning and memory had a 2-3 fold safety margin when compared with exposure levels in paediatric subjects at the maximum recommended therapeutic dose (8 mg/kg/day). No growth or development effects were seen in the clinical studies in paediatric studies; however the subject numbers were small and therefore cannot be considered as conclusive. As a result adverse effects on growth and development in the paediatric population has been added as an important potential risk in the RMP. Decreases in body weight and effects on kidney were however observed in paediatric subjects but were again consistent with those seen in adults.

The juvenile animal toxicity indicates no new safety concerns for Zonisamide as compared to adult animals.

Overall, the CHMP concluded that while safety margins for toxicity findings seen in juvenile studies were low and non-existent at the NOAEL, the findings were generally comparable to adult rat data and were consistent with that seen clinically (e.g. decrease in body weight and effects on kidney). Safety margins for clinical signs and behavioural changes were lower in juvenile animals compared to adults but these findings were considered related to exaggerated pharmacology and were reversible or at least partially for kidney findings. The adverse effects on growth and development in the paediatric population are being addressed as an important potential risk in the RMP. A drug utilisation study is planned to monitor effects on kidney, most notably kidney stones.

A final conclusion on the environmental risk posed by Zonisamide cannot be drawn due to missing information on the potential effects on sediment dwelling organisms and algae growth. The Applicant is recommended to submit a valid algae growth inhibition test and a sediment organism toxicity test.

**1.3. Clinical aspects**

**1.3.1. Introduction**

**GCP**

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community (Study E2090-E044-312 in India and Ukraine, and Study ZNS-505 in USA), were carried out in accordance with the ethical standards of Directive 2001/20/EC.

**1.3.2. Pharmacokinetics and Pharmacodynamics**

No individual pharmacology study results are provided in this application. Rather, pooled population analyses were conducted for epileptic patients aged between 5 and 77 years from Studies AN46046-225, AN46046-302, E2090-E044-312.

Population PK analysis was conducted using data from all three studies and population PK/PD analysis was conducted on Studies 302 and 312 only.
Table 1. Description of the Studies

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Study Design</th>
<th>Treatment duration</th>
<th>Age range (yrs)</th>
<th>Dose received (mg/day)</th>
<th>Subjects included</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN46046-225</td>
<td>Open-Label Study to Evaluate the Pharmacokinetics Profile and Safety of Zonisamide in Pediatric Patients with Epilepsy</td>
<td>9 weeks</td>
<td>5–15</td>
<td>12.5 to 600</td>
<td>PK: n=33</td>
</tr>
<tr>
<td>AN46046-302</td>
<td>Double-Blind, Placebo-controlled Randomized Study of the Safety and Efficacy of Zonisamide (add on therapy) for the Treatment of Seizures in Refractory Patients</td>
<td>24 weeks</td>
<td>12-77</td>
<td>100, 300, 500</td>
<td>PK: n=175, PK/PD: n=282</td>
</tr>
<tr>
<td>E2090-E044-312</td>
<td>A Multi-center, Randomized, Double-blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Adjunctive Zonisamide in Pediatric Partial Onset Seizures</td>
<td>20 weeks</td>
<td>6–17</td>
<td>25 to 500</td>
<td>PK: n=102, PK/PD: n=197</td>
</tr>
</tbody>
</table>

Population PK analysis

The objectives of the population PK analysis were to:

- Describe the PK of zonisamide in subjects with epilepsy aged 5 to 77 years (Studies AN46046-225, AN46046-302 and E2090-E044-312).
- Identify covariates that explain between subject variability in zonisamide PK, including demographics, laboratory results and concomitant medication with other anti-epileptic drugs (AEDs).

Results

PK Data and Demographics

The final data for population PK analysis consisted of 1524 observations from a total of 310 patients. There were 151 (49%) males and 159 (51%) females. Population age and weight ranged from 5 to 77 years (median = 18 years) and 15.7 kg to 128 kg (median = 61 kg), respectively. A total of 113 (36%) children between the ages of 6 and 12 years were included. The AED PK populations for drug interaction analyses included: 140 (45%) subjects for carbamazepine (CBZ), 85 (27%) subjects for lamotrigine (LT), 34 (11%) subjects with phenytoin (PT), 22 (7%) subjects with phenobarbital (PB), 27 (9%) subjects with oxcarbazepine (OXC), 33 (11%) subjects with topiramate (TOP), 88 (28%) subjects with valproic acid (VPA), and 6 (2%) subjects with primidone (PRI). In total 212 (68%) subjects were on known cytochrome P450 (CYP3A4) inducers (PT, PB, CBZ, OXC, TOP and/or PRI).

Evaluation of Weight and Time Effect on Zonisamide Exposure

Zonisamide CL/F decreased with time and increased with increasing body weight (Fig 2.4.2.1).

Figure 1. Predicted Zonisamide Clearance vs. Time for 15, 60, and 130 kg Body Weight Subjects
The increase of CL/F with body weight results in lower exposure at higher body weight, if given at a fixed dose. Simulations (n=500) were performed to predict Zonisamide steady-state exposure given at a fixed daily dose of 500 mg per day, or per body weight at 8 mg/kg/day. Dosing per body weight resulted in comparable exposure across a range of body weights. Therefore the Zonisamide PK model indicated that in children, dosing based on per unit body weight will result in comparable Zonisamide exposure to that in adults.

**Fig. 2.4.2.2. Predicted Zonisamide Steady-State Concentration (N = 500 Simulations) for Subjects Given a Fixed Daily Dose of 500 mg/day and 8mg/kg/day for 8 Weeks.**

Figure 2.4.2.2 is based on the simulation performed using the final PK model for Zonisamide. Weight was the only significant covariate in the model. After taking into account body weight differences, age had no further effect on Zonisamide PK. Thus during simulations, age of the subjects was not considered. The Population PK model was developed based on data from Study 312 in which subjects received nominal doses of 8 mg/kg and for which the age range was 6 through 17 years. In Study 302, the 500 mg cohort had an age range of 12 through 77 years.

The similarity in average exposure between children and adults can be observed, when the actual doses are corrected for body weight. Summary model-predicted Cav (μg/mL) estimates for approximate doses of 4 to 5 and 8 to 9 mg/kg/day are presented in Table 2.4.2.1. In general, the range of exposures between children aged 6 to 12 years and those subjects between 13 and 77 years for the same dose level were similar.
Table 2.4.2.1 Summary Predicted Zonisamide Exposure in Subjects aged 6-12 and 13-77 years following Body Weight-Corrected Doses of 4-5 and 8-9 mg/kg/day.

<table>
<thead>
<tr>
<th>Zonisamide Dose</th>
<th>6 to 12 years</th>
<th>13 to 77 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-5 mg/kg/day</td>
<td>8-9 mg/kg/day</td>
</tr>
<tr>
<td>N</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Mean</td>
<td>20.974</td>
<td>22.337</td>
</tr>
<tr>
<td>SD</td>
<td>7.216</td>
<td>9.889</td>
</tr>
<tr>
<td>Min</td>
<td>12.19</td>
<td>5.32</td>
</tr>
<tr>
<td>Max</td>
<td>34.19</td>
<td>46.60</td>
</tr>
</tbody>
</table>

Note: These data are calculated from Cmin values in CPMS-E2060-001R, Table 11-1.

The MAH was requested to provide summary predicted exposure data in subjects aged 13 to 18 and 19 to 77 years rather than 13 to 77 years and estimations of exposure (Cminss, Cmaxss and AUC) in more age groups instead of the current two (6-12 and 13-18) as these are found to be too wide for confirming similar exposure in all paediatric groups as compared to adults. Simulations were requested to be done in different weight groups and dosages. Further, the MAH was requested to provide an overview of the numbers of patients in different age and weight groups included in the PK/PD model, and the administered dosages.

The MAH stated that Study 312 and 302 had sparse sampling so it was not possible to derive exposure parameters of Cmin, Cmax and AUC. The paediatric PK study (Study 225) showed that at steady state, the PK profile of zonisamide during a 12-hour dosing interval was almost flat due to a long half-life. Therefore, at steady state, the PK sample at any time during the dosing interval gives a reasonably good estimate of the Cav concentration.

The MAH presented box plots showing observed steady state zonisamide plasma concentrations in those participating in Study 312 by age-group (8mg/kg) along with box plots for adults at the 300mg and 500mg doses. Average zonisamide concentrations in the paediatric age-groups overlap with those of the 300mg and 500mg doses in adults, though they appear to be closer to those for the 500mg dose. A box plot of concentration versus body weight shows a similar picture with overlap in average concentration between paediatric 8mg/kg doses and adult 300mg and 500mg doses.

A somewhat similar picture is seen for a box plot of the 6mg/kg paediatric dose in different age-groups compared to the 300mg and 500mg adult dose with the 6mg/kg dose resulting in an exposure in the
range between the adult doses. There is also overlap in exposure of the 6mg and 8mg/kg paediatric doses.

Overall, the overlap in exposure between the 6mg/kg and 8mg/kg raised the question as to whether a dose of 6mg/kg might be equally efficacious or minimally less efficacious as the 8mg/kg dose with the additional benefit of a possible lower frequency of adverse events.

The MAH was also asked to provide further evidence on zonisamide exhibiting time-dependent pharmacokinetics and on the population PK-PD models used to draw conclusions about similarity in exposure-response between different age groups.

In relation to co-administration of AEDs (PT, PB, CBZ, OXC, TOP, PRI, VPA, LT), they did not affect the pharmacokinetics of Zonisamide, hence there is no need for dose adjustment with any of the AEDs including CYP3A4 inducers (PT, PB, CBZ, OXC, TOP and/or PRI).

### 1.3.3. Conclusion on clinical pharmacology

The CHMP noted that the highest dose in the adults study was 500mg/day which would amount, in an average weighing adult of 70kg, to 7mg/kg/day, while 300mg/day would amount to 4mg/kg/day. The MAH stated that the available data from previous paediatric studies indicated that zonisamide exposures in children aged 6 years and above and adolescents were similar to those observed in adults when adjusted for body weight. These studies were used to provide data for the population pharmacokinetic modelling and PK/PD modelling. The MAH predicted that a dose of 8mg/kg/day in children and adolescents will produce levels of exposure similar to those in adults produced by a dose of 300 to 500mg zonisamide. Given that the efficacy of zonisamide is well established in the adult adjunctive use population at a dose of 300mg to 500mg, it was anticipated that a dose of 8mg/kg should be efficacious in the paediatric population

At the request of CHMP the MAH provided an overview of the numbers of patients in different age and weight groups included in the PK/PD model, and the administered dosages.

Based on the achieved plasma concentrations, and the results of the PK-pop simulations, the dosage based on body weight was agreed with. However, the CHMP believed that based on the average plasma concentrations, a lower dosage than 8 mg/kg could also result in comparable exposure to adults.

The MAH provided an overview of responder rate per achieved maintenance dose in the pivotal trial, to explore whether a lower target dose than 8 mg/kg was effective.
The CHMP noted that there appears to be a more robust response in those treated with a 7 to 9mg/kg dose compared to those treated with 4 -<7mg/kg dose. However the numbers treated with the lower dose are lower and it is possible that the lower response in this group could have occurred through chance.

The MAH acknowledged that the target dose of 8 mg/kg/day was originally proposed instead of a range in order to fit more closely the design of the study. In practice, the actual dose received by the majority of subjects varied between 6.3 and 9.5 mg/kg/day depending on a subject’s position within each weight grouping. Additionally, subjects who opted for the lower initial target dose of 7 mg/kg/day permitted in event of tolerability issues during the titration period would have received doses down to 5.4 mg/kg/day (see Figure 2). Ten subjects fell outside the permitted range: 6 subjects received doses below 5.4 mg/kg/day and 4 subjects above 9.5 mg/kg/day.

**Table 6  Primary Efficacy Analysis: Statistical Analysis of Proportion of Responders in Maintenance Period – LOCF (Intent To Treat Population) for Study 312**

<table>
<thead>
<tr>
<th>Maintenance Dose</th>
<th>Placebo (N=100)</th>
<th>ZNS (N=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 –&lt;7 mg/kg</td>
<td>n</td>
<td>20</td>
</tr>
<tr>
<td>Proportion of Responders: RR (95% CI)</td>
<td>0.30 (0.119;0.543)</td>
<td>0.46 (0.266;0.666)</td>
</tr>
<tr>
<td>7 –&lt;9 mg/kg</td>
<td>n</td>
<td>59</td>
</tr>
<tr>
<td>Proportion of Responders: RR (95% CI)</td>
<td>0.29 (0.178;0.421)</td>
<td>0.55 (0.418;0.669)</td>
</tr>
<tr>
<td>9 –&lt;12 mg/kg</td>
<td>n</td>
<td>14</td>
</tr>
<tr>
<td>Proportion of Responders: RR (95% CI)</td>
<td>0.57 (0.289;0.823)</td>
<td>0.43 (0.099;0.816)</td>
</tr>
</tbody>
</table>

Dose is at maintenance before any down titrations. Weight at baseline is used in the calculation. Subjects who withdrew prior to the maintenance period are excluded from this analysis.

CI = confidence interval, N = total number of subjects in each study arm, n = number of responders, RR = response rate.

Source: Attachment 1. CHMP Study 312 Ad hoc Table 1

The CHMP noted that there appears to be a more robust response in those treated with a 7 to 9mg/kg dose compared to those treated with 4 -<7mg/kg dose. However the numbers treated with the lower dose are lower and it is possible that the lower response in this group could have occurred through chance.

The MAH acknowledged that the target dose of 8 mg/kg/day was originally proposed instead of a range in order to fit more closely the design of the study. In practice, the actual dose received by the majority of subjects varied between 6.3 and 9.5 mg/kg/day depending on a subject’s position within each weight grouping. Additionally, subjects who opted for the lower initial target dose of 7 mg/kg/day permitted in event of tolerability issues during the titration period would have received doses down to 5.4 mg/kg/day (see Figure 2). Ten subjects fell outside the permitted range: 6 subjects received doses below 5.4 mg/kg/day and 4 subjects above 9.5 mg/kg/day.

**Figure 2. Actual dose of ZNS received (mg/kg/day) per subject weight (kg) in Study E2090-E044-312**
Thus the posology section of the product information was amended to include a dosing range.

The posology agreed was a dose range of 6 to 8mg/kg in those weighing less than or equal to 55kg (once a day); the proposed dose range for a paediatric population weighing more than 55 kg is 300 - 500 mg per day (once a day).

1.4. **Clinical efficacy**

Study 312 is the pivotal study that substantiates the efficacy of ZNS as adjunctive therapy in paediatric subjects (6-7). This Phase 3 study was a double-blind, randomized, placebo-controlled study, conducted at 41 sites in 11 countries. In addition, as supportive data, results are presented from:

- **Study 313**, the double-blind extension of Study 312 designed to assess long-term efficacy and safety in paediatrics patients.
- **Study 302**, an add-on fixed dose study, from the initial submission for the adult indication which included adolescents and adults aged 12 years old or older. Altogether out of 294 patients included in the ITT analysis of this study, 32 were aged 12-17; 17 received one of 3 doses of Zonegran and 15 placebo. Due to the small numbers, no conclusions regarding adolescents could be drawn from the results of this study.
### Overview of clinical studies

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study Identifier</th>
<th>Objective(s) of Study</th>
<th>Study Design and Type of Control</th>
<th>Test Product(s); Dosage Regimen; Route of Administration</th>
<th>Number of Subjects</th>
<th>Diagnosis / study population</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3 efficacy and safety</td>
<td>E2090-E044-312</td>
<td>To assess the efficacy and safety of adjunctive zonisamide in pediatric partial onset seizures. To further explore the efficacy and safety of ZNS. To explore the effect of ZNS on cognition, and growth and development.</td>
<td>Double-blind, randomized, placebo-controlled trial</td>
<td>ZNS 8 mg/kg/day once daily orally</td>
<td>N = 207</td>
<td>Epilepsy with partial onset seizures with or without secondary generalisation aged 6-17 years.</td>
<td>4-week or 8-week Screening Period, an 8-week Titration Period, a 12-week Maintenance Period, and for subjects not entering extension Study 313, a Down-Titration Period of 3 to 4 weeks.</td>
</tr>
<tr>
<td>Phase 3 safety study*</td>
<td>E2090-E044-313</td>
<td>To assess the longterm safety of adjunctive zonisamide in pediatric partial onset seizures.</td>
<td>Follow on open label study form Study 312</td>
<td>ZNS 8 mg/kg/day once daily orally</td>
<td>N = 144</td>
<td>Epilepsy with partial onset seizures with or without secondary generalisation aged 6-17 years.</td>
<td></td>
</tr>
<tr>
<td>Phase 3 Study</td>
<td>AN46046-302</td>
<td>To evaluate the safety and efficacy of zonisamide (500 mg/day) versus placebo when used in combination with existing treatment regimens in subjects with refractory partial seizures.</td>
<td>Double-blind, randomized, placebo-controlled trial</td>
<td>Zonisamide doses of 100mg, 300mg and 500mg</td>
<td>N = 351</td>
<td>Refractory partial epilepsy and with unsatisfactory seizure control despite a stable regimen of 1-3 licensed anti-epileptic drugs.</td>
<td>Titrination phase (6 weeks), stabilisation phase (2 weeks), Fixed Dose assessment phase (16 weeks) and controlled withdrawal (Down Titratin) phase (4 weeks).</td>
</tr>
</tbody>
</table>

#### 1.4.1. Dose response studies

No dose finding study reports were submitted.

The study protocol of the pivotal study 312, provides the rationale for the choice of dose used, based on the results of study 302 with adults, which showed that efficacious doses for adults were within the dose range of 300 to 500 mg/day (the 100mg/day dose did not separate from placebo).

The dosing rational also refers to three previous studies conducted in paediatric subjects with zonisamide as add-on treatment (AN46046-225, 226 and 354).

Based on the limited pediatric PK information available prior to Study 312 (primarily Study 225 and Study 354), the data indicated that the Zonisamide exposure (including variability) seen at 300 through 500 mg per day in adults was likely realized in children when dosing at a target of 8 mg/kg per day. Other information suggested that clearance was generally increased only in children much below the lowest age range in Study 312. A literature review suggested little if any systematic PK differences for Zonisamide between adults and children aged 6 years and above. The data suggested that a body-weight correction was appropriate and hence a target dose of 8 mg/kg (minimum of 6 mg/kg) was selected and used in Study 312.

