Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Zonisamide

Proprietary Product Name: Zonegran

Sponsor: SciGen Australia Pty Ltd

July 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations used in this AusPAR

Abbreviation	Meaning
95% CI	95% Confidence Interval
ABNAS	Aldenkamp-Baker Neuropsychological Assessment Schedule
ADR	Adverse Drug Reaction
AE	Adverse Event
AED	Anti-Epileptic Drug
ANCOVA	Analysis Of Covariance
ANOVA	Analysis Of Variance
ASR	Annual Safety Report
Bid	bis in die (Twice Daily)
CBZ	Carbamazepine
CHMP	Committee For Human Medicinal Products
Cr-CL	Creatinine Clearance
CSR	Clinical Study Report
CYP 3A4	Cytochrome P450 3A4
EEG	Electroencephalogram
ETS	Ethosuximide
EU	European Union
FDA	Food and Drug Administration
GBP	Gabapentin
GCP	Good Clinical Practice
ILAE	International League Against Epilepsy
ITT	Intention To Treat
LTG	Lamotrigine
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Meaning
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
PV	Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TBG	Tiagabine
TEAE	Treatment Emergent Adverse Events
TPM	Topiramate
US	United States (Of America)

I. Introduction to product submission

Submission details

Type of Submission:	Extension of indications
Decision:	Approved
Date of Decision:	4 April 2013
Active ingredient:	Zonisamide
Product Name:	Zonegran
Sponsor's Name and Address:	SciGen Australia Pty Ltd PO Box 377 Frenchs Forest NSW 2086
Dose form:	Hard capsules
Strengths:	25 mg, 50 mg and 100 mg
Container:	Blister pack
Pack sizes:	14's (starter pack for 25 mg only), 56's (blister pack).
Approved Therapeutic use:	*Zonisamide is indicated as monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy who are intolerant to other agents or where other agents are contraindicated.*
Route of administration:	Oral (PO)
Dosage:	Treatment with zonisamide should be initiated with a dose of 100 mg/day (once a day). The dose should be titrated on the basis of clinical effect with increases on a fortnightly basis by increments of 100 mg/day up to a maximum dose of 500 mg/day (once a day).
ARTG Numbers:	125869, 125870, 125871

Product background

Zonisamide is a sulphonamide with weak carbonic anhydrase activity. It is structurally unrelated to other antiepileptic agents.

Zonisamide is thought to exert its actions by blockade of the neuronal voltage-sensitive sodium and calcium channels, thereby disrupting synchronised neuronal firing, reducing the spread of seizure discharges and disturbing subsequent epileptic activities. In addition, it also has some effects on the synthesis, release, and degradation of a number of different neurotransmitters, including glutamate, Gamma-aminobutyric acid (GABA), dopamine, serotonin and acetylcholine which may lead to enhancement of synaptic inhibition.

The currently approved indication for Zonegran in Australia is for the adjunctive therapy of partial seizures with or without secondary generalization in adult patients.

This AusPAR describes the application by the sponsor for an additional indication:

> *Zonisamide is indicated as monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy.*

Partial epilepsies (focal or localization-related) account for more than 60% of epilepsies, and they include most of the difficult-to-treat subjects. Partial epilepsies include simple partial seizures (without impairment of consciousness), complex partial seizures (with impairment of consciousness and often more disabling), and secondarily generalized tonic-clonic seizures.

The goals of treatment for adults with epilepsy are the best quality of life achievable, with no seizures, and the fewest possible adverse effects from treatment.

The majority of newly diagnosed subjects (50% – 70%) achieve seizure freedom on monotherapy.

No new dosage forms or strengths are proposed.

Regulatory status

Zonisamide was initially registered in Australia for adjuvant treatment of partial epilepsy in adults in 2007.

Zonisamide was first authorised in Japan on 31 March 1989 and in Europe on 10 March 2005. It is approved in 42 countries worldwide including the United States (US) and EU member states.

The monotherapy indication is approved in Japan. A similar application to extend the indications was approved in the EU in June 2012 and is under evaluation in Switzerland (see Table 1). No such submission has been made in the USA, Canada or NZ.

Table 1. International regulatory status for Zonegran extension of indication to include monotherapy.

Country	Marketing Status	Proposed Indication	Marketing approval date	Approved Indication*
EU (centralised procedure)	Approved	*Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy.*	27 June 2012	*Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy.*
Switzerland	Submitted	*Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy.*	Pending	Pending
USA	Authorised for adjunctive use only			

*EU, Switzerland and the US have an existing adjunctive use indication.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found at Attachment 2 of this AusPAR.