Studies 225 and 226 included subjects aged 5 to 15 and 5 to 18 respectively. These studies showed an acceptable safety profile with doses of 2-12mg/kg of zonisamide with a starting dose of 1mg/kg. The target maintenance dose in these trials was 12mg/kg or 600mg whichever was the lowest dose. Study
225 and 226 used a rapid titration schedule with weekly dose increases, where the maximum dose of 12 mg/kg was reached in 8 weeks; the drop-out rate due to AEs was 30%. In Study 354, a much slower titration rate was used where a dose of 8 mg/kg was reached in week 8, and 12 mg/kg in week 12. In this study a markedly lower drop-out rate (9%) was observed, suggesting that a slower titration was better tolerated. Therefore, dosing regimen in study 312 replicates the initial part of the titration Period used in Study 354, with the target dose of 8 mg/kg being reached at the end of Week 8.

As previously highlighted, the dose recommendations in the SmPC proposes a dose range of 6 to 8mg/kg in those weighing less than or equal to 55kg (once a day).

The proposed dose range for a paediatric population weighing more than 55 kg will be 300 - 500 mg per day (once a day).

Dosing titration in the SmPC are the same as in the study for patients with cytochrome p450 3a4-inducing agents but are twice as slow for patients without cytochrome p450 3a4-inducing agents as already recommended in the SmPC for adults.

1.4.2. Main studies

Study E2090-E044-312

Methods

The pivotal study (Study E2090-E044-312) was a double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy and safety of adjunctive Zonisamide in paediatric partial onset seizures. The study was conducted in India and Europe with the largest number of subjects coming from Ukraine (70), Hungary (42), India (35), Latvia (21) and Poland (21). A total of 207 subjects were enrolled in the trial across 41 sites in 11 countries.

A brief summary of the trial is shown in Table 8.

<table>
<thead>
<tr>
<th>Table 8. Summary of Study E2090-E044-312</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of study sites</td>
</tr>
<tr>
<td>Design</td>
</tr>
<tr>
<td>Posology</td>
</tr>
<tr>
<td>Objective</td>
</tr>
<tr>
<td>Subjects by arm entered/completed</td>
</tr>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Median age</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Primary endpoint</td>
</tr>
</tbody>
</table>
Study participants

Study participants were aged between 6 to 17 years with a clinical diagnosis of epilepsy with partial onset seizures with or without secondary generalisation according to the ILAE classification of epileptic seizures (1981). Diagnosis should have been established by clinical history, EEG, and CT/MRI imaging of the brain consistent with localization-related epilepsy. Subjects had to have had at least 4 partial seizures per month over the 8-week baseline period with at least one seizure in each 4-week period, and with no 21-day period being seizure free. Subjects should have been taking a stable regimen of one or two other AEDs.

Subjects were excluded if they had a body weight < 20 kg at screening, progressive neurological disease, a history of generalised epilepsy, Lennox-Gastaut syndrome, absence, myoclonic, clonic and/or tonic (other than secondary generalised), and atonic seizures or a history of status epilepticus within one year of screening whilst taking AEDs, a history of renal calculi or renal insufficiency, a history of psychiatric illness or suicide attempt.

The CHMP considered the inclusion and exclusion criteria acceptable.

Subjects were randomised to either a zonisamide or a placebo treatment arm. Randomization was stratified by site and weight group. Weight bands of 20 – <29 kg, 29 – <42 kg, 42 – <56 kg, and ≥56 kg were used to stratify dosing.

The study drug (Zonegrón or placebo) was taken once daily in the evening. The dose was titrated upwards from 1-mg/kg/day starting dose, with weekly dose increases in increments of 1 mg/kg/day, until a maximum dose of 8 mg/kg/day was reached at the end of week 8. In the event of dose-limiting adverse events (AEs) during the 8-week titration period, one down-titration to a lower dose was permitted; this could happen at any point in the Titration Period. For patients who undertook this single allowable down-titration, the dose during the maintenance Period was less than 8 mg/kg/day. For patients heavier than 55 kg the maximum dose was 500 mg, or 400 mg if the patient received the 1 down-titration allowed during the Titration Period. During the titration period, patients whose dose had been down-titrated had their dose increased again as soon as tolerability improved. Patients who required further down-titration steps were withdrawn from the study. No changes to the dose were allowed during the maintenance period.

Concomitant Anti-epileptic drug Therapy

Subjects had to be taking a stable regimen of 1 or 2 other Anti-epileptic drugs (AED) for at least 2 months before the start of the screening period.

Prohibited medications

Subjects who had taken any antipsychotic drug, MAOIs, TCAs, benzodiazepine with barbiturate for treatment of disorders other than epilepsy, and stimulants (amphetamine derivatives) had to have discontinued their use within 3 months prior to Screening.

Acetazolamide, carbonic anhydrase inhibitors (for example topiramate), any drugs with anticholinergic activity, feverfew, St John’s Wort, and felbamate were not permitted for use during the study. Subjects could not take any prescription medications during their participation in this study without the prior knowledge and consent of the investigator, unless required for emergency treatment.

Study Plan

Subjects underwent a 4 to 8 week Screening period followed by an 8 week titration period which was in turn followed by a 12 week Maintenance period (See Figure 3)
The study plan, with a screening titration and maintenance period, was considered acceptable by CHMP. The maintenance period is in line with similar studies of AEDs in adjunctive use.

**Objectives**

**Primary objective:**

To assess the efficacy of zonisamide (Zonisamide) in paediatric epilepsy with partial onset seizures (POS) treated with one or two other AEDs.

**Secondary objectives:**

To further explore the efficacy and safety of Zonisamide.

To explore the effects of Zonisamide on cognition, growth and development.

**Endpoints**

**Primary endpoints**

The primary efficacy endpoint was the proportion of responders in the Zonisamide group compared to placebo in the ITT population. A responder was defined as a subject with a decrease in seizure frequency of at least 50% during the maintenance period compared to seizure frequency during the baseline period (i.e. 28 day seizure frequency during weeks 8 to 20 compared to weeks -8 to 0).

Seizure count was derived from daily diaries (maintained by the parent or guardian). Seizure frequency of simple partial, complex partial, and partial seizures with secondary generalization were counted.

The primary analysis was over the period of fixed dosing (the maintenance period). Sensitivity analyses included the combined titration period and maintenance period. Baseline was the seizure frequency in the 8 weeks before randomization. The primary analysis population was the intent-to-treat (ITT) population with LOCF during the maintenance period.

**Secondary endpoints**

- Median percentage change from baseline in the 28 day seizure frequency during the maintenance period only and during the combined maintenance and titration periods
The proportion of subjects with a decrease from baseline in the 28-day seizure frequency of ≥ 50% to < 75% and ≥ 75% during the maintenance period only and the combined maintenance and titration periods

The proportion of subjects with an increase from baseline in 28 day seizure frequency of ≥ 25% and > 100% during the maintenance period and during the combined titration and maintenance period.

There were a number of other efficacy variables including percentage change from baseline in 28 day seizure frequency by seizure type, proportions of subjects seizure free, the number of seizure free days and the relationship between plasma level of Zonisamide and seizure frequency.

The CHMP noted that the primary and efficacy endpoints are acceptable and are in line with EMA guidance.

Sample size

A sample size of 91 subjects in each group was estimated to have an 80% power to detect a difference in the proportion of responders of 20% in the placebo group and 40% for the treatment group. Previous adjunctive studies were taken as a reference point for the proportions. A 10% drop out rate was expected meaning that each group required a sample of 102 subjects.

A sample size for a separate sub-sample formed of those with an IQ ≥ 75 to be assessed for cognitive outcome was calculated. A sample size of 38 was estimated to be required to detect a difference in means of power of attention of 130msec (SD=199msec). Given that there was expected to be a drop-out rate of 10% it was calculated that a sub-sample size of 42 subjects would be required in each group.

Statistical methods

The analysis population for the primary efficacy variable was the intention to treat (ITT), defined as all randomised subjects who received at least 1 dose of double-blind study medication.

Efficacy analyses were also carried out on the per protocol population defined as all subjects in the ITT population who had no major protocol violations.

Analyses were performed by comparing zonisamide to placebo. A 5% significance level was used. No adjustments were made for multiplicity. No interim analyses were planned or conducted.

The primary comparison of interest was the Zonisamide treatment group versus the placebo group in the ITT population on last observation carried forward (ITT-LOCF) data during the maintenance period.

The secondary comparison of interest was the Zonisamide versus placebo group in the ITT population on observed case data (ITT-OC) during the maintenance period and during the combined titration and maintenance period.

Data that was not normally distributed was log transformed or, if this was unsuccessful non-parametric methods were used.

The percentage change from baseline was calculated and an analysis of covariance (ANCOVA) was performed on rank-transformed data to test for the effects of treatment of seizure data. The median percentage change from baseline, a non-parametric Hodges-Lehmann confidence interval and a p value were presented.

For non-seizure data evidence of normality was provided if a parametric test was used.
For the primary efficacy variable (responder rate) the proportion of responders in each group was compared using the Pearson’s chi-square test. P values were presented for the association in treatment and responder rate. The responder analysis was originally planned to be a Cochran-Mantel-Haenszel (CMH) test which included the strata for site and weight as per randomisation. After further investigation it was decided that site and weight should be removed from the analysis. Due to the lack of covariates for the primary analysis of responders, the analysis was changed to a Pearson’s chi-squared test.

The primary endpoint (responder rate) was also analysed by sub-group e.g. subjects who took enzyme inducing AEDs v subjects who took non-enzyme inducing AEDs and subjects who took 1 AED vs. subjects who took 2 AEDs.

The percentage change in 28 day seizure frequency from baseline during the maintenance period and during the combined titration maintenance period was analysed using rank ANCOVA with baseline seizure frequency included as a covariate. Initially it was planned to conduct the analysis using ANOVA however ANCOVA was used because the assumptions of normality were not expected to be satisfied for seizure endpoints.

A plot for percentage change in baseline seizure frequency per 28 day seizure frequency over the 20-week treatment phase was produced.

The proportion of subjects with decrease of 28 day seizure frequency of ≥ 50% to < 75% was summarised. The proportion of subjects with a 28 day seizure frequency decrease from baseline of at least 75% was during the maintenance period was analysed using Pearson’s chi-square test and similarly for 28-day seizure frequency reduction during the combined titration maintenance period.

A similar approach was used to analyse increase in 28 day seizure frequency during the maintenance period and during the combined titration maintenance period.

In general, the CHMP considered the statistical methods used appropriate. Analysis of the primary efficacy variable in the ITT population on last observation carried forward is acceptable as it provides a more realistic assessment of efficacy given that those in whom the treatment is not efficacious or who experience TEAEs are likely to drop out and would not be included in an ITT OC population.

**Results**

**Participant flow**

**Patients’ disposition:** The investigators screened 242 patients for entry into the study. Of these, 35 patients were screen failures and 207 patients were randomized into the study (107 to the Zonegran group and 100 to the placebo group). The reasons for failing screening are summarized in Figure 2 below.
Protocol amendments

There was one amendment specific to France and four other amendments. The major amendments included a change in the screening period from 8 to 4 weeks with seizure frequency in the 4 weeks prior to the screening period captured in a seizure diary used as part of standard clinical practice. Only subjects with a stable baseline phase and good quality of data were randomized. There were changes in the statistical analysis plan and a reduction in the sample size with a reduction in power from 90% to 80%. In addition the use of benzodiazepines as rescue medication was permitted once a week whereas previously it has only been allowed once a month.

The proportion of subjects recruited with a 4 week screening period is small (7.2%) and unlikely to have had an impact on efficacy results and no subjects in this study required benzodiazepine rescue.

Baseline data

Both treatment groups were largely similar in terms of demographic characteristics. In terms of baseline characteristics related to epilepsy the two groups were similar with regard to median time since diagnosis (54.7 months v 52.4 months for placebo and Zonegran respectively) and the number of concomitant AEDs taken. Median number of seizures in the baseline period was 10 for the placebo arm and 10.5 for the Zonegran arm. Baseline mean seizure frequency was higher in the placebo group (43.8) than the Zonegran group (32.9). The higher mean value for baseline seizure frequency in the placebo group reflects one outlier patient who had 882 seizures. The proportion of subjects by seizure type was similar in both groups.
In the Zonegran treatment group a lower proportion of subjects had unknown aetiology compared to the placebo group (Zonegran 56.1% v placebo 65%) and a slightly higher proportion had structural brain abnormalities (Zonegran 19.6% v placebo 13%). This was more marked in the 12 to 17 age-group (59.6% (Zonegran) v 75.6% (PLB) for unknown aetiology and 21.2% v 6.7% for structural brain abnormalities.

Summary of main efficacy results

Summary of efficacy for trial E2090-E044-312

| Title: | A Double-blind, Randomised, Placebo-controlled, Multi-centre Study to Assess the Efficacy and Safety of Adjunctive Zonisamide in Paediatric Partial Onset Seizures. |
| Study identifier | E2090-E044-312 |
| Design | A double blind randomized placebo controlled study of the efficacy and safety of zonisamide in adjunctive use in a population aged between 6 and 18. |
| Duration of main phase: | 6 week titration phase and 12 week maintenance period |
| Duration of Run-in phase: | 4 to 8 week |
| Hypothesis | Superiority Trial to assess the efficacy of zonisamide in paediatric epilepsy subjects with partial onset seizures treated with one or two other AEDs compared to placebo in a similar population. |
| Treatments groups | | |
| Zonisamide | Zonisamide + usual AEDs (1 or 2). <duration>, n = 107 |
| Placebo | Placebo + Usual AEDs (1 or 2). <duration>, n=100 |
| Endpoints and definitions | Primary endpoint | The primary efficacy endpoint was the proportion of responders in the Zonisamide group compared to placebo in the ITT population. A responder was defined as a subject with a decrease in seizure frequency of at least 50% during the maintenance period compared to seizure frequency during the baseline period (i.e. 28 day seizure frequency during weeks 8 to 20 compared to weeks -8 to 0.) |
| | Secondary endpoints | - Median percentage change from baseline in the 28 day seizure frequency during the maintenance period only and during the combined maintenance and titration periods |
| | | - The proportion of subjects with a decrease from baseline in the 28-day seizure frequency of ≥ 50% to < 75% and ≥ 75% during the maintenance period only and the combined maintenance and titration periods |
| | | - The proportion of subjects with an increase from baseline in 28 day seizure frequency of ≥ 25% and > 100% during the maintenance period and during the combined titration and maintenance period. |
| other endpoints | There were a number of other efficacy variables including percentage change from baseline in 28 day seizure frequency by seizure type, proportions of subjects seizure free, the number of seizure free days and the relationship between plasma level of Zonisamide and seizure frequency. |
Results and Analysis. Main outcome (ITT population, LOCF, maintenance period)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Zonisamide</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-randomised</td>
<td>100</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>n-completed</td>
<td>90</td>
<td>93</td>
<td></td>
</tr>
</tbody>
</table>

### Seizure frequency

<table>
<thead>
<tr>
<th></th>
<th>Median (range)</th>
<th>Difference CI 95%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.0 (4-882)</td>
<td>5.3 (0-2044)</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>9.5 (0-244)</td>
<td>5.3 (0-458)</td>
<td></td>
</tr>
</tbody>
</table>

### Responders

<table>
<thead>
<tr>
<th>Responders</th>
<th>Placebo</th>
<th>Zonisamide</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 AED n=39</td>
<td>38%</td>
<td>64%</td>
<td>26%</td>
<td>0.0220</td>
</tr>
<tr>
<td>2 AEDs n=60</td>
<td>25%</td>
<td>41%</td>
<td>16%</td>
<td>0.0557</td>
</tr>
<tr>
<td>Enzyme inducers n=42</td>
<td>24%</td>
<td>44%</td>
<td>20%</td>
<td>0.0392</td>
</tr>
<tr>
<td>Non-enzyme inducers</td>
<td>36%</td>
<td>56%</td>
<td>20%</td>
<td>0.0317</td>
</tr>
</tbody>
</table>

**Secondary efficacy analysis**

| Median percentage change in seizure frequency | -24.5% | -50% | -25% | -38.7% ; -12.2% | < 0.0001 |
| All Seizures                                         |       |      |      |                |          |
| Simple Partial                                      | -43.0% | -61.3% | -16% | -34.0% ; 0.4% | 0.075    |
| Complex Partial                                    | -24.2% | -45.2% | -20.7% | -45.1% ; -0.0% | 0.046    |
| Secondary generalized                             | -51.1% | -86.1% | -7.8% | 43.3% ; 0.0% | 0.139    |

**Primary efficacy variable**

The percentage of subjects in the ITT-LOCF group who experienced a decrease in 28 day seizure frequency of 50% or more relative to baseline in the maintenance period was 50% in the Zonisamide group and 31% in the placebo group. This result was statistically significant. Responder rates were similar in the ITT-OC population and in the PP-LOCF population.

The responder rate in the combined titration and maintenance periods for the ITT-OC population was consistent with those for the ITT population in the maintenance period (44% in the Zonisamide group and 18% in the placebo group, P < 0.0001.

**Sub-group analysis**

In the maintenance period (LOCF) a higher percentage of Zonisamide subjects taking one AED had a response compared to subjects taking two AEDs (64% v 41% respectively) and similarly for those taking placebo (38% v 25% respectively).

In the maintenance period, subjects in both treatment groups had a lower response if they were receiving enzyme inducing AEDs compared to subjects receiving non-enzyme inducing AEDs (Zonisamide 44% v 56%, placebo 24% v 36% LOCF).

In order to assess consistency of results across seizure types, MAH was requested to provide responders rate by seizure type.

A table of response rate by seizure type is presented in Table 8. The response rate for Zonisamide was similar across seizure types. The treatment difference varied across seizure types with the largest treatment difference being observed in patients with secondary generalized tonic clonic seizures.
However it should be noted that the subgroups are not large enough to confirm differences between treatments by seizure type.