Scope of the clinical dossier

The submission included:

One clinical pharmacology study (ELN46046-108) that evaluated the effect of race on 100mg single-dose PKs of zonisamide in healthy White, Black, and Asian subjects.

Two efficacy studies:

- Pivotal noninferiority study E2090-E044-310 that compared zonisamide used as a monotherapy to treat newly diagnosed partial epilepsy in adults vs. carbamazepine.
- Study AN46046-304 evaluated the dose-response relationships of zonisamide monotherapy in adults with newly diagnosed epilepsy and complex partial seizures.

Safety data from two extension studies:

- StudyE2090-E044-314 from the ongoing double-blind extension of StudyE2090-E044-310, as of the data cut-off of 31 December 2010 (targeted to end in June 2011).
- Study ELN46046-355 from the open-label extension of Study ELN46046-304, completed in 2005 planned duration of treatment was up to 24 months. However, the study was terminated early, upon receipt of marketing approval in the EU.

Good clinical practice

The studies were carried out in accordance with Good Clinical Practice.

Pharmacokinetics

Summary of pharmacokinetics

The information in the following summary is derived from the PI.

Absorption

Zonisamide is almost completely absorbed after oral administration, generally reaching peak serum or plasma concentrations within 2 to 5 hours of dosing. First-pass metabolism is believed to be negligible. Absolute oral bioavailability is estimated to be approximately 100% and is not affected by food, although peak plasma and serum concentrations may be delayed.

Zonisamide plasma AUC and C_{max} values increased almost linearly after a single dose over the dose range of 100-800 mg and after multiple doses over the dose range of 100-400mg once daily. The increase following a single dose and at steady state were slightly more than expected on the basis of dose, probably due to the saturable binding of zonisamide to erythrocytes. Steady state was achieved within 13 days of a change in dose. Concentrations of zonisamide at steady state are up to six-fold higher than following an equivalent single dose at the recommended dosing interval.

Distribution

Zonisamide is 40 - 50 % bound to human plasma proteins, with in vitro studies showing that this is unaffected by the presence of various antiepileptic medicinal products (i.e., phenytoin, phenobarbitone, carbamazepine, and sodium valproate). The apparent volume of distribution is about 1.1 – 1.7L/kg in adults indicating that zonisamide is extensively distributed to tissues. Zonisamide binds saturably to erythrocytes, and erythrocyte/plasma C_{max} ratios are about 11 at low drug concentrations in plasma and about 3 at therapeutic concentrations.

Metabolism

Zonisamide is metabolised primarily through reductive cleavage of the benzisoxazole ring of the parent drug by CYP3A4 to form 2-sulphamoylacetylphenol (SMAP) and also by N-acetylation to form N-acetyl zonisamide. Parent drug and SMAP can additionally be glucuronidated. The metabolites, which could not be detected in plasma, are devoid of anticonvulsant activity. There is no evidence that zonisamide induces its own metabolism.

Elimination

Apparent clearance of zonisamide from plasma at steady-state after oral administration is about 0.70L/h and the terminal elimination half-life is about 60 hours in the absence of concomitant therapy with CYP3A4 inducers. However, the apparent clearance is increased by up to 2-fold in patients also receiving the antiepileptic drugs phenobarbitone, phenytoin, carbamazepine and/or sodium valproate, and elimination half-life is reduced by up to 50%. The elimination half-life is independent of dose and not affected by repeat administration. Fluctuation in serum or plasma zonisamide concentrations over a dosing interval is low (< 30 %). The rate of clearance from erythrocytes is approximately 0.3L/h at steady state. The main route of excretion of zonisamide metabolites and unchanged drug is via the urine. In healthy volunteers, 62% of the dose was recovered in urine and a further 3% in faeces over 10 days. Renal clearance of unchanged zonisamide is relatively low (approximately 3.5 mL/min); about 15 - 30 % of the dose is eliminated unchanged, with the remainder being excreted as metabolites.

Effect of zonisamide on cytochrome P450 enzymes

In vitro studies using human liver microsomes show no or little (< 25%) inhibition of cytochrome P450 isoenzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4 at zonisamide concentrations approximately two-fold or greater than clinically relevant unbound serum concentrations. Clinical studies have demonstrated that zonisamide does not significantly affect the pharmacokinetics of carbamazepine, phenytoin, lamotrigine, sodium valproate, levonorgestrel, norethindrone, ethynylestradiol and desipramine in vivo. The potential effects of zonisamide on the pharmacokinetics of other compounds, including phenobarbitone, are unknown.