### Table 8  Statistical Analysis of Proportion of Responders in Maintenance Period by Seizure Type: ITT Population (LOCF)

<table>
<thead>
<tr>
<th>Seizure Types¹</th>
<th>Placebo (N = 100)</th>
<th>Zonisamide (N = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Partial with Motor Signs, n</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>Proportion of Responders (CI)</td>
<td>0.38 (0.222, 0.564)</td>
<td>0.50 (0.338, 0.662)</td>
</tr>
<tr>
<td>Simple Partial without Motor Signs, n</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Proportion of Responders (CI)</td>
<td>0.60 (0.262, 0.878)</td>
<td>0.64 (0.308, 0.891)</td>
</tr>
<tr>
<td>All Simple Partial, n</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td>Proportion of Responders (CI)</td>
<td>0.41 (0.256, 0.579)</td>
<td>0.50 (0.346, 0.654)</td>
</tr>
<tr>
<td>Complex Partial, n</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>Proportion of Responders (CI)</td>
<td>0.36 (0.240, 0.499)</td>
<td>0.47 (0.343, 0.609)</td>
</tr>
<tr>
<td>All Partial, n</td>
<td>77</td>
<td>88</td>
</tr>
<tr>
<td>Proportion of Responders (CI)</td>
<td>0.38 (0.269, 0.494)</td>
<td>0.50 (0.391, 0.609)</td>
</tr>
<tr>
<td>Secondary Generalized Tonic-Clonic, n</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>Proportion of Responders (CI)</td>
<td>0.18 (0.070, 0.355)</td>
<td>0.52 (0.325, 0.706)</td>
</tr>
</tbody>
</table>

CI = Confidence Interval, ITT = Intent to Treat, LOCF = last observation carried forward.

Proportion of responders for each treatment = responders/N.

A responder is defined as a subject with a decrease from baseline in 28-day seizure frequency of ≥50% in the Maintenance Period.

Confidence Interval is calculated using the Clopper-Pearson method.

a: Subjects may have had more than one type of seizure.

It was noted that a very small difference in responder rates is observed between the treatment and placebo arm in simple partial without signs, all simple partial and complex partial subgroups, where a high percentage of responders is observed in the placebo group. Differences in responder rates are observed also in the analysis of results according to aetiology.

The MAH highlighted that placebo response rates tend to be higher in paediatric populations than adult populations with drug-resistant partial epilepsy making reference to a published meta-analysis.

Although study 312 was not powered to detect efficacy in individual seizure types, at the request of CHMP the MAH also presented an analysis of the data by seizures type or aetiology.

Overall it was agreed that the effect of Zonegran does not seem to be driven by one sub-group.

### Secondary efficacy analysis

The median percentage change in seizure frequency between baseline and the maintenance period was assessed in the ITT-LOCF, ITT-OC, PP-LOCF maintenance periods and in the ITT-OC and PP-OC entire double blind period. Subjects in the Zonisamide group experienced a reduction of approximately 50% in seizure frequency from baseline in the maintenance period compared to approximately 25% in the placebo arm in the ITT-LOCF population. The size of the reduction was similar in the ITT-OC and PP-LOCF populations. The difference between the medians of -25.2% (95% CI: -38.7, -12.2) was statistically significant (P < 0.0001; rank ANCOVA).
Sub-group analysis

Seizure type

The results of the sub-group analysis, median seizure reduction by seizure type, is difficult to interpret given the small numbers in each category.

Age

The percentage of responders (decrease of ≥ 50% in seizure frequency relative to baseline) by age group is presented in the table below. A higher percentage of responders in the Zonegran compared to placebo treatment group were observed both among the 6 to 11 years of age (47% vs. 31%; difference=16%, 95% CI: -2 ; 33) and the 12 to 17 age group (54% vs. 31%; difference=23%, 95% CI: 3 ; 40).

Table: Percentage change from baseline in seizure frequency in study 312, ITT-LOCF population

<table>
<thead>
<tr>
<th></th>
<th>Age 6-11</th>
<th>Age 12-17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>n</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>&gt; 50% decrease</td>
<td>17 (30.9%)</td>
<td>26 (47.3%)</td>
</tr>
<tr>
<td>&gt; 75% decrease</td>
<td>7 (12.7%)</td>
<td>15 (27.3%)</td>
</tr>
<tr>
<td>25%-10% increase</td>
<td>10 (18.2%)</td>
<td>5 (9.1%)</td>
</tr>
<tr>
<td>&gt; 100% increase</td>
<td>5 (9.1%)</td>
<td>2 (3.6%)</td>
</tr>
</tbody>
</table>

Enzyme-inducing AEDs and Number of AEDs

Subjects taking two AEDs in combination with Zonisamide appear to show a smaller reduction in seizure frequency compared to subjects taking one AED in combination with Zonisamide for the maintenance period relative to baseline, (-60.5% v -38.8% in the Zonisamide group for one and two AEDs respectively, and for placebo (-33.3% v -12.4% respectively).

The Percentage change in median frequency of seizures by seizure type is difficult to interpret as the numbers in each sub-type are low.

The CHMP noted that although a lower response was observed in patients receiving enzyme-inducing AEDs compared to patients receiving non-enzyme-inducing AEDs, the difference between Zonegran and placebo arms is similar in both subgroups of patients and hence there is no concern of less efficacy in patients receiving enzyme-inducing AEDs.

As the current SPC of Zonegran indicates, the only difference between patients receiving enzyme inducers or non-inducers AEDs is in the titration schedule, while the final dose is the same.

The effect in the strata of patients with 2 AEDs at baseline is lower (a difference of 16% between the treatment groups) and just not statistically significant compared to those with 1 AED (a difference of 26%). This result may be interpreted as indicating less effect obtained in a more refractory population, which is expectable.

It is reassuring to observe that the effects are in the same direction in all strata that were examined (Enzyme-inducing AEDs and Number of AEDs).

The CHMP concluded that the results remain consistent across different types of patient population.
A cumulative distribution curve was used to display the data on change in median seizure frequency. See figure 2.7.3-2 below. The effect on seizure frequency consistently favoured Zonisamide across the range of outcomes.

Twenty seven percent of the subjects in the Zonisamide group compared with 12% of subjects in the placebo group had ≥ 75% decrease in seizure frequency during the Maintenance Period. Fourteen percent of subjects in the Zonisamide group compared with 3% of subjects in the placebo group had a decrease in seizure frequency of 100%.

In contrast 10% of the subjects in the Zonisamide group compared with 21% in the placebo group had an increase in seizure frequency of ≥ 25%. Five percent of subjects in the Zonisamide group compared with 9% of subjects in the placebo group had an increase in seizure frequency of ≥ 100%.

![Cumulative Distribution Function of Percent Change in Seizure Frequency: ITT Population (Maintenance-LOCF)](image)

**Figure 2.7.3-2** Cumulative Distribution Function of Percent Change in Seizure Frequency: ITT Population (Maintenance-LOCF)

**Percentage of subjects who achieved seizure free status**

In the ITT-LOCF Population for the Maintenance Period, 14% of those in the Zonisamide group and 3% of those in the placebo group achieved seizure-free status during the whole of the Maintenance Period, \( P \) value = 0.0049 for the Zonisamide group. For the combined Titration Period and Maintenance Period (ITT-OC), the percentages of subjects who achieved seizure-free status were 4% in the Zonisamide group and 2% in the placebo group, \( P \) value = 0.4563 for the Zonisamide group.

The CHMP noted the results and agreed that the proportion of patients being seizure free is of limited value given the short observation period of 12 weeks. Longer observation would diminish these figures even further.

### 1.4.3. Supportive studies

#### Study 302

This was a double-blind, dose response, placebo-controlled, randomized, parallel-group study of the safety and efficacy of Zonegran as adjunctive therapy in patients with refractory partial epilepsy.

**Design:** Following screening, a 12-week prospective Baseline Phase was used to gather reliable pre-treatment seizure frequency data. Patients were randomized to receive one of four treatments: Zonegran 500 mg/day, 300 mg/day, 100 mg/day, or placebo, in the ratio 2:1:1:2. The treatment period consisted of a Titration Phase (6 weeks), a Stabilization Phase (2 weeks), and a Fixed Dose
Assessment Phase (16 weeks). Patients then entered a controlled Withdrawal (down-titration) Phase (4 weeks) or participated in an extension study (AN46046-353; initially receiving a Zonegran dose, after suitable titration, of 500 mg/day).

**Inclusion criteria:** Patients had to be adolescent and adult aged ≥ 12 years with a diagnosis of refractory epilepsy characterized by partial seizures with or without secondary generalization. Patients were required to have an abnormal EEG consistent with the diagnosis of epilepsy and a CT/MRI scan confirming the absence of a progressive neurological lesion. They were required to have had ≥ 12 partial seizures during the 12-week Baseline Period with no more than a 3-week seizure-free interval during this time. Patients were also required to have unsatisfactory seizure control despite a stable regimen of one to three licensed AEDs.

**Dose:** Study drug was administered orally, twice daily, at an initial dose of 50 mg/day, increasing to 100 mg/day, 300 mg/day, or 500 mg/day.

**Endpoints:** The primary efficacy variable was the proportion of responders, defined as ≥ 50% from baseline in seizure frequency during the maintenance period. The primary analysis used the ITT Population. Secondary efficacy included the median percentage change from baseline in complex partial seizures during the fixed dose period.

**Results**

Altogether, 39 adolescents (12-18) were included in this study: 7 in the 100mg/day group, 8 in the 300mg/day group, 9 in the 500mg/day group, and 15 in placebo. Of these patients, 32 were eligible to be included in the ITT analysis.

The proportion responders for the entire study population (including adolescents and adults) was 52.3% in the 500mg/day group, 36.0% in the 300mg/day group, 22.5% the 100mg/day group compared to 21.3% in the placebo group. The effect was statistically significant for the 500mg/day and 300mg/day doses.

A total of 31 adolescent patients were evaluable for efficacy. This small number means that these data are of limited value. Still, the proportion of responders in the treatment groups in this study were: 3 of the 5 adolescent patients (60.0%) in the 500-mg/day treatment group, 1 of 1 (100%) in the 300-mg/day group and 1 of 5 (20.0%) in the 100-mg/day group compared to 2 of 10 (20.0%) in the placebo group. None of these differences were statistically significant.

The difference between the 500-mg/day group (n=5) and placebo group (n=10) in the median percentage change from baseline in complex partial seizure frequency was -18.7%, with a 95% CI of -81.28 to 41.57 (P = 0.8366). No statistical comparison was performed for the 100-mg/day and 300-mg/day treatment groups, but decreases in seizure frequency were observed.

Altogether, the CHMP was of the opinion that the number of paediatric patients included in study 302 is too small to allow any inference about efficacy.

**Study 313**

Study E2090-E044-313 was an open-label extension study following a double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy and safety of adjunctive zonisamide in paediatric partial onset seizures.

**Primary Objective**

- To assess the long term safety of zonisamide used as an adjunctive treatment in pediatric subjects treated with one or two other antiepileptic drugs (AEDs)
Secondary Objectives

- To explore long-term maintenance of efficacy
- To assess the influence on growth and development

Methodology

This was an open-label extension study to assess long-term safety and efficacy, and the influence on growth and development in subjects following participation in a double-blind, randomized, placebo-controlled, multicentre study (E2090-E044-312 [Study 312]), and to assess the efficacy and safety of adjunctive zonisamide in pediatric subjects (aged 6 through 17 years) with partial onset seizures.

Subjects who completed Study 312 were invited to participate in this extension study, except for those enrolled at sites in India, where the Study 313 protocol was not approved in time for subjects to rollover. As Study 312 was a placebo-controlled study, subjects completed it on either zonisamide or placebo. Therefore, in order to preserve the blind of Study 312, Study 313 started with a double-blind Transition Period during which subjects already on zonisamide continued on the same dose of zonisamide for their weight, and those who were taking placebo during Study 312 were up-titrated to an appropriate dose of zonisamide. At the end of the Transition Period subjects entered the Open-label Period, in which all subjects took zonisamide at a known dose level. At the end of the Open label Period subjects either down-titrated or continued taking zonisamide under Eisai’s Compassionate Use policy; subjects who down-titrated were permitted to up-titrate a replacement AED at the same time.

For those subjects in the placebo group in Study 312, dosing with zonisamide started with a dose of approximately 1 mg/kg and the titration schedule followed that of Study 312. The total daily dose of zonisamide was gradually increased until it equaled the maintenance dose of placebo the subject had been receiving at the end of Study 312. When this point was reached, the subject stopped receiving placebo.

Those subjects previously in the zonisamide arm of Study 312 continued on zonisamide, supplemented with an increasing number of placebo capsules, thereby mirroring the up-titration regimen being followed by those subjects previously randomized to placebo in Study 312.

During the Open-label Period, subjects could be down-titrated, if necessary (e.g., as a result of an adverse event). This could occur as many times as required until the minimum dose at each level was reached. If a subject was down-titrated they could be re-up-titrated, if required, to control seizures; this could be repeated until the maximum dose in that weight group was reached.

Study 313 is discussed in the safety section.

1.4.4. Conclusion on clinical efficacy

The MAH has submitted one pivotal study (a randomised placebo controlled trial) in support of the indication for adjunctive use of Zonisamide in children aged over 6 years and in adolescents (6-17 years).

The design of the study was broadly in line with the Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders. Inclusion and exclusion criteria were considered appropriate and included subjects with inadequately controlled partial seizures in the age-group for which the indication is sought.

The choice of primary and secondary endpoints (responder rates and decrease in seizure frequency) was appropriate.
Given that a dose range from 300mg to 500mg is recommended for adjunctive use in adults, the CHMP recommended also a dose range for children and adolescents, which was agreed by the MAH.

The proportion of subjects with a 50% or greater reduction in seizure frequency in the Zonisamide arm was 50% compared to 31% in the placebo arm in the ITT-LOCF analysis. Similar results were seen in the ITT-OC and PP-LOCF population. A higher placebo response rate (31%) than that seen in similar trials, was noted for the primary endpoint in all populations assessed (ITT-LOCF, ITT-OC and PP-LOCF) in the maintenance period. Zonisamide was superior to placebo in terms of the reduction of median seizure frequency and seizure freedom. The reduction in median seizure frequency in the maintenance period compared to baseline was greater for Zonisamide than placebo in the ITT-LOCF, ITT-OC, and PP-LOCF populations (median difference approximately 25%).

The effect is consistent in the younger and older age groups (6-11 and 12-17) as well as in patients receiving different kinds of AEDs and in patients with different types of seizures.

Efficacy results in the paediatric study are consistent with those in the adults study (study 302) where % responders in the 500mg group was 44% compared to 20% in placebo.

Indirect comparison to other AED which are already indicated for adjunctive therapy in children with partial seizure, showed that the efficacy of Zonegran is in the same order of magnitude. In terms of % responders (>50% reduction in seizure frequency) a study in lamotrigine in a similarly defined sample (Duchowny et al., 1999) showed 42% responders in the lamotrigine arm compared to 16% in placebo, and a study in Topiramate (cited in French et al., 2004) showed 39% responders compared to 20% in the topiramate and placebo arms, respectively. Another study which is also cited by French et al. (2004) of oxcarbazepine achieved 41% response in the active arms compared to 22% in placebo and a study of Levetiracetam described in the SPC of this product showed response rates of 45% vs. 20% in the active arm compared to placebo, respectively. Hence all these studies achieved a 20%-25% difference between active arm and placebo in percent responders, which is consistent with the difference that was obtained for Zonegran, except that in the Zonegran study the % responders was slightly higher in both treatment arms (50% compared to 39-45% in the active arm and 31% vs. 20-25% in the placebo arm).

Overall, zonisamide has demonstrated efficacy in adjunctive use in the paediatric population.

1.5. Clinical safety aspects

1.5.1. Introduction

The overall analysis of safety presents data from the pivotal Phase 3 study (Study 312) and its double-blind extension study (Study 313).

In addition, a supportive analysis of pooled safety data across 17 Zonisamide studies with paediatric subjects is also presented. The objective of the pooled safety analysis was to assess the safety of Zonisamide in the paediatric population from all available completed studies at the time of submission which: recruited more than 3 paediatric Zonisamide-treated subjects (aged 3 through 16 years at first dose); were conducted to ICH standards; and for which a report compliant with ICH E3 was available. A total of 398 Zonisamide and 109 placebo paediatric subjects from 17 studies were identified as eligible for the analysis. Results of study 313 are not part of the pooled safety data.

1.5.2. Patient exposure

**Patient exposure**

**Study 312:** A total of 107 patients received Zonegran and 100 received placebo. The majority of patients were exposed for 5-6 months, with a median of 4.5 month. During the maintenance period (12 weeks), the majority of patients (93%) were treated with 5-9 mg/kg/day of Zonegran. The remaining patients (7%) received 9-12 mg/kg/day.

**Table 25. Exposure (Study 312 Safety Population)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo</th>
<th>ZNS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 6-11 y (n=59)</td>
<td>Age 12-17 y (n=45)</td>
</tr>
<tr>
<td>Number of Months Completed on Study, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (1.8)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>2</td>
<td>2 (3.6)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>3</td>
<td>1 (1.8)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>5</td>
<td>40 (82.1)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>6</td>
<td>1 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time on Study (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>Mean</td>
<td>134.3</td>
<td>129.5</td>
</tr>
<tr>
<td>SD</td>
<td>33.15</td>
<td>26.85</td>
</tr>
<tr>
<td>Median</td>
<td>140.0</td>
<td>140.0</td>
</tr>
<tr>
<td>Range</td>
<td>27-167</td>
<td>6-147</td>
</tr>
<tr>
<td>Duration of Exposure (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>Mean</td>
<td>134.1</td>
<td>129.5</td>
</tr>
<tr>
<td>SD</td>
<td>25.46</td>
<td>23.15</td>
</tr>
<tr>
<td>Median</td>
<td>140.0</td>
<td>140.0</td>
</tr>
<tr>
<td>Range</td>
<td>20-366</td>
<td>6-167</td>
</tr>
</tbody>
</table>

Number of months completed = Number of months subject received at least one dose of study drug.

Number of months completed on study was calculated as (Duration of exposure/365.25)*12, rounded up to the next month.

Time on trial = date of last dose prior to down-titration – date of first dose + 1.

Duration of exposure = date of last dose prior to down-titration – date of first dose + 1 – any drug holidays or dose interruptions.

y = years; Zonisamide = zonisamide

**Pooled data** (this included study 312): A total of 398 patients received Zonegran (191 patients were younger than 12 years and 207 were 12-16 years old). The median duration of exposure to Zonegran was 147 days in the <12 years old and 141 days in the 12-16 years old. Maximum dose was 12mg/kg/day for patients from paediatric studies while higher doses were used in adolescents included in adults studies.

Mean duration of follow-up on Zonegran was 319 days, on placebo 133 days.
Table 24 Study Overview by Age Group (Pooled Safety Population)

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo, n (%)</th>
<th>ZNS, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 12 years</td>
<td>Age 12 - 16 years</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 12 years</td>
<td>Age 12 - 16 years</td>
</tr>
<tr>
<td>810-920</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>810-921</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>810-921-EXT</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>810-922</td>
<td>0</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>AN46046-225</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AN46046-226</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AN46046-302</td>
<td>0</td>
<td>10 (18.5)</td>
</tr>
<tr>
<td>AN46046-304</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AN46046-353*</td>
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<td>0</td>
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<tr>
<td>AN46046-354</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AN46046-355</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E2096-044-312</td>
<td>55 (100)</td>
<td>40 (74.1)</td>
</tr>
<tr>
<td>ZNS-401</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ZNS-501</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ZNS-502</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ZNS-504</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ZNS-505</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>55 (100)</td>
<td>54 (100)</td>
</tr>
</tbody>
</table>

Zonisamide = zonisamide

a: Some subjects were enrolled in more than one study.
b: Placebo subjects < 12 years old were only recruited in Study 312.
c: Placebo subjects 12 through 16 years old were recruited in Studies 312, 302, and 922.
d: Four subjects in Study 922 were treated with placebo for the first 12 weeks before starting Zonisamide treatment. These subjects are counted in both the placebo and Zonisamide arms.
e: Placebo subjects from Study 302, who entered Study 353, received Zonisamide in Study 353. These subjects were counted in both the placebo and Zonisamide arms.

There were differences in exposure between placebo and Zonisamide and differences in exposure to Zonisamide across studies included both in terms of study duration and Zonisamide dose.

In the Zonisamide < 12 years group, the majority of subjects were from Study 354 (55.0%) or Study 312 (28.8%). The maximum dose was 12 mg/kg/day in Study 354 and 8 mg/kg/day in Study 312. However, although the maximum dose was 12 mg/kg/day in Study 354, approximately one third had a dose up to 6.2 mg/kg/day, 16% to 20% had a dose of 6.2 to 8.8 mg/kg/day, and approximately one third had a dose > 11.75 mg/kg/day. The proposed target dose is 8 mg/kg/day.

Studies that recruited adult and paediatric subjects were dosed on a fixed-dose basis, rather than adjusted according to weight. Thus, the majority of paediatric subjects included in the pooled summaries were titrated to a higher dose of Zonisamide than is proposed in the Summary of Product Characteristics.

In terms of the Zonisamide subgroups, the Zonisamide < 12 years subgroup included a greater proportion of subjects from studies with a faster titration than that in the 12 through 16 years age subgroup. Faster titration was associated with a higher incidence of TEAEs. The rate of titration was adjusted during the clinical development.

The mean duration of exposure was substantially longer in the Zonisamide than placebo group (318.7 days compared with 132.8 days). The mean duration of exposure was similar in the age groups of < 12 years and 12 to 16 years. The mean duration of exposure was slightly lower in the Zonisamide 6 to 11 years age group (296.0 days) and higher in the < 6 years group (390.8 days).
The mean, modal and last doses of Zonisamide were lower in the < 12 years compared with the 12 through 16 years group. This is likely to reflect the dosing schedule in the < 12 years group since many of the subjects aged < 12 years were treated on a mg/kg basis rather than with a fixed dose (160/191 [84%] from Study 312 and Study 354.

Table 26. Summary of Exposure to Zonisamide (Pooled Safety Population)

<table>
<thead>
<tr>
<th>Duration (days)</th>
<th>Age &lt; 12 years (n=191)</th>
<th>Aged 12 - 16 years (n=207)</th>
<th>Total (n=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>191</td>
<td>207</td>
<td>398</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>318.3 (279.40)</td>
<td>319.0 (415.30)</td>
<td>318.7 (356.17)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>147.0 (1 – 1429)</td>
<td>141.0 (6 – 2311)</td>
<td>142.0 (1 – 2311)</td>
</tr>
<tr>
<td>Last Dose (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>191</td>
<td>204</td>
<td>395</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>252.2 (131.54)</td>
<td>357.5 (188.84)</td>
<td>306.6 (171.74)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>200.0 (25 – 650)</td>
<td>400.0 (13 – 850)</td>
<td>275.0 (13 – 850)</td>
</tr>
<tr>
<td>Mean Dose (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>191</td>
<td>204</td>
<td>395</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>211.1 (106.23)</td>
<td>292.3 (156.77)</td>
<td>253.1 (140.55)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>189.5 (25 – 577)</td>
<td>310.7 (13 – 721)</td>
<td>229.7 (13 – 721)</td>
</tr>
<tr>
<td>Modal Dose (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>191</td>
<td>204</td>
<td>395</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>250.7 (132.00)</td>
<td>344.1 (181.43)</td>
<td>299.0 (165.97)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>212.5 (13 – 650)</td>
<td>400.0 (13 – 800)</td>
<td>275.0 (13 – 800)</td>
</tr>
</tbody>
</table>

The data initially presented by the MAH with the variation application was not considered sufficient to properly assess the safety of this product in children and adolescents and the number of patients exposed for longer time was not considered sufficient. The guideline for epilepsy studies requires for the assessment of safety, the inclusion of at least 100 children for duration of at least one year to better assess long-term safety.

The MAH subsequently submitted the results of study 313. The total number of subjects exposed to Zonisamide for over 1 year including Study 313 and the pooled population is 230.

A total of 144 subjects entered Study 313 and received Zonisamide (72 subjects from the Study 312 Zonisamide group and 72 subjects from the Study 312 placebo group). Subjects entered an initial 2- to 11-week double-blind Transition Period during which subjects already on Zonisamide continued on the same dose of Zonisamide for their weight, and those who were taking placebo during Study 312 were up-titrated to an appropriate dose of Zonisamide.

Exposure data from Study 312 and Study 313 were combined for subjects who were on Zonisamide in Study 312; i.e., for subjects from the Study 312 Zonisamide group, the exposure data included the time on Zonisamide in Study 312. The duration of the treatment period in Study 312 prior to entering the extension study was 20 weeks (140 days [4.6 months]). Median exposure for the combined group was 444.5 days (14.6 months; 526 days [17.3 months] in subjects from the Study 312 Zonisamide group and 385 days [12.6 months] in subjects from the Study 312 placebo group).

A total of 108 (75%) subjects in Study 313 (59 [81.9%] from the Study 312 Zonisamide group and 49 [68.1%] from the Study 312 placebo group), were on the study for more than 1 year and were exposed to Zonisamide treatment for more than 1 year.
1.5.3. Adverse events

TEAEs in Study 312 and the pooled analysis were defined as those AEs that started on or after the first dose of study drug until 15 days after the date of last dose (including down-titration where appropriate, i.e., within 15 days of the last dose of study drug which was > 0 mg). In the pooled analysis, AEs that occurred after a subject switched from placebo to Zonisamide were reported as Zonisamide AEs. AEs were also summarized by the following time periods for onset: Study Weeks 0 to 12 weeks, 13 to 24 weeks, and 25+ weeks.

In Study 312 the overall rates of TEAEs were similar between the Zonisamide and placebo groups (55.1% and 50.0%, respectively). In the age-group 6 – 11, TEAEs were reported for 49.1% of Zonisamide subjects and 54.5% of placebo subjects. In the age-group 12 - 17 years, TEAEs were reported for 61.5% of the Zonisamide group and 44% of those on placebo.

Common TEAEs (incidence ≥ 2% in any treatment group) are presented in table 25 below. TEAEs with frequency higher by more than 1% (1 patient) in the Zonegran group compared to placebo were: Somnolence (Zonegran: 4.7%; placebo: 2.0%), vomiting (Zonegran: 3.7%; placebo: 2.0%), diarrhoea (Zonegran: 3.7%; placebo: 1.0%), decreased weight (Zonegran: 4.7%; placebo: 3.0%), decreased appetite (Zonegran: 6.5%; placebo: 4.0%), and cough (Zonegran: 2.8%; placebo: 1.0%).

Headache, decreased appetite, and weight decreased occurred in similar proportions of patients in each treatment group during the Titration Period and the Maintenance Period. All reports of somnolence occurred during the Titration Period.

All these AEs (i.e. somnolence, vomiting, diarrhoea, decreased weight and decreased appetite) except cough were also found in the adults studies of Zonegran and are therefore not unexpected. Nevertheless, the implications for children of somnolence, decreased appetite and weight, and vomiting, diarrhoea and dehydration have different implications in terms of effects on growth and maturation and effect of somnolence on education.
Table 27. Treatment-Emergent Adverse Events with an Incidence at least 2% in any Treatment Group by System Organ Class and Preferred Term (Study 312 Safety Population)

<table>
<thead>
<tr>
<th>MedDRA System Organ Class Preferred Term</th>
<th>Placebo (n=100) n (%)</th>
<th>ZNS (n=100) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>50 (50.0)</td>
<td>59 (59.1)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>4 (4.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>15 (15.0)</td>
<td>14 (14.1)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>6 (6.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (4.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (2.0)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (3.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.0)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>9 (9.0)</td>
<td>6 (6.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (3.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (3.0)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>22 (22.0)</td>
<td>28 (28.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9 (9.0)</td>
<td>6 (6.0)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3 (3.0)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>3 (3.0)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2 (2.0)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>5 (5.0)</td>
<td>5 (5.0)</td>
</tr>
<tr>
<td>Fall</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Investigations</td>
<td>5 (5.0)</td>
<td>11 (11.0)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>3 (3.0)</td>
<td>5 (5.0)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>5 (5.0)</td>
<td>16 (16.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4 (4.0)</td>
<td>7 (7.0)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>18 (18.0)</td>
<td>18 (18.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (7.0)</td>
<td>7 (7.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5 (5.0)</td>
<td>5 (5.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Complex partial seizures</td>
<td>2 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Ureteral colicostolithiasis</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>4 (4.0)</td>
<td>5 (5.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (1.0)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

In the pooled data in contrast to Study 312 TEAEs occurred in 82.9% of those on Zonisamide and 55% of those on placebo.

Common TEAEs (≥ 5%) according to 3 age categories (< 6 years, 6-11 years, 12-16 years) in the pooled safety population are presented in Table 2.5-8 below.

The mean duration of exposure for the 6-11 years old was similar to that in the 12-17 years old (391 days and 319 days, respectively).

The most common TEAEs (≥ 10%) in the 6-11 years group were pyrexia (21.9%), headache (21.2%), upper respiratory tract infection (21.1%), decreased appetite (20.5%), rash (12.3%), somnolence (18.5%), vomiting (14.4%), fatigue (13.7%), nasopharyngitis (13.7%), sinusitis (11.0%), viral infection (11.0%), abdominal pain upper (10.3%), cough (10.3%), insomnia (10.3%), and nasal congestion (10.3%).

The most common TEAEs (≥ 10%) in the 12-16 years group included headache (18.4%), decreased appetite (17.4%), fatigue (12.6%), dizziness (12.1%), and somnolence (11.1%).
Most of the AEs with a frequency $\geq 10\%$ are already described in the SPC of Zonegran (pyrexia, decreased appetite, rash, somnolence, vomiting, fatigue, abdominal pain, insomnia, and dizziness) or in study 312 described above (headache, upper respiratory tract infection, nasopharyngitis, and cough). Except for cough, the other AEs appeared in study 312 in similar frequencies in the Zonegran and placebo groups. Only sinusitis, viral infection, and nasal congestion are new AEs that were not found in the short-term trial or the SPC of Zonegran. However, these AEs are not unexpected in a paediatric population.

The CHMP in any case considered that the events of decreased appetite and weight, vomiting, and somnolence have a different implication for children and adolescents in terms of impact on growth, cognitive development, and risk of dehydration, respectively. These events are analysed in detail in section 2.5.4.

| Table 2.5-8 Summary of Treatment-Emergent Adverse Events Occurring in at Least 5% of Pediatric Subjects in any Zonisamide age group (Pooled Safety Population) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| MedDRA System Organ Class | Preferred Term | Placebo | N (%) | ZNS | N (%) |
| Gastrointestinal disorders | Vomiting | 1 (1.8) | 2 (3.7) | 3 (2.8) | 10 (35.0) | 21 (44.4) | 19 (9.2) | 36 (24.1) |
| | Diarrhoea | 1 (1.8) | 0 | 1 (1.8) | 8 (17.8) | 13 (8.9) | 12 (5.8) | 33 (8.3) |
| | Abdominal pain upper | 2 (3.0) | 4 (7.4) | 6 (5.5) | 5 (11.1) | 15 (10.3) | 11 (5.3) | 31 (7.8) |
| | Constipation | 1 (1.8) | 1 (1.9) | 2 (1.8) | 9 (20.0) | 13 (8.9) | 6 (2.5) | 28 (7.0) |
| | Nausea | 3 (5.5) | 1 (1.9) | 4 (3.7) | 2 (4.4) | 7 (4.8) | 13 (6.3) | 22 (5.5) |
| | Abdominal discomfort | 0 | 0 | 0 | 0 | 9 (6.2) | 4 (1.9) | 13 (3.3) |
| General disorders and administration site conditions | Prexysma | 1 (1.8) | 2 (3.7) | 3 (2.8) | 25 (55.6) | 32 (31.9) | 15 (7.2) | 72 (18.1) |
| | Fatigue | 2 (3.6) | 2 (3.7) | 4 (3.7) | 5 (11.1) | 20 (13.7) | 26 (12.6) | 51 (12.8) |
| | Insomnia | 0 | 1 (1.9) | 1 (1.4) | 22 (44.4) | 31 (31.1) | 17 (8.2) | 68 (17.1) |
| Infections and infestations | Upper respiratory tract infection | 5 (9.1) | 5 (9.1) | 16 (9.2) | 9 (20.0) | 20 (13.7) | 19 (9.2) | 48 (12.1) |
| | Nasopharyngitis | 0 | 0 | 0 | 6 (13.3) | 16 (11.0) | 9 (4.1) | 31 (7.8) |
| | Influenza | 1 (1.8) | 1 (1.9) | 2 (1.8) | 7 (15.0) | 6 (4.1) | 13 (6.3) | 26 (6.5) |
| | Otitis media | 1 (1.8) | 0 | 1 (1.4) | 7 (15.0) | 10 (6.8) | 6 (2.9) | 22 (5.5) |
| | Viral infection | 1 (1.8) | 0 | 1 (1.4) | 3 (6.7) | 16 (11.0) | 4 (1.9) | 23 (5.5) |
| | Pharyngitis streptococcal | 0 | 0 | 0 | 6 (13.3) | 10 (6.8) | 3 (1.4) | 19 (4.6) |
| | Ear infection | 0 | 0 | 0 | 8 (17.8) | 7 (4.8) | 3 (1.4) | 18 (4.5) |
| | Pneumonia | 0 | 0 | 0 | 4 (9.1) | 6 (4.1) | 1 (1.4) | 31 (7.8) |
| Injury, poisoning, and procedural complications | Contusion | 0 | 0 | 0 | 5 (6.7) | 6 (4.1) | 8 (3.9) | 17 (4.5) |
| | Skin laceration | 1 (1.8) | 0 | 1 (1.4) | 1 (2.2) | 19 (6.8) | 2 (1.0) | 33 (9.3) |
| | Fall | 1 (1.8) | 0 | 1 (1.4) | 3 (6.7) | 4 (2.7) | 2 (1.0) | 9 (2.3) |
| | Weight decreased | 2 (3.6) | 3 (5.9) | 5 (4.6) | 3 (6.7) | 7 (4.8) | 18 (8.7) | 28 (7.0) |
| Metabolism and nutrition disorders | Decreased appetite | 4 (7.3) | 0 | 4 (3.7) | 12 (26.7) | 20 (20.5) | 26 (17.4) | 78 (19.6) |

TEAEs observed at a higher incidence in paediatric subjects than adults subjects with adjunctive Zonisamide use.

The following TEAEs were reported at a higher incidence in the pooled paediatric population than in the pooled adult population: pneumonia (3.8% v 1.6%); dehydration (2.3% v 0.2%); sweating decreased (2.6% v 0%); and liver function abnormalities (0.5% to 2.3% v 0.09% to 0.3%). In addition the following TEAEs were reported at a higher incidence in the paediatric than adult population (but are
commonly observed in paediatric subjects with epilepsy receiving AEDs): otitis media, pharyngitis, sinusitis, upper respiratory tract infections, cough, epistaxis, rhinitis, abdominal pain, vomiting, rash, eczema and fever.

The MAH was unable to exclude the possibility that pneumonia, dehydration, sweating decreased and liver function abnormalities were causally associated with Zonisamide treatment. Therefore it was proposed to add warnings to section 4.8 of the SPC regarding a relatively higher reporting frequency for these TEAEs in paediatric subjects compared to adult subjects.

Additional AEs that were added to section 4.8 as they were commonly observed in paediatrics patients receiving other AEDs including levetiracetam, lamotrigine, and topiramate are: Otitis media, pharyngitis, sinusitis and upper respiratory tract infection, cough, epistaxis and rhinitis, abdominal pain, vomiting, rash and eczema, and fever.

Additional AE also added to 4.8 with higher frequency in the paediatrics population included amnesia (5 (1.3%) vs. 1 (0.9%)), blood creatine phosphokinase increased (1 (0.3%) vs. 1 (0.09%)), creatinine increased (2 (0.5% vs. 0), lymphadenopathy (4 (1.0%) vs. 5 (0.4%)), and thrombocytopenia (2 (0.5%) vs. 1 (0.9%)).

**Treatment related adverse events**

In Study 312, a higher proportion of TEAEs in Zonisamide-treated subjects were considered by the Investigator to be related to study drug compared with placebo-treated subjects (Zonisamide: 33.6%; placebo: 24.0%). However, the only treatment-related TEAE reported at a ≥ 2% higher incidence in the Zonisamide compared with placebo group was somnolence (Zonisamide: five subjects [4.7%] and placebo: two subjects [2.0%]; all TEAEs of somnolence were reported as treatment-related). Few subjects had severe TEAEs that were treatment-related and the incidence was similar between the two treatments groups (Zonisamide: 2.8%; placebo: 3.0%).

Overall, 7 subjects (3.4%) had TEAEs which were considered probably related to study medication, 4 subjects (3.7%) in the Zonisamide group and 3 subjects (3.0%) in the placebo group. In the Zonisamide group, somnolence, tremor, altered state of consciousness, fall, and dermatitis allergic were considered probably related to study medication.

Few subjects had severe TEAEs which were treatment-related and the incidence was similar between the two treatment groups (Zonisamide: 2.8%; placebo: 3.0%).

In the pooled analysis, few subjects had serious TEAEs that were reported as treatment-related: six subjects (4.1%) in the 6 through 11 years group and eight subjects (3.9%) in the 12 through 16 years group. The only event reported as treatment-related in more than one subject in either age group was status epilepticus in the 12 through 16 years group (two subjects, < 1%). There were no SAEs of rash reported.

**Serious AEs (SAEs)**

**Study 312**

Table 28 below summarizes key features about the SAEs in study 312. Altogether, 3 patients in the Zonegran group had a total of 5 SAEs (not including the patient who died) and 2 patients in the placebo group had a total of 3 SAEs. The SAEs were considered treatment related in 2 patients in the Zonegran group (with 4 events) and in 1 patient in the placebo group (with 2 events).

No SAEs required a change in dose or discontinuation, and all of the SAEs other than the SAE leading to death resolved without sequelae.
Although it is noted that in all cases of SAEs in the Zonegran group, the dose was not changed and the event was resolved, these findings raised nevertheless a concern.

**Pooled data**

SAEs were reported for 57 patients (14.3%) in the Zonegran group of whom 23 patients (15.8%) were aged 6 through 11 years and 23 patients (11.1%) were aged 12 through 16 years (the remaining patients were aged < 6 years). Other than those SAEs in the Zonegran group that were fatal, the majority of serious TEAEs resolved. The most frequently reported SAEs overall were convulsion (4.3%), status epilepticus (2.5%), and dehydration (1.8%).

The most frequently reported SAEs in the Zonegran group in the 6 through 11 years group were convulsion (10 patients, 6.8%), status epilepticus (five patients, 3.4%), dehydration (four patients, 2.7%), and pneumonia (four patients, 2.7%). Other SAEs reported in more than one patient in the Zonegran group included sepsis (two patients, 1.4%), and overdose (two patients, 1.4%).

The most frequently reported serious SAEs in the Zonegran group in the 12 through 16 years group were status epilepticus (four patients, 1.9%), convulsion (three patients, 1.4%), and unintended pregnancy (three patients, 1.4%). Other SAEs reported in more than one patient in the Zonegran group included abdominal pain (two patients, < 1%).
Altogether, the incidence of serious SAEs in the paediatric population of 14.3% is slightly lower than that found in the adult Zonegran add-on studies (19.0%). The majority of these events suggest lack of efficacy. The next most common SAE includes dehydration.

Serious TEAEs which were not resolved included visual impairment (one subject) and aggression and vomiting (in one subject) in the 6 through 11 years group, and nephrolithiasis (one subject) in the 12 through 16 years group.

Few subjects had serious TEAEs that were reported as treatment-related: six subjects (4.1%) in the 6 through 11 years group and eight subjects (3.9%) in the 12 through 16 years group. The only event reported as treatment-related in more than one subject in either age group was status epilepticus in the 12 through 16 years group (two subjects, < 1%).

There were no SAEs of rash reported.

**Summary of study 313**

Patients who completed study 312 had the option to continue in study 313. The initial phase of this study consisted of double-blind transition period in which Zonegran treated patients continued their treatment and placebo treated patients were up-titrated to Zonegran during the first 11 weeks. After the transition period the study became open label for up to 72 weeks (according to protocol amendment 2) or up to 59 weeks (according to protocol amendment 3). Following the open-label period, patients who discontinued or ended the study entered a down titration period.

Altogether, 72 patients from the Zonegran group and 72 patients from the placebo group of study 312 enrolled in this study.

The safety results were:

- The incidence of treatment-emergent adverse events (TEAEs) during the treatment period in the Study 313 extension study was 48.6%. In Study 313, TEAEs were reported by 37 (51.4%) subjects previously treated with Zonisamide in Study 312, and 33 (45.8%) subjects previously treated with placebo in Study 312. Differences in the incidence of individual TEAEs between subjects previously on Zonisamide in Study 312 versus subjects newly exposed to Zonisamide in Study 313 were small, and did not indicate differences between short-term and long-term Zonisamide treatment. There were no new TEAEs occurring during longer term treatment with Zonisamide compared with TEAEs observed during Study 312.

- In the combined group, 41 (28.5%) subjects reported at least one TEAE in the Transition Period and 55 (39.9%) subjects reported at least one TEAE in the Open-label Period. In subjects from the Study 312 Zonisamide group, 24 (33.3%) reported at least one TEAE in the Transition Period and 29 (42.0%) in the Open-label Period. In subjects from the Study 312 placebo group, 17 (23.6%) subjects reported at least one TEAE in the Transition Period and 26 (37.7%) in the Open-label Period.

- Overall, most TEAEs were of mild or moderate severity. The most common TEAEs reported were nasopharyngitis, weight decreased, and headache.

- No subjects died during the study. Treatment-emergent serious adverse events (SAEs) occurred in 10 (6.9%) subjects; 7 subjects from the Study 312 Zonisamide group and 3 subjects from the Study 312 placebo group. The events were considered treatment-related for 3 subjects (renal colic, foot fracture, and abdominal pain).

- A low proportion of subjects had TEAEs that resulted in discontinuation of therapy (4 [2.8%] subjects: 2 subjects from each group in Study 312).
• The proportions of subjects with TEAEs by age group (age 6 through 11 and 12 through 18 years) were similar (34 [50.7%] subjects and 36 [46.8%] subjects, respectively). There were no TEAEs that were reported at a notably different frequency by age group.

• While serious rashes have been reported previously in association with Zonisamide therapy, including cases of Stevens-Johnson syndrome, in the current study no subjects had serious rash. There were three cases of popular rash in 2 subjects, all of which resolved. These occurred during the Transition Period in subjects who had received placebo in Study 312. Two of these cases were considered by the Investigator to be related to study drug (the other case was considered related to overeating of candy sweets). No subjects had hypersensitivity reactions.

• There were no reports of depression, depressive symptoms, or suicidal ideation.

• No subjects had abnormal vital signs or electrocardiogram parameters of clinical concern.

• There were no clinically significant treatment-emergent laboratory abnormalities.

• Decreases in bicarbonate levels of at least 3.5 mmol/L were observed in 64 (44.4%) subjects overall; a bicarbonate value of less than or equal to 16 mmol/L and a decrease from baseline of at least 6 mmol/L was observed in 4 (2.8%) subjects overall. No TEAEs of decreased bicarbonate were reported. The decreased bicarbonate levels in Zonisamide-treated subjects (mean -1.8 mmol/L at Open-label Visit 4) were generally small to moderate, and were similar to what has been described in previous clinical trials of Zonisamide and to the value of mean -3.5 mmol/L documented in the Zonegran SmPC. There were no reports of metabolic acidosis.

• Tanner stages, time between transitions of Tanner stages, and skeletal development results showed no consistent evidence of a detrimental effect on long-term growth or development.

• The data from Study 313 on effects on cognitive development were difficult to interpret given the lack of a control arm; however, they could be consistent with the effect observed for category fluency during Study 312 in Zonisamide-treated subjects.

Overall, no new or unexpected safety findings emerged from this study evaluating Zonisamide as adjunctive therapy for the treatment of pediatric subjects with partial onset seizures. The overview of the safety results confirm the safety concerns identified from the short term exposure.

However, from the long term exposure data weight decrease, dehydration and decrease in bicarbonate levels were of concern to CHMP, since these may lead to deterioration of general health and comorbidities.

1.5.4. TEAEs of special interest

There are a number of TEAEs associated with zonisamide which are of special interest e.g. loss of appetite, weight loss, metabolic acidosis, disordered body temperature, nephrocalcinosis and nephrolithiasis, skin eruptions, suicidal ideation and behaviour.

Loss of appetite and weight loss

In Study 312, a decrease in weight of ≥ 5% was observed in 29.0% of Zonegran patients and 7.0% of the placebo patients and a decrease of ≥ 10% was observed in 4.7% of Zonegran patients and 2.0% of placebo patients.

Weight decrease was reported as an adverse event in five patients (4.7%) in the Zonegran group compared to three patients (3.0%) in the placebo group. These events were considered severe in two patients (1.9%) and serious in one patient in the Zonegran group. The latter involved > 10% weight
loss reported at follow-up. The event was severe and considered related to treatment by the investigator. The patient’s dose was unchanged and the event resolved without treatment.

In study 312, the mean height of patients in the Zonegran group increased at Week 12 and Week 26 by a similar amount as in the placebo group, although data were limited. The mean height continued to increase during study participation.

In the pooled safety population decrease in weight of ≥ 5% was observed in 35.0% of the Zonegran patients and a decrease of ≥ 10% was observed in 10.7% of Zonegran patients.

In the pooled population, a total of 31 patients (7.8%) in the Zonegran group reported TEAEs relating to weight loss. Two of these events were considered serious. In one patient the weight loss resolved after 22 days, the other patient was lost to follow-up; the events were considered severe and related to treatment. Weight decreased was considered to be severe in five patients (1.3%). None of the TEAEs relating to weight loss led to discontinuation of Zonegran.

In Study 313, 24 (16.7%) subjects had a decrease in weight of 10% or more from baseline at any time during the study; 14 (19.4%) from the Study 312 Zonisamide group and 10 (13.9%) from the Study 312 placebo group. A decrease in weight of 20% or more from baseline was reported in 2 subjects (1.4%); 1 (1.4%) from the Study 312 Zonisamide group and 1 (1.4%) from the Study 312 placebo group. A decrease in weight of 5% or more from baseline at any time during the study was reported 51 subjects (35.4%); 29 (40.3%) from the Study 312 Zonisamide group and 22 (30.6%) from the Study 312 placebo group. Although more subjects (8.3%) from the Study 312 placebo group reported TEAEs of weight decrease in Study 313 compared with subjects from the Study 312 Zonisamide group (5.6%), fewer of them had weight decreases of 10% or more compared with subjects who were already on Zonisamide. This apparent discrepancy may be due to the longer duration of treatment of the subjects who were initially assigned to Zonisamide in Study 312, leading to greater overall weight loss, while these subjects were less likely to report weight loss as an adverse event (AE) in Study 313 because it was already present during their participation in Study 312.

In study 312, seven patients (6.5%) had decreased appetite in the Zonegran group compared with four patients (4.0%) in the placebo group. The TEAEs in the Zonegran group were not considered serious, not severe, and did not lead to discontinuation.

In the pooled population, a total of 78 patients (19.6%) in the Zonegran group reported TEAEs of decreased appetite. The event was considered serious and related to treatment in one patient (< 1%) in the Zonegran group. In three patients (< 1%) the event was considered severe. Decreased appetite led to discontinuation in 3 patients (< 1%). The events leading to discontinuation were considered moderate in two patients (< 1%) and severe in one patient (< 1%).

The MAH presented a number of scatterplot analysis of bone age and delay in maturation versus weight change. Analyses of the bone age, skeletal development, and sexual maturation data did not indicate an association between weight change and effects on growth and maturation; however it is acknowledged that data are limited.

In addition, a scatterplot analysis showing that nausea, vomiting, and dehydration tended to be transient in nature, therefore, in their opinion, it was unlikely they would have a long-term effect on bone age, skeletal development and sexual maturation. Decreased appetite and weight loss were generally of an extended duration (from under 1 month to over 16 months). A markedly low calcium level was only reported in one subject in Study 313 and only 3 subjects had blood phosphate levels below the LLN at any time point. In all cases, the abnormal laboratory values were restricted to a single time point. As most subjects stayed within normal ranges, long term effects are likely to be minimal according to the MAH.
The MAH believes that Zonisamide did not appear to have any effects on bone age, skeletal development and sexual maturation. However, the MAH accepts that these results are based on relatively small subject numbers, and that there is a possibility that sustained weight loss could cause delays in development and maturation. Therefore, it was proposed to include warnings in the PI about the potential serious nature of weight loss in children, and the potential impact on growth and development. The MAH will also perform intensive monitoring, and a drug-utilization study, to monitor risks of effects on growth, development, pubertal maturity, and bone health.

The CHMP agreed that the addition of information to the SmPC advising monitoring of weight using growth charts and to the PIL advising parents to monitor their children’s weight should mitigate the risks of weight loss in the paediatric population.

The proposed drug utilization study should provide evidence of the effectiveness of the advice on monitoring of weight, and the intensive monitoring programme should provide information on long term effects on growth, development, pubertal maturity, and bone health.

**Diarrhoea, vomiting and dehydration**

**Diarrhoea**

In Study 312, TEAEs of diarrhoea were reported for 4 (3.7%) subjects in the Zonisamide group and 1 (1.0%) in the placebo group. In Study 313 TEAEs of diarrhoea were reported for 4 (2.8%) subjects. In the pooled dataset, 33 subjects reported diarrhoea, and 56 subjects vomiting.

With regard to diarrhoea it is agreed that the incidence is relatively rare. However the duration of this TEAE is variable.

In Study 312 the longest duration appears to be three days (experienced by 2 out of 4 subjects with diarrhoea), whereas in Study 313, of the 4 subjects experiencing diarrhoea, two had a duration of 7 days, one of 6 days and one of 1 day. In the pooled data analysis one subject had a duration of 30 days, one a duration of 27 days, one 16 days, one 11 days and one was reported as having on-going diarrhoea. Most of the remainder had a duration ranging from 1 to 3 days. In addition some subjects had more than one episode of diarrhoea.

For the MAH, events of vomiting, and diarrhoea do not appear to be a concern in paediatric patients given the low incidence and the transient nature

The CHMP agreed that events of diarrhoea appear to be relatively mild, however a significant minority have had prolonged diarrhoea, which might have a negative effect on compliance.

The PI was therefore amended to highlight the occurrence of these events.

**Vomiting**

In Study 312, of the five subjects reported as having experienced vomiting as a TEAE, three had a duration of 1 day, one of 2 days and one of 6 days.

In Study 313 one of the two subjects reporting a TEAE of vomiting had duration of 7 days and the other of 1 day. The subject with duration of 7 days also had a TEAE of diarrhea.

In the pooled analysis 7 out of 56 subjects experienced vomiting greater than 7 days duration.

Some subjects had more than 1 reported TEAE of vomiting.

The MAH’s notes that for a number of the extended periods of TEAEs of diarrhea and vomiting, these were concurrent with infections. All except one event were reported as mild. Thus, for the MAH these events are not considered likely to have a long-term effect on weight gain.
Whilst vomiting tended to be short in duration, the CHMP was concerned that some subjects experienced quite prolonged vomiting, which is of concern not only because it leads to weight loss and dehydration, but also because it may reduce treatment compliance. The PI was therefore amended to highlight the occurrence of these events.

**Dehydration**

Dehydration was one of the TEAEs reported with an outcome of death.

The MAH provided details of all cases on dehydration, including the effects of vomiting and diarrhoea on risk of dehydration.

In Study 312, 1 (0.9%) subject in the Zonisamide group had a TEAE of dehydration. This was not preceded by diarrhoea or vomiting.

No subjects in Study 313 had a TEAE of dehydration.

In the pooled dataset 9 (2.3%) subjects had a TEAE of dehydration. For 6 subjects, no prior events of diarrhoea or vomiting had occurred. No subjects were discontinued from treatment because of dehydration, but dehydration was reported serious for 7 (1.8%) subjects. This is of concern for this young and already vulnerable patient population. As mentioned before, for one subject, dehydration was one of the TEAEs reported with an outcome of death. For 2 subjects, there was no apparent concurrent infection. For the remaining 6 subjects, the subject had concurrent infections or illnesses predisposing to dehydration:

For the MAH, the majority of TEAEs of dehydration appear unrelated to Zonisamide treatment. However, the possibility cannot be excluded and it is proposed to include warnings in the PI related to dehydration. In the MAH’s opinion these events are not considered likely to have a long-term effect on weight gain.

The CHMP concluded that there does not seem to be a marked relationship between the adverse events of vomiting and diarrhoea and dehydration. Nevertheless, warnings on the risk for dehydration have been highlighted in the product information since it may lead to serious consequences.

**Disordered body temperature (oligohydrosis and hyperthermia)**

In Study 312 four (3.7%) Zonisamide subjects (one of which was reported as serious) and 3 (3%) placebo subjects had a TEAE relating to the above. No TEAEs led to study discontinuation.

In the pooled analysis 84 (21.1%) subjects reported a TEAE of disordered body temperature. Most reports for disordered body temperature were due to pyrexia (72/84). This event is reported frequently in paediatric studies and could be confounded by childhood infections.

Ten subjects (2.5%) in the Zonisamide group had TEAEs considered to be serious: seven (1.8%) with dehydration (2 moderate and 5 severe); two (<1%) with moderate pyrexia and one with moderate hypohidrosis. One event of moderate dehydration and the event of hypohidrosis were considered to be related to Zonisamide treatment.

In addition, in the PSUR covering the period 1 Apr 2011 to 31 Mar 2012, a fatal case of anhidrosis and hyperthermia in an 11 year old male was reported. The patient had been camping and experienced anhidrosis and hyperthermia. Temperature was 40.9 degrees Celsius (outside temperature reported as 40 degrees Celsius). Four days later, the patient died.

The wording of the PI has been strengthened to advise discussion with patients regarding the risk of heat stroke with focus on the prevention and reduction of the occurrence of heat stroke associated
with exposure to Zonisamide and on how to reduce the severity and impact on the patient should oligohidrosis/heat stroke arise.

**Effects of kidney function on growth.**

Decreases in bicarbonate were observed with Zonegran treatment in Study 312 and in the pooled safety population. There were no corresponding reports of respiratory alkalosis or metabolic acidosis with Zonegran treatment.

In study 312, decreases of > 3.5 mmol/L in the bicarbonate value were observed in 54 subjects (50.5%) in the Zonisamide group and 16 subjects (16.0%) in the placebo group. Six Zonisamide-treated subjects (5.6%) and no subjects who received placebo had a bicarbonate value of ≤ 16 mmol/L and a decrease from baseline of > 6 mmol/L. Decreased bicarbonate was reported as an AE in one subject in the Zonisamide group. The lowest value for bicarbonate was 14 mmol/L, (175 mg Zonisamide) who had a 6 mmol/L decrease from baseline at the Final Visit. This was not reported as an AE.

In the pooled data, 29 subjects (9.4%) in the Zonisamide group had a bicarbonate level below 16mmol/L and a drop from baseline of ≥ 6mmol/L. This included 21 subjects (11.1%) aged < 12 years and seven subjects (6.5%) aged 12 through 16 years. In these 28 patients, bicarbonate levels were transiently abnormal in 21 leaving 7 patients with continuously abnormal levels.

Similarly to the data from study 312, bicarbonate levels below 16 mmol/l were observed also in study 313, but in a lower percentage (4 subjects, 2.8%). No metabolic acidosis was reported, which was reassuring. The MAH explained that these findings are similar to what is reported in the Zonisamide SPC already.

The MAH provided data on duration of low bicarbonate (i.e., <22mmol/L). A total of 126/179 (70.4%) subjects who received Zonisamide in either Study 312 or Study 313 had at least one treatment-emergent bicarbonate measurement below 22 mmol/L. Duration was calculated from the visit where the bicarbonate values was below 22 mmol/L to the day before the next visit where bicarbonate value was greater than or equal to 22 mmol/L or up to the last dose date. Based on these data, the median duration of low bicarbonate was 188 days (mean: 215 days), with a range of 14 through 654 days.

Low bicarbonate values are prolonged in some cases, consistent with the pharmacological profile of Zonisamide.

At the request of CHMP the MAH analysed the implications of phosphate loss on growth by presenting data on growth parameters in the individuals in which bicarbonate decrease has been observed in study 313. Tanner Stage transition time, bone age and skeletal maturation data was analysed for trends amongst subjects who had a decrease in bicarbonate level of more than 3.5 mmol/L from baseline. The MAH concludes that the data do not indicate that reductions in bicarbonate levels have a detrimental effect on growth and development. There were no reports of metabolic acidosis in these subjects and no other adverse event reports which could have been linked to low bicarbonate levels. However, it is acknowledged that data are limited.

The MAH also presented individual data on all subjects in Study 313 who had a blood phosphate level below 0.65 IU/L (the LLN) at any time during the study. Only 3 subjects had blood phosphate levels below the LLN, and in all cases, this finding was restricted to a single time point. The MAH therefore concludes that Zonisamide does not have significant effects on blood phosphate levels.

In the assessment of Study 313 it was noted that median levels of bicarbonate dropped below baseline levels and remained below baseline levels throughout Study 313 especially in those who had been in the Zonegran arm of Study 312. This raises the prospect of prolonged low bicarbonate levels.
The CHMP noted the information on subjects with a bicarbonate decrease of >3.5mmol/L from baseline and impact on skeletal maturity and transition times to Tanner stages. It appears that delay or advancement in skeletal maturity was similar in those with decreased bicarbonate and those with normal levels in the population at maturity and those ‘not yet at maturity’. However, data was limited and there is no long term data.

The current SmPC for Zonegran already contains warning on the risk of metabolic acidosis, which may be more frequent and severe in younger patients. The SPC recommends monitoring of serum bicarbonate levels in patients at risk and advises to take appropriate measures if elevations persist. An additional warning has been introduced to recommend appropriate evaluation and monitoring of serum bicarbonate in paediatric subjects. The MAH also committed to a drug-utilization study to monitor that physicians follow this advice.

**Kidney stones**

Effects on the kidney have been observed in paediatric studies that were consistent with the effects seen in adult subjects. There were no reported events of nephrolithiasis in Study 312 and one reported event in Study 313, which led to discontinuation. In the pooled analysis (which does not include Study 313), 4 (1%) subjects had a treatment-emergent adverse event (TEAE) of nephrolithiasis and 1 (<1%) subject in the Zonisamide group had a TEAE of nephrocalcinosis; none of these events led to discontinuation.

Nephrolithiasis was reported as mild in most subjects. Nephrolithiasis was reported as severe in one subject.

Adverse event data and laboratory parameters of interest for possible kidney damage (albumin, blood urea nitrogen [BUN], calcium, chloride, creatinine, and bicarbonates) were reviewed. None of the subjects had TEAEs indicative of chronic kidney damage.

Nephrolithiasis is a known complication of treatment with Zonegran. The MAH concur with CHMP that for subjects with nephrolithiasis, this may lead to alteration of kidney function in some cases, which may translate into chronic kidney damage. Thus the current warning in section 4.4 and Section 4.5 of the Zonegran SmPC have been amended to reflect that some patients may be at increased risk for renal stone formation and associated signs and symptoms, and that nephrolithiasis might lead to chronic kidney damage. The MAH also committed to intensive monitoring for renal effects, including a drug-utilization study; therefore, these measures are considered sufficient to address this risk.

**Skin eruptions**

In Study 312 three subjects (2.8%) in the Zonisamide group and one in the placebo group had skin eruptions (dermatitis, dermatitis allergic, eczema, or rash morbilliform), one of which led to study discontinuation and none of which were reported as serious.

In the pooled analysis 54 subjects (13.6%) in the Zonisamide group reported TEAEs relating to skin eruptions. The majority (41) of the events were rash. No serious TEAEs were reported. TEAEs relating to skin eruptions led to discontinuation for four subjects (1%) in the Zonisamide group (two with rash and one each with drug eruption and urticaria). There were no reports of Stevens Johnson Syndrome or toxic epidermal necrolysis.

A warning about rash is already included in the SPC of Zonegran including a warning about Stevens Johnson Syndrome.

**Suicidal ideation and behaviour**

Study 312 did not report any TEAEs related to suicidal ideation or behaviour.
The pooled analysis reported 1 case of suicidal ideation (<1%) and 9 cases (2.3%) of psychiatric disorder (all depression) in the Zonisamide group. All were considered mild or moderate and one patient discontinued from a study.

The CHMP noted that the significance of these findings on suicidality and depression difficult to interpret however the MAH should continue to monitor these kinds of events in PSURs.

An appropriate warning on this issue is already included in section 4.4 of the SPC of Zonegran.

**Pancreatitis and elevated amylase and lipase**

In Study 312, there were no TEAEs of pancreatitis. In the pooled population, one patient (< 1%) aged 10 years had a serious TEAE of pancreatitis. The pancreatitis was severe, led to discontinuation from treatment, and resolved after 6 days. The event was considered to be related to Zonegran treatment. The patient had been receiving concomitant valproate treatment prior to this event.

No events of increased pancreatic enzymes were reported in any of the studies.

The CHMP acknowledged that risk of pancreatitis is already known and is mentioned in the warning section (4.4) of Zonegran.

**Immune system and thyroid hormones**

Immune system and thyroid hormones were evaluated in Study 312 as requested by the EMA. The mean values for immune system and thyroid hormone evaluations were within the normal range at baseline and the Final Visit for both treatment groups. There were no clinically important changes in either mean immune system or thyroid hormone values from baseline to the end of therapy for either treatment group. Immune system and thyroid hormones were not evaluated in the pooled data.

**Effects on cognition and behaviour**

A cognitive assessment battery was planned to be performed on the first 84 patients (42 per arm) with an IQ $\geq$ 75 in study 312. The battery was administered at Screening, Randomisation (Week 0, Baseline), Week 8 (start of the maintenance period) and Final Study Visit/Early Termination Visit. Change from baseline scores for cognition measures were assessed using Analysis of Covariance (ANCOVA) at Final Visits to compare treatment groups. The table below presents the number of patients that were analysed.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Visit</th>
<th>Placebo N</th>
<th>Zonisamide N</th>
</tr>
</thead>
<tbody>
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<tr>
<td>LOCF</td>
<td>Week 8</td>
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</tr>
<tr>
<td></td>
<td>Final Visit</td>
<td>34</td>
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<td></td>
<td>Week 8</td>
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</tr>
<tr>
<td></td>
<td>Final Visit</td>
<td>29</td>
<td>37</td>
</tr>
</tbody>
</table>

The results of this sub-study show no statistically significant differences between treatment groups for the primary cognition safety variable, power of attention. However, several components of the tests showed evidence for an impairment with Zonegran at the final visit, i.e. results were statistically significantly worse for the Zonegran group, in some analysis, depending on whether baseline was controlled for not and on whether LOCF or OC was used. This included: Speed of Memory (complex information processing speed), colour trail test (CTT), and category fluency.
At the request of CHMP, the MAH presented additional data on effects on cognitive aspects. Somnolence was reported for 5 (4.7%) subjects in the Zonisamide group and 2 (2.0%) subjects in the placebo group in the short term study, and in 2 (1.4%) subjects in the extension study. The effect was transient for most subjects similar to what is observed with other antiepileptic treatments. The results presented for cognition are complicated to interpret in particular for the extension study without a control arm and because they were carried out in a relatively small population (i.e. only in those with an IQ of 70 or greater (64 out of 144 subjects in Study 313 had baseline tests) and in addition for the COWAT test in Study 313 data appears to be missing for a large number of subjects for Open label visit 5).

The proposal of the MAH to include a warning in 4.4. of the SPC about possible impact on cognition is considered acceptable.

### Tanner Stage

In the two treatment groups there were a similar percentage of subjects in the different Tanner Stages at the baseline and FV for all assessments. The $P$ values for the differences relative to placebo were 0.075 for pubic hair growth, 0.497 for genitals (males) and 0.102 for breasts (female). For each Tanner Stage assessment, the percentages of subjects transitioning from baseline to FV were similar in each treatment group.

The PI has been amended to highlight that in some cases of weight decrease there was a delay in transition to the next Tanner stage and in bone maturation.

### Skeletal Development

The change from baseline in bone age at the FV was small in both treatment groups, the means (±SD) were 0.5 (1.28) and 0.3 (0.78) for Zonisamide and placebo, respectively. There were similar delays in bone maturation in both treatment groups. For subjects who had reached bone maturity (i.e., ≥ 15 years for females, ≥ 17 years for males), there was little evidence in either treatment group of any changes in bone age or delay in maturation.

For subjects under the age of bone maturity, ANCOVA showed little evidence of any difference in bone age, with a difference in LS means of 0.12 years. The $P$ value for the difference relative to placebo was 0.453.

The MAH considered that data from long-term treatment with Zonisamide in Study 313 do not indicate any detrimental effects on growth or development. To support this they refer to data on sexual and endocrine maturation and skeletal age.

Skeletal development was evaluated through height and bone age. The results were as expected for the population under study and delays in bone maturation were minimal. Of the 5 subjects with a more than 10% weight loss in Study 312, 4 subjects continued into Study 313, and data on bone age after long-term treatment were available for 3 subjects. A delay in maturation was not apparent for these subjects; bone age was similar to subject age at the last assessment for all subjects.

The CHMP considered that it was difficult to draw conclusions from the skeletal survey in females with a bone age under 15 and males with a bone age under 17 given that a large number of subjects have do not have data for both baseline and open visit 5 visits. To mitigate the problem of appetite and weight loss warnings have been included in the SmPC and PIL to monitor for weight loss and appetite loss and a drug utilisation study will provide evidence on the effectiveness of these warnings.

The long term effect is not known due to lack of longer exposure data.
1.5.5. Other significant events: Death

In Study 312, one patient (<1%) in the Zonegran group and none in the placebo group had TEAEs resulting in death. The patient was a 14-yr-old male who died due to severe status epilepticus. It appears from the narrative that weight loss and diarrhoea weakened the condition of the patient up to a point where the patient was unable to take his anti-epileptic agents which triggered the fatal status.

In the pooled data, seven patients (1.8%) in the Zonegran group had a TEAE resulting in death (including the patient who died in Study 312).

There were no deaths in Study 313 (the extension study of Study 312), which was reassuring. The number of deaths observed in paediatric subjects treated with Zonisamide is 7 in 465 (1.5%) subjects. This equates to an incidence rate of 14.6/1000 person-years. This incidence is similar to the incidence rate of death in paediatric subjects receiving other AEDs: a long term prospective study found a rate of 15.9/1000 person years in paediatric subjects who were not seizure free (Sillanpaa M, Sinnar S 2010) and a review of lamotrigine use in paediatric subjects found a rate of 15.7 per 1000 person-years in 9/1096 subjects (0.8%) over a median duration of 27 weeks (Messenheimer JA et al 2000).

The MAH highlighted that the ZNS database included clinical trials that enrolled patients with severe seizures associated with other neurological deficits. Literature data from population-based cohort studies indicate that the presence of a neurological disorder sufficient to cause a functional neurological deficit is a recognised risk factor for increased mortality (Camfield et al. 2002, Breningstall 2001). Children with functional neurological deficit are 22 times more likely to die compared to those without deficit (Camfield et al. 2002).

Four of the seven deaths occurred in subjects with pre-existing functional neurological conditions/remote symptomatic epilepsy. One of these deaths in a subject who developed pneumonia, sepsis, multi-organ failure and raised liver function tests was considered to be related to Zonegran, in that the raised LFTs and multi-organ failure was considered to be related but the pneumonia and sepsis were not.

It is agreed that the risk of death in patients with epilepsy is considerably higher in those with pre-existing functional neurological impairment/remote symptomatic epilepsy and death is often related to the underlying condition rather than epilepsy per se (Camfield 2002, Sallinpaa 2010, Berg AT et al 2004.). This may explain the high death rates seen.

In those without pre-existing functional neurological impairment, there were three deaths, one of which was considered related to Zonegran. In this case, as described above, the subject was underweight and continued to lose weight over a three month period, stopped taking his AEDs and developed status epilepticus. This subject would not be eligible for treatment with Zonegran according to the final agreed SmPC. It is agreed that the other two deaths, one due to status epilepticus in a subject receiving three AEDs and with a vagal stimulator in situ, and one in a female with a head injury are unlikely to be related to Zonegran.

The SmPC has been amended with:

-warnings in relation to the risk of decreased appetite and weight loss,
-recommendations not to use zonegran in paediatric patients who are underweight or have a decrease appetite,
-recommendations to monitor weight and to consider a dietary supplement or increased food intake in case of weight loss
-recommendations to discontinue zonegran if substantial undesirable weight loss occurs
Additionally, the PIL has been amended to encourage parents or carers to monitor their child’s weight regularly and to return to their doctor in the event of failure to gain weight.

Body weight is a parameter that can be relatively easily monitored over time and routinely performed in paediatric patients. Therefore parents or carers should be able to monitor their child’s weight regularly and report back to their physician if weight loss occurs.

Therefore, The CHMP concluded that that the risk of decreased appetite and weight loss can be controlled via the risk minimisation measures included in the product information.

1.5.6. Other Laboratory findings

Liver function abnormalities

No liver function abnormalities were reported in Study 312. In the pooled analysis liver function abnormalities were reported in 15 subjects (3.8%), 9 subjects (6.2%) were aged 6 through 11, four (1.9%) aged 12 through 16 and two aged under-6 years.

Five patients in the pooled safety database had markedly abnormal hepatobiliary parameters defined as NCI grade change from baseline >=2 on at least 2 consecutive post baseline visits or the last on-treatment post baseline visit NCI change grade from baseline >=2. High GGT values (>100; while normal values are 0-33 IU/L) and high bilirubin were recorded in (some) of these patients. Two of the events were reported as AEs, one as mild and one as moderate. Some were considered related to study medication and all 5 events were not resolved during the study.

Hepatocellular damage is mentioned as a risk in section 4.8 of the SPC of Zonegran. Based on these results it is recommended to add a warning to the SPC about this risk with a recommendation to monitor liver function in children and adolescents.

Haematological abnormalities

In Study 312 three subjects (2.8%) in the Zonisamide arm reported had haematological TEAEs reported. None were deemed to be severe or serious and none led to study discontinuation. In the pooled analysis there were 9 reports (2.3%) of haematological TEAEs. All were considered to be mild or moderate and none led to discontinuation.

1.5.7. Safety in special populations

Analysis of pooled data was provided by age-group but not by sex or race.

No studies were carried out in paediatric subjects with renal or hepatic insufficiency.

No subjects became pregnant in Study 312. Three subjects in the pooled analysis became pregnant and were discontinued from the study drug. No information was provided on the outcomes of pregnancy in these subjects.

1.5.8. Safety related to drug-drug interactions and other interactions

Concomitant AEDs at baseline included carbamazepine, lamotrigine, levetiracetam, topiramate, and valproic acid. The incidence of all TEAEs and a number of specific TEAEs were reported at a higher rate in the topiramate group compared with the other baseline AEDs. The incidences of any TEAE with topiramate was 92% compared to 83.3% with lamotrigine, 78.0% with levetiracetam, 76.7% with valproic acid, and 69.3% with carbamazepine. Specific TEAEs which had higher incidence in the
topiramate group included Upper respiratory tract infection, 32.0% with topiramate compared with 9.3% to 16.7% with other baseline AEDs; somnolence, 30.0% compared with 9.3% to 18.3%, respectively; pyrexia, 30.0% compared with 6.7% to 19.8%, respectively; sinusitis, 20.0% compared with 5.3% to 7.5%, respectively; fatigue, 20.0% compared with 5.1% to 14.2%, respectively; nasal congestion, 18.0% compared with 4.0% to 8.5%, respectively; rhinorrhea, 14.0% compared with 1.3% to 8.5%, respectively; and abdominal pain upper, 12.0% compared with 1.3% to 8.3%, respectively.

The SPC of Zonegran indicates that it should be used with caution in patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate, as there are insufficient data to rule out a pharmacodynamic interaction.

An additional warning that Zonegran should not be used with other carbonic anhydrase inhibitors (e.g. topiramate and acetazolamide) in the paediatric population has been added to Section 4.4 and 4.5 of the SmPC.

**Discontinuation due to adverse events**

Discontinuation rates were low in Study 312 (Zonisamide 0.9% v 3% placebo group). All events occurred during the titration period. The Zonisamide subject had an allergic dermatitis which led to discontinuation.

<table>
<thead>
<tr>
<th>Treatment / Subject ID</th>
<th>Age (Y, Sex)</th>
<th>Study Period</th>
<th>MedDRA Preferred Term</th>
<th>Study Day**</th>
<th>Severity/ Relationship to Study Drug</th>
<th>Action Taken</th>
<th>Outcome</th>
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<tbody>
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<td>Titration 250 mg</td>
<td>Abdominal pain upper</td>
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<td>Mod / Poss</td>
<td>Drug withdrawal from study</td>
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<td>9, F</td>
<td>Titration 50 mg</td>
<td>Aggression</td>
<td>21 / 27</td>
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<td>Zonisamide</td>
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<td>15 / 21</td>
<td>Mod / Prob</td>
<td>Drug withdrawal from study</td>
</tr>
</tbody>
</table>

**Pooled data**

TEAES leading to discontinuation were reported for 41 patients (10.3%) in the Zonisamide group of whom 13 (8.9%) were aged 6 through 11 years and 22 subjects (10.6%) were aged 12 through 16 years (the remainder were aged under six).
Overall, the most frequently reported TEAEs leading to discontinuation in the Zonisamide group were lethargy and fatigue (four subjects (1.0%) each), and decreased appetite, gamma-glutamyltransferase (GGT) increased, irritability, confusional state, and unintended pregnancy (three subjects [<1%] each).

The most frequently reported TEAEs leading to discontinuation in the Zonisamide group in the 6 through 11 years group were GGT increased (3 subjects [2.1%]), AST increased, fatigue, and lethargy (2 subjects [1.4%] each).

The most frequently reported TEAEs leading to discontinuation in the Zonisamide group in the 12 through 16 years group were confusional state and unintended pregnancy (three subjects [1.4%] each), aphasia, aggression, dizziness, decreased appetite, fatigue, insomnia, irritability, and rash (two subjects [< 1%] each). Altogether, the incidence of AEs leading to discontinuation in the paediatrics population of 10.3% is lower than that found in the adult Zonegran add-on studies (24.6%).

1.5.9. Conclusion on clinical safety

The safety issues that emerged with Zonegran show that although in general the safety profile is similar to that in adults, there are several important issues that raise important concerns since they may have greater implications in the paediatric population.

Overall, the number of patients that died during the studies is of concern, though similar to mortality rates in subjects receiving other anti-epileptic drugs: (14.6 per 1000 person-years vs. 15.7-15.9 per 1000 person-years) (Messenheimer 2000, Sillanpaa 2010)

Nevertheless, the CHMP agreed that there should be intensive monitoring of mortality as well as the events that preceded mortality in the cases described (including weight loss, dehydration and loss of efficacy).

One of the patients whose death was considered related to Zonegran was a subject underweight who continued to lose weight over a three month period, stopped taking his AEDs and developed status epilepticus. This subject would not be eligible for treatment with Zonegran according to the current proposed Product Information and warnings regarding weight loss, advice to monitor growth and to discontinue treatment in the event of failure to gain weight should mitigate the risks in the paediatric population. Although data is limited, no evidence for a consistent delay in bone maturation in subjects with weight loss was seen.

Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients. Heat stroke requiring hospital treatment was diagnosed in some cases and heat stroke requiring hospital treatment and leading to death has been reported. Most reports occurred during periods of warm weather. This has been highlighted in the Product Information, requesting physicians to discuss with patients and their carers the potential seriousness of heatstroke, situations in which it might arise, as well as action to take in the event of any signs or symptoms.

The risk of induced metabolic acidosis, which appears to be more frequent and severe in paediatric patients, has been highlighted in the Product Information with a request to monitor serum bicarbonate levels.

Warnings regarding the unknown long-term effects of all these events on growth and development have also been included.

The MAH will perform intensive monitoring, and a drug-utilization study, to provide evidence of the effectiveness of SmPC warnings on concomitant use of carbonic anhydrase inhibitors and
anticholinergic drugs, monitoring of serum bicarbonate levels as well as weight and height in the paediatric population and use in children below 20 kg.

1.6. Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

1.7. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure which included a risk minimisation plan.

**Table 1.** Summary of the risk management plan (changes related to the application presented)

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimization activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>• Routine pharmacovigilance</td>
<td>• Contraindications in Section 4.3 of the SmPC when there is hypersensitivity to the active substance, to any of the excipients or to sulphonamides.</td>
</tr>
<tr>
<td></td>
<td>• Cumulative review within the PSUR</td>
<td>• Undesirable effects in Section 4.8: hypersensitivity, DIHS, and DRESS.</td>
</tr>
<tr>
<td>Skin eruptions</td>
<td>• Routine pharmacovigilance</td>
<td>• Warning in Section 4.4 of the SmPC that zonisamide may cause serious rashes including Stevens Johnson syndrome, and action to take in event of unexplained rashes.</td>
</tr>
<tr>
<td></td>
<td>• Cumulative review within the PSUR</td>
<td>• Undesirable effects in Section 4.8: Rash, pruritis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and ecchymosis.</td>
</tr>
<tr>
<td>Hematologic events</td>
<td>• Routine pharmacovigilance</td>
<td>• Warning in Section 4.4 of the SmPC that zonisamide may cause cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis.</td>
</tr>
<tr>
<td></td>
<td>• Cumulative review within the PSUR</td>
<td>• Undesirable effects in Section 4.8: Ecchymosis, agranulocytosis, aplastic anaemia, leucocytosis, leucopenia, lymphadenopathy, pancytopenia, and thrombocytopenia.</td>
</tr>
<tr>
<td>Safety concern</td>
<td><strong>Proposed pharmacovigilance activities (routine and additional)</strong></td>
<td><strong>Proposed risk minimization activities (routine and additional)</strong></td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Kidney stones                                      | • Routine pharmacovigilance  
• Cumulative review within the PSUR  
• Intensive monitoring of adverse events relating to renal function in paediatric patients  
• Drug utilization study on effectiveness of risk minimization measures directed at paediatric patients (concomitant carbonic anhydrase inhibitors). | • Warning in Section 4.4 of the SmPC that zonisamide may cause kidney stones, as well as information on risk factors and preventative measures.  
• Information in Section 4.5 of the SmPC that concomitant administration with other products that lead to urolithiasis may increase the risk.  
• Undesirable effects in Section 4.8: Nephrolithiasis and calculus urinary. |
| Disordered body temperature (oligohidrosis and hyperthermia) and dehydration | • Routine pharmacovigilance  
• Cumulative review of oligohidrosis within the PSUR  
• Intensive monitoring of adverse events relating to disordered body temperature (oligohydrosis, hyperthermia) and dehydration in paediatric patients  
• Drug utilization study on effectiveness of risk minimization measures directed at paediatric patients (concomitant carbonic anhydrase inhibitors and anticholinergic agents). | • Boxed Warning in Section 4.4 of the SmPC that zonisamide may cause decreased sweating & elevated body temperature, as well as risk factors and preventative measures.  
• Undesirable effects in Section 4.8: Anhidrosis, pyrexia, and heat stroke.  
• Boxed warning in the PIL directed at parents and carers of paediatric patients on prevention of and action to take in event of heat stroke. |
| Pancreatitis and elevated amylase and lipase        | • Routine pharmacovigilance | • Warning in Section 4.4 of the SmPC that zonisamide may cause pancreatitis, as well as action to take in event of signs and symptoms.  
• Undesirable effects in Section 4.8: Pancreatitis |
| Muscle disorders                                   | • Routine pharmacovigilance | • Warning in Section 4.4 of the SmPC that zonisamide may cause rhabdomyolysis, as well as action to take in event of symptoms.  
• Undesirable effects in Section 4.8: Rhabdomyolysis and blood creatine phosphokinase increased. |
| Weight loss                                         | • Routine pharmacovigilance  
• Drug utilization study on effectiveness of risk minimization measures directed at paediatric patients (monitoring of weight and use in children below 20kg). | • Warning in Section 4.4 of the SmPC that zonisamide may cause weight loss, as well as action to take in event of occurrence.  
• Undesirable effects in Section 4.8: Weight decreased. Additional information regarding pediatric patients. |
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimization activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis and its potential for osteopenia</td>
<td>• Routine pharmacovigilance</td>
<td>• Warning in Section 4.4 of the SmPC that metabolic acidosis and its potential for osteopenia is associated with zonisamide treatment as well as risk factors, and action to take in event of occurrence.</td>
</tr>
<tr>
<td></td>
<td>• Intensive monitoring of adverse events relating to bone health in paediatric patients.</td>
<td>• Undesirable effects in Section 4.8: Metabolic acidosis and decreased bicarbonate. Additional information regarding pediatric patients.</td>
</tr>
<tr>
<td></td>
<td>• Drug utilization study on effectiveness of risk minimization measures directed at paediatric patients (concomitant carbonic anhydrase inhibitors and serum bicarbonate testing).</td>
<td>• Statement in Section 5.1 that decreased bicarbonate levels may have deleterious implications for growth and development.</td>
</tr>
<tr>
<td>Suicide/suicidal thoughts</td>
<td>• Routine pharmacovigilance</td>
<td>• Warning in Section 4.4 of the SmPC that zonisamide may cause suicidal ideation and behaviour as well as preventative measures.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Undesirable effects in Section 4.8: Suicidal ideation and suicide attempt.</td>
</tr>
<tr>
<td>Important potential risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures following sudden withdrawal</td>
<td>• Routine pharmacovigilance</td>
<td>• Warning in Section 4.4 of the SmPC that zonisamide may cause seizures on withdrawal, as well as advice on prevention.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Information in Section 4.2 of the SmPC providing posology of gradual withdrawal.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Undesirable effects in Section 4.8: Convulsion, status epilepticus, and grand mal seizure.</td>
</tr>
<tr>
<td>Effects on ability to drive and use machines</td>
<td>• Routine pharmacovigilance</td>
<td>• Information in Section 4.7 of the SmPC indicating that patients should be advised to exercise caution when driving or operating machinery.</td>
</tr>
<tr>
<td>Use in renal impairment</td>
<td>• Routine pharmacovigilance</td>
<td>• Information in Section 4.2 and 5.2 of the SmPC providing data on correlation of plasma AUC of zonisamide with creatinine clearance to inform posology for renally impaired patients.</td>
</tr>
<tr>
<td>Pregnancy issues</td>
<td>• Routine pharmacovigilance</td>
<td>• Information in Section 4.6 of the SmPC indicating that there are no adequate data from the use of zonisamide in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Zonegran must not be used during pregnancy unless clearly necessary, in the opinion of the physician, and only if the potential benefit is considered to justify the risk to the fetus.</td>
</tr>
<tr>
<td></td>
<td>• Monitoring of pregnancy registries</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimization activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in the elderly</td>
<td>• Routine pharmacovigilance • Cumulative review of ADRs in the elderly</td>
<td>• Statement in Section 4.2 of the SmPC indicating that caution should be exercised at initiation of treatment. • Undesirable effects in Section 4.8 to indicate the higher reporting rate of oedema peripheral and pruritus in the elderly compared to the adult population • Information in Section 5.2 that no clinically significant differences were observed in the pharmacokinetics between the young and elderly.</td>
</tr>
<tr>
<td>Developmental and maturational impairment in children and adolescents</td>
<td>• Routine pharmacovigilance • Review of events associated with zonisamide use in children • Intensive monitoring of adverse events relating to growth, development, pubertal maturity, and bone health. • Drug utilization study on effectiveness of risk minimization measures directed at paediatric patients (monitoring of weight).</td>
<td>• Statement in Section 4.8 that in some cases of weight decrease there was a delay in transition to the next Tanner stage and in bone maturation. • Statement in Section 5.1 that weight loss may have deleterious implications for growth and development, • Changes will be made to the SmPC if warranted</td>
</tr>
</tbody>
</table>

**Missing Information**

| Use in impaired liver function                      | • Routine pharmacovigilance | • Statement in Section 4.2 and 5.2 of the SmPC indicating that neither the safety and efficacy nor the pharmacokinetics of zonisamide has been studied in patients with impaired liver function. |
| Use in children below 6 years.                      | • Routine pharmacovigilance | • Statement in Section 4.2 of the SmPC indicating that safety and efficacy have not been established in patients below 6 years or weighing less than 20 kg, and that there are limited data from clinical studies in patients with a body weight of less than 20 kg, therefore children aged 6 years above with a body weight less than 20 kg should be treated with caution. |

No additional risk minimisation activities were required

**1.7.1. PSUR cycle**

The current yearly PSUR cycle should remain unchanged.

**1.8. Update of the Product information**

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.6, 4.8, 5.1, 5.2, 5.3, and 6.6 of the SmPC have been updated as shown below:
4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zonegran is indicated as:

- monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy (see section 5.1);
- adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents and children aged 6 years and above.

4.2 Posology and method of administration

**Paediatric population (aged 6 years and above)**

**Dosage escalation and maintenance**

Zonegran must be added to existing therapy for paediatric patients aged 6 years and above. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 2. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

Physicians should draw the attention of paediatric patients and their parents/carers to the Patient Alert Box (in the package leaflet) on preventing heatstroke (see section 4.4: Paediatric Population).

**Table 2. Paediatric population (aged 6 years and above) – recommended dosage escalation and maintenance regimen**

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Titration Phase</th>
<th>Usual Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunctive therapy</td>
<td>Week 1</td>
<td>1 mg/kg/day (once a day)</td>
</tr>
<tr>
<td>- with CYP3A4- inducing agents (see section 4.5)</td>
<td>Weeks 2 to 8</td>
<td>Increase at weekly intervals in increments of 1 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients of weight &gt; 55 kg</td>
</tr>
<tr>
<td>- without CYP3A4- inducing agents</td>
<td>Week 1 + 2</td>
<td>1 mg/kg/day (once a day)</td>
</tr>
<tr>
<td></td>
<td>Weeks ≥ 3</td>
<td>Increase at two-weekly intervals in increments of 1 mg/kg</td>
</tr>
</tbody>
</table>

**Note:**
a. To ensure a therapeutic dose is maintained the weight of a child should be monitored and the dose reviewed as weight changes occur up to a weight of 55kg. The dose regime is 6-8mg/kg/day up to a maximum dose of 500 mg/day.

The safety and efficacy of Zonegran in children aged below 6 years or those below 20 kg have not yet been established.

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 and with a body weight less than 20 kg should be treated with caution.

**Withdrawal**

When Zonegran treatment is to be discontinued, it should be withdrawn gradually (see section 4.4). In clinical studies of paediatric patients, down-titration was completed by dose reductions at weekly intervals in increments of about 2 mg/kg (i.e. in accordance with the schedule in Tablet 3).
### Table 3. Paediatric population (aged 6 years and above) – recommended down-titration schedule

<table>
<thead>
<tr>
<th>Weight</th>
<th>Decrease at weekly intervals in increments of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 28 kg</td>
<td>25 to 50 mg / day*</td>
</tr>
<tr>
<td>29 – 41 kg</td>
<td>50 to 75 mg / day*</td>
</tr>
<tr>
<td>42 – 55 kg</td>
<td>100 mg / day*</td>
</tr>
<tr>
<td>&gt;55 kg</td>
<td>100 mg / day*</td>
</tr>
</tbody>
</table>

**Note:**
* All doses are once daily.

### Paediatric population

The safety and efficacy of Zonegran in children and adolescents have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

### 4.4 Special warnings and precautions for use

#### Kidney stones

Some kidney stones have occurred in patients treated, especially those with zonisamide. Zonegran should be used with caution in patients who have risk factors for predisposition to nephrolithiasis, including prior stone formation, a family history of nephrolithiasis and hypercalciuria. Such patients may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Nephrolithiasis may lead to chronic kidney damage. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during zonisamide treatment. In addition, patients taking other medications associated with nephrolithiasis may be at increased risk. Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors.

... Zonegran should be used with caution in adult patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate or acetazolamide, as there are insufficient data to rule out a pharmacodynamic interaction (see also section 4.4 Paediatric Population and section 4.5).

#### Heat stroke

Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients (see section 4.4 Paediatric Population for full warning). Caution should be used in adults. Heat stroke requiring hospital treatment was diagnosed in some cases. Most reports occurred during periods of warm weather. Patients or their carers must be warned to take care to maintain hydration and avoid exposure to excessive temperatures. Caution should be used when Zonegran is prescribed with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity. (see also section 4.4 Paediatric Population)

... Zonegran may cause weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight or is underweight whilst on this medication. If substantial undesirable weight loss occurs, discontinuation of Zonegran should be considered. Weight loss is potentially more serious in children (see section 4.4. Paediatric Population).

#### Body weight

There is limited data from clinical studies in patients with a body weight of less than 40 kg. Therefore these patients should be treated with caution.

... Zonegran can cause children to sweat less and overheat and if the child is not treated this can lead to brain damage and death. Children are most at risk especially in hot weather.

### Paediatric Population

The warnings and precautions mentioned above are also applicable to adolescent and paediatric patients. The warnings and precautions mentioned below are more relevant to paediatric and adolescent patients.

#### Heat stroke and dehydration

**Preventing overheating and dehydration in children**

Zonegran can cause children to sweat less and overheat and if the child is not treated this can lead to brain damage and death. Children are most at risk especially in hot weather.

**When a child is taking Zonegran:**

- The child should stay cool especially in hot weather
- The child must avoid heavy exercise especially when the weather is hot
• The child must drink plenty of cold water
• The child must not take any of these medicines:
  carbonic anhydrase inhibitors (like topiramate and acetazolamide), and anticholinergic agents (like clomipramine, hydroxyzine, diphenhydramine, haloperidol, imipramine and oxybutynin).

**IF ANY OF THE FOLLOWING OCCUR, THE CHILD NEEDS URGENT MEDICAL ATTENTION:**
The skin feels very hot with little or no sweating, or the child becomes confused or has muscle cramps, or the child’s heartbeat or breathing become rapid.

- Take the child to a cool, shaded place
- Keep the child’s skin cool with water
- Give the child cold water to drink

Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients. Heat stroke requiring hospital treatment was diagnosed in some cases. Heat stroke requiring hospital treatment and leading to death has been reported. Most reports occurred during periods of warm weather. Physicians should discuss with patients and their carers the potential seriousness of heatstroke, situations in which it might arise, as well as action to take in the event of any signs or symptoms. Patients or their carers must be warned to take care to maintain hydration and avoid exposure to excessive temperatures and strenuous physical exercise depending on the condition of the patient. Prescribers should draw the attention of paediatric patients and their parent/carers to the advice in the Packaging Leaflet on preventing heatstroke and overheating in children as provided. In the event of signs or symptoms of dehydration, oligohydrosis, or elevated body temperature, discontinuation of Zonegran should be considered.

Zonegran should not be used as 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.

**Body weight**
Weight loss leading to deterioration of general condition and failure to take anti-epilepsy medication has been related to a fatal outcome (see section 4.8). Zonegran is not recommended for paediatric patients who are underweight (definition in accordance with the WHO age adjusted BMI categories) or have a decreased appetite.

The incidence of decreased body weight is consistent across age groups (see section 4.8); however, given the potential seriousness of weight loss in children, weight should be monitored in this population. A dietary supplement or increased food intake should be considered if the patient is failing to gain weight in accordance with growth charts, otherwise Zonegran should be discontinued.

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.

**Metabolic acidosis**
The risk of zonisamide induced metabolic acidosis appears to be more frequent and severe in paediatric and adolescent patients. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in this population (see section 4.4 - Metabolic acidosis for full warning; see section 4.8 for incidence of low bicarbonate). The long term effect of low bicarbonate levels on growth and development is unknown.

Zonegran should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and acetazolamide (see section 4.5).

**Kidney stones**
Kidney stones have occurred in paediatric patients (see section 4.4 Kidney stones for full warning). Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Nephrolithiasis may lead to chronic kidney damage. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during zonisamide treatment.

Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors. Renal ultrasound should be performed at the discretion of the physician. In the event kidney stones are detected, Zonegran should be discontinued.

**Hepatic dysfunction**
Increased levels of hepatobiliary parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and bilirubin have occurred in paediatric and adolescent patients, without any consistent pattern in the observations of values above the upper limit of normal. Nevertheless, if a hepatic event is suspected, liver function should be evaluated and discontinuation of Zonegran should be considered.

**Cognition**
Cognitive impairment in patients affected by epilepsy has been associated with the underlying pathology and/or the administration of anti-epileptic treatment. In a zonisamide placebo-controlled study conducted in paediatric and adolescent patients, the proportion of patients with impaired cognition was numerically greater in the zonisamide group compared with the placebo group.

Excipients

Zonegran 100 mg hard capsules contain a yellow colour called sunset yellow FCF (E110), and a red colour called allura red AC (E129), which may cause allergic reactions.

Zonegran orodispersible tablets contain a sweetener called aspartame (E951), which is a source of phenylalanine and may be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Carbonic anhydrase inhibitors

Zonegran should be used with caution in adult patients treated concomitantly with carbonic anhydrase inhibitors such as topiramate and acetazolamide, as there are insufficient data to rule out a possible pharmacodynamic interaction (see section 4.4).

Zonegran should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and acetazolamide (see section 4.4 Paediatric Population).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Fertility

There are no clinical data available on the effects of zonisamide on human fertility. Studies in animals have shown changes in fertility parameters (see section 5.3).

4.8 Undesirable effects

Paediatric Population

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. Among 465 subjects in the paediatric safety database (including a further 67 subjects from the extension phase of the controlled clinical trial) there were 7 deaths (1.5%; 14.6/1000 person-years): 2 cases of status epilepticus, of which one was related to severe weight loss (10% within 3 months) in an underweight subject and subsequent failure to take medication; 1 case of head injury/haematoma, and 4 deaths in subjects with pre-existing functional neurological deficits for various causes (2 cases of pneumonia-induced sepsis/organ failure, 1 SUDEP and 1 head injury). A total of 70.4% of paediatric subjects who received ZNS in the controlled study or its open label extension had at least one treatment-emergent bicarbonate measurement below 22 mmol/L. The duration of low bicarbonate measurements was also long (median 188 days).

A pooled analysis of safety data on 420 paediatric subjects (183 subjects aged 6 to 11 years, and 237 subjects aged 12 to 16 years with a mean duration of exposure of approximately 12 months) 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% (see section 4.4). In some cases of weight decrease there was a delay in transition to the next Tanner stage and in bone maturation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paediatric Population

Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adolescent and paediatric patients (aged 6 years and above)

In paediatric patients (aged 6 years and above), efficacy has been demonstrated with zonisamide in a double-blind, placebo-controlled study, which included 207 subjects and had a treatment duration of up to 24 weeks. A 50% or
greater reduction from baseline in seizure frequency during the 12-week stable dose period was seen in 50% of the zonisamide-treated subjects and 31% of the patients on placebo.

Specific safety issues that were encountered in the paediatric studies were: decreased appetite and weight loss, decreased bicarbonate levels, increased risk of kidney stones and dehydration. All these effects and specifically weight loss may have deleterious implications for growth and development, and may lead to general deterioration of health. Altogether, data on effects on long-term growth and development are limited.

5.2 Pharmacokinetic properties

Linearly / non-linearity

Zonisamide exposure increases with time until steady state is achieved by approximately 8 weeks. When comparing the same dose level, subjects of higher total body weight appear to have lower steady-state serum concentrations, but this effect appears to be relatively modest. Age (≥ 12 years) and gender, after adjustment for body weight effects, have no apparent effect on zonisamide exposure in epileptic patients during steady-state dosing. There is no need for dose adjustment with any of the AEDs including CYP3A4 inducers.

Pharmacokinetic-pharmacodynamic relationship

Zonisamide lowers the 28-day average seizure frequency and the decrease is proportional (log-linear) to zonisamide average concentration.

Other characteristics

No clear Zonegran dose-concentration-response relationship has been defined. When comparing the same dose level, subjects of higher total body weight appear to have lower steady-state serum concentrations, but this effect appears to be relatively modest. Age (≥ 12 years) and gender, after adjustment for body weight effects, have no apparent effect on zonisamide exposure in epileptic patients during steady-state dosing.

5.3 Preclinical safety data

In a repeated-dose oral toxicity study in juvenile rats, at exposure levels similar to those observed in paediatric patients at the maximum recommended dose, decreases in body weight and changes in renal histopathology and clinical pathology parameters and behavioural changes were observed. Changes in renal histopathology and clinical pathology parameters were considered to be related to carbonic anhydrase inhibition by zonisamide. The effects at this dose level were reversible during the recovery period. At a higher dose level (2-3-fold systemic exposure compared to therapeutic exposure) renal histopathological effects were more severe and only partially reversible. Most adverse effects observed in the juvenile rats were similar to those seen in the repeated-dose toxicity studies of zonisamide in adult rats, but renal tubular hyaline droplets and transitional hyperplasia were observed in the juvenile study only. At this higher dose level, juvenile rats showed a decrease in growth, learning, and developmental parameters. These effects were considered likely related to the decreased body weight and exaggerated pharmacologic effects of zonisamide at the maximum tolerated dose.

In rats, decreased numbers of corpora lutea and implantation sites were observed at exposure levels equivalent to the maximum therapeutic dose in humans; irregular oestrus cycles and a decreased number of live foetuses were observed at exposure levels three times higher.

6.6 Special precautions for disposal

No special requirements for disposal.

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

The Package Leaflet has been updated accordingly.

In addition, changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP.

A user consultation was not conducted. The PIL was last tested in April 2011 and in September 2011. The MAH submitted a justification for not repeating the user consultation, which was considered acceptable. In both cases the MAH showed that the package leaflet met the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
2. Benefit-Risk Balance

Benefits

Beneficial effects

Zonegran (zonisamide) is an antiepileptic medication that is currently indicated as mono therapy and as adjunctive therapy in partial seizures with or without secondary generalization in adult patients.

This application seeks to extend this indication to include adjunctive therapy of partial seizures with or without secondary generalization in children and adolescents aged 6 years and above.

In support of this indication, the applicant submitted a population pharmacokinetic analysis, a PK/PD analysis and one pivotal efficacy and safety study in the child and adolescent population (6-17 years) with partial onset seizures and its open label 1 year extension study. Evidence on safety is also based on additional studies in which children and adolescents were included.

The design of the pivotal study was broadly in line with the Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders. Inclusion and exclusion criteria appear to have been appropriate and included subjects with inadequately controlled partial seizures in the age-group for which the indication is sought. The choice of primary and secondary endpoints (responder rates and decrease in seizure frequency) was appropriate.

The pivotal study consisted of a 4-8 weeks screening period, an 8 week titration period and a 12 weeks maintenance period. Children and adolescents with at least 4 partial seizures per month and on a stable regimen of 1 or 2 AEDs for at least 1 month before the start of the study were included. They were randomized to receive either Zonegran at a maintenance dose of 8 mg/kg/day or placebo. The primary efficacy endpoint was defined as the percentage of responders, defined as ≥ 50% reduction from baseline in seizure frequency during the maintenance period.

A total of 107 patients were randomized to Zonegran and 100 to placebo. These patients were all included in the ITT analysis. A total of 13% and 10% discontinued from the study in the active and placebo arms, respectively.

Efficacy results from the pivotal study are supportive of short-term efficacy: 50% responders (≥50% reduction in seizure frequency from baseline) in the Zonegran arm compared to 31% in the placebo arm (p=0.0044), resulting in a NNT of 5. Efficacy results in the paediatric study are consistent with those in the adult study (study 302) where % responders in the 500mg group was 44% compared to 20% in placebo.

This analysis was performed after removing site and weight group as stratifying variables. Upon request from CHMP an additional Cochran-Mantel-Haenszel analysis including these strata has been provided. The result from this analysis are still statistically significant, however with a p value of 0.0360. The secondary efficacy endpoint demonstrated a likewise worthwhile treatment effect on the median percentage reduction from baseline in seizure frequency (50% in Zonegran vs. 25% in placebo).

The effect was consistent in the younger (6-11) and older age groups (12-17) and in patients receiving different concomitant AEDs. The differences in the effect size across different types of seizures are considered a chance finding and not to be of clinical significance.

Compared to other AED which are already indicated for adjunctive therapy in children with partial seizure, the efficacy of Zonegran is in the same order of magnitude. In terms of % responders (>50% reduction in seizure frequency) a study in lamotrigine in a similarly defined sample (Duchowny et al., 1999)3 showed 42% responders in the lamotrigine arm compared to 16% in placebo, and a study in

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Topiramate (cited in French et al., 2004)\(^4\) showed 39% responders compared to 20% in the topiramate and placebo arms, respectively. Another study which is also cited by French et al. (2004) of oxcarbazepine achieved 41% response in the active arms compared to 22% in placebo and a study of Levetiracepam described in the SPC of this product showed response rates of 45% vs. 20% in the active arm compared to placebo, respectively. Hence all these studies achieved a 20%-25% difference between active arm and placebo in percent responders, which is consistent with the difference that was obtained for Zonegran.

**Uncertainty in the knowledge about the beneficial effects**

Uncertainties were raised regarding the lack of a dose range initially proposed for the paediatric population as in the adult population. PK modelling suggested an overlap in exposure between the 8mg/kg and 6mg/kg dose in the paediatric population, which raised the question as to whether a 6mg/kg dose might be as equally efficacious with the additional benefit of a possible lower frequency of adverse events. The applicant therefore proposed a dose range of 6 to 8 mg/kg for those with a weight < 55kg and a dose range of 300 to 500mg for those with a weight above 55kg.

**Unfavourable effects**

The safety profile is in general similar to that in adults. However, there are several important identified risks that may have greater implications in the paediatric population.

In the pooled safety database, seven patients (1.5%) who were treated with Zonegran had a TEAE resulting in death. The number of deaths in the studies were a reason for concern. Two of these death were attributed to Zonegran by the investigator. In a further case of death attributed to SUDEP a relationship could neither be confirmed or excluded. The remaining four deaths are thought to be unlikely to be related to Zonegran.

The mortality rates observed in this population were however similar to those observed in a paediatric population exposed to lamotrigine (Messenheimer et al). In addition death rates have been noted to be higher in those with functional neurological impairment/remote symptomatic epilepsy. This may be a partial explanation for the high death rates seen with Zonegran (Camfield).

Decreased appetite and weight loss are reasons for concern, as this might have an impact on general health, immunity and increased vulnerability to infection. In addition, these AEs may have effects on growth and development and sexual maturation. Likewise, decreases in bicarbonate levels, which were observed very frequently and for a long duration may also have adverse effects on growth and maturation, although a scarcity of data in this respect did not allow this conclusion to be drawn with certainty. Cases of delay in bone maturation and delay in transition to next Tanner stage have been observed. No data from longer than one year exposure is available, so the long term impact of Zonegran treatment remains unknown.

A clear correlation with time since start of treatment and time of onset of AEs has not been established, but the data showed that some AEs as vomiting, diarrhoea, dehydration can be persistent. Persistent vomiting and diarrhoea is of concern not only because it leads to weight loss and dehydration, but also because it may reduce treatment compliance.

Metabolic acidosis has not been reported in the safety database. Renal function does not seem to be affected in terms of concentration capacity, but proteinuria and haematuria have been observed indicating vulnerability of the urinary system in these patients. There seemed to be an increased risk of kidney stones as well, which is of concern since this may lead to renal damage.

The implication of somnolence for educational attainment is a concern. The additional results of the cognitive assessment presented did not allow further judgement to which extent the treatment contributed to cognitive and performance impairment in treated subjects. This remains an uncertainty.

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Compared to other AEDs that are registered for the same indication in paediatric patients (e.g. oxcarbazepine, lamotrigine), dermatologic effects and sedation played less of a role in the safety profile of Zonegran.

Uncertainty in the knowledge about the unfavourable effects

The effect on renal function is not completely clear since concentration capacity was not affected, but a proportion of the subjects had haematuria and proteinuria, possibly indicating vulnerability of the urinary system in these patients. In addition the increased risk for kidney stones could lead to chronic renal damage in the long term.

The long term effect of decreases in bicarbonate levels (which were observed very frequently and for a long duration) on long term growth and development are not known although this is subject to specific risk minimisation measures and it is noted that there were no reports of metabolic acidosis.

Other concerns regarding long-term safety pertain to the effects of loss of appetite and loss in weight on nutritional status and general condition, in addition to effect on growth and maturation.

In addition there are uncertainties regarding the impact of treatment with Zonegran on educational attainment.

Balance

Discussion on the benefit-risk assessment

Altogether, the efficacy of Zonegran has been demonstrated in a group of children and adolescents aged 6-17 with % responders of 50% in the Zonegran arm compared to 31% in placebo. The effect in the paediatric study is consistent with that found in adults and with that of other AED in paediatric samples.

The sought indication extension is to include adjunctive therapy of partial seizures with or without secondary generalization in children and adolescents aged 6 years and above. In general this is considered a treatment resistant patient population which does not respond sufficiently to 1 or 2 other AEDs, hence adjunctive therapy should provide additional efficacy in terms of further reduction of seizure frequency.

The results from the presented evidence in this dossier indicate that adjunctive therapy with Zonegran can induce a further reduction in seizures, as indicated by the proportion of responders in the Zonegran arm (50%) as compared to placebo (31%). This results in a NNT of 5. The efficacy of Zonegran is in the same order of magnitude as that of other AEDs which are already indicated for adjunctive therapy in children with partial seizures (42% vs 16% in lamotrigine; 39% vs 20% in topiramate; 41% vs 22% oxcarbazepine; 45% vs. 20% in levetiracetam, for active arm vs. placebo, respectively). This difference of about 20%-25% between active treatment and placebo in percent responders, was also observed for Zonegran, however with a higher placebo response.

Against these efficacy results, the safety issues that emerged with Zonegran show that although the safety profile is similar to that in adults, there are important issues that that have different implication in children which need to be monitored.

Mortality rates observed are of concern, although they are similar to those seen in other paediatric trials with other AED, and some of the deaths occurred in subjects with functional neurological impairment, a group, noted to have a higher risk of death, often related to their underlying condition rather than epilepsy. Nevertheless, as part of the routine pharmacovigilance activities there should be intensive monitoring of fatalities in the paediatric population as well as the events that preceded such events in the cases described (including weight loss, dehydration and loss of efficacy), i.e. these safety concerns should be closely followed up and reviewed as adverse events of special interest and should be discussed in detail within future PSURs.
The long-term effects of decreased appetite and weight loss and long-term effects of bicarbonate loss on nutritional status and general condition apart from growth and development need to be closely monitored. Furthermore, proteinuria and haematuria as well as an increased risk of kidney stones have been observed indicating vulnerability of the urinary system, which is of concern since this may lead to renal damage over time.

The CHMP concluded that the safety issues identified could be minimised through additional warnings in the SmPC, highlighting these risks, and requesting physicians, parents and carers to monitor these events. The MAH will perform a drug-utilization study, to provide evidence of the effectiveness of SmPC warnings on concomitant use of carbonic anhydrase inhibitors and anticholinergic drugs, monitoring of serum bicarbonate levels as well as weight and height in the paediatric population and use in children below 20 kg.

Despite the availability of a number of AEDs that are approved for paediatric use, not all patients achieve satisfactory seizure control. The benefit risk balance of adding Zonegran to the treatment arsenal for adjunctive therapy to one or two other AEDs in reducing seizures in the target paediatric population is deemed to be positive.

### Description of post-authorisation measures

1. The applicant is recommended to submit a valid algae growth inhibition test and a sediment organism toxicity test.
2. A drug utilisation study will be performed to measure the effectiveness of risk minimisation measures in the paediatric population as described in the RMP.

### 3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable by a majority of 25 out of 29 votes and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one

Extension of the indication “adjunctive treatment of partial seizures with or without secondary generalisation” to include adolescents and children aged 6 years and above.

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, and 6.6 of the SmPC have been updated. The Package Leaflet was updated accordingly.

Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template (version 9.0).

The variation proposed amendments to the SPC, Annex II, and Package Leaflet.

Divergent positions are presented in Appendix to this report.
**Conditions and requirements of the marketing authorisation**

- **Periodic Safety Update Reports**

  The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

**Conditions or restrictions with regard to the safe and effective use of the medicinal product**

- **Risk management plan**

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

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

  If the dates for submission of a PSUR and the update of an RMP coincide, they can be submitted at the same time.
APPENDIX

DIVERGENT POSITIONS
Divergent Positions

The undersigned members of CHMP did not agree with the CHMP’s opinion recommending the adoption of the variation to the terms of the Marketing Authorisation, concerning the extension of the indication “adjunctive treatment of partial seizures with or without secondary generalisation” to include adolescents and children aged 6 years and above

The reasons for the divergent opinion were as follows:

The Benefit-Risk balance of Zonegran in the treatment of paediatric patients is considered unfavourable. The benefit of adding Zonegran to one or two other antiepileptic drugs on adjunctive treatment of partial seizures in the target paediatric population does not outweigh the increased risk of mortality, kidney damage and long term effects of weight loss and decreased appetite, on the nutritional status, growth and development.

London, 25 July 2013

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Harald Enzmann                                Daniela Melchiorri

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Jan Mueller Berghaus                          Ondřej Slanař