Special patient groups

In subjects with renal impairment, renal clearance of single doses of zonisamide was positively correlated with creatinine clearance. The plasma AUC of zonisamide was increased by 35% in subjects with creatinine clearance < 20mL/min.

Patients with an impaired liver function: The pharmacokinetics of zonisamide in patients with impaired liver function have not been adequately studied.

Elderly: No clinically significant differences were observed in the pharmacokinetics between young (aged 21-40 years) and elderly (65-75 years).

Adolescents (12-18 years): Limited data indicate that pharmacokinetics in adolescents dosed to steady state at 1, 7 or 12mg/kg daily, in divided doses, are similar to those observed in adults, after adjustment for bodyweight.

Other characteristics

No clear zonisamide 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.

Evaluator's overall conclusions on pharmacokinetics

The ratios of the geometric means indicated that the Black and Asian race groups had 4% lower and 20% higher peak serum zonisamide exposure (that is, C_{max}), respectively, compared to the White race group. Meanwhile, serum zonisamide cumulative exposure (that is, area under the plasma concentration time curve from time zero to the last time point or infinity, that is, AUC_{last} and AUC_{∞}, respectively) was 7.11% and 14.15% higher in the Black and Asian race groups, respectively, compared to the White race group.

As race has no apparent clinically relevant effect on single-dose serum zonisamide PKs, modification of zonisamide dosing based on race should not be necessary.

Pharmacodynamics

No new data were submitted.

Dosage selection for the pivotal studies

Study AN46046-304 (monotherapy in the treatment of newly diagnosed epilepsy) dose-response results suggested a possible effect at a dose of 300mg/day. In that the proportion of subjects who were seizure-free for at least 6 months was 60.0% in the 300 mg/day group and 30.8% and 33.3% in the 25 and 100 mg groups. There were no unexpected findings that would suggest a differential tolerability or safety profile from that demonstrated in the adjunctive setting. Higher doses led to slightly more withdrawals than the lower dose, and a higher percentage of subjects had SAEs in the 300 mg arm compared to the 100 and 25 mg arms.

Efficacy

The relevant guideline is CHMP/EWP/566/98 Rev. 2/Corr. Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders.[1] It contains the following quotations:

> ***4.3 Assessment of efficacy***
>
> *In monotherapy (adults and children)*
>
> *a) in newly or recently diagnosed patients, the primary efficacy variable should be based on the proportion of patients remaining seizure free for at least six months (excluding the dose escalation period). The trial should have a minimum duration of one year in order to assess safety and maintenance of efficacy*
>
> ***4.4 Statistical analyses***
>
> *The analysis of efficacy will usually be intended to demonstrate superiority based on the ITT principle as referred in ICHE9 and the period when patients are established on a fixed dose of either the study product or placebo/comparator i.e. the maintenance dose.*
>
> *The primary analysis of efficacy should be unadjusted except for factors used to stratify randomisation. Factors known to influence outcome such as aetiology, seizure type, baseline seizure frequency, seizure severity and epilepsy syndrome should be taken into account in supportive analyses. The use of concomitant anti-epileptic products should be summarised and the potential impact on efficacy evaluated and discussed.*

Evaluator's conclusions on clinical efficacy for monotherapy of partial seizures with or without secondary generalization in adults with newly diagnosed epilepsy

The pivotal Study 304 population was not restricted to the proposed indication. The wording of inclusion and exclusion criteria regarding generalized epilepsy indicates that the electroencephalogram (EEG) result together with other clinical investigations (not named) was used to exclude idiopathic (primary) generalized epilepsy, leaving a group that were considered compatible with being localisation-related epilepsy, but not established as such.

It included within it patients with generalized tonic-clonic seizures (that were not clearly secondary); 37 (13.2%) in the zonisamide group and 38 (12.7%)on carbamazapine. This is in accordance with the protocol inclusion criterion.

> 2. Subjects with untreated, newly diagnosed epilepsy having at least two well documented, unprovoked, clinically evaluated and classified partial seizures (with or without secondary generalization) **or generalized tonic-clonic seizures** (*without clear focal origin*) within 12 months of the Screening Visit, of which at least one seizure occurred within three months of the Screening Visit (> one seizure within a 24 hour period will be counted as one seizure).

It should be noted, that carbamazepine can cause an exacerbation of epilepsy in subjects with primary generalized epilepsy, so possible inclusion of such subjects was inappropriate, and might have biased this study against the carbamazepine cohort.

A subgroup analysis was undertaken but the *All Partial* and S*econdary Generalised Tonic-Clonic* were not combined. Thus, the indication applied for has a differing population from the population in this study.

[1] <http://www.tga.gov.au/pdf/euguide/ewp56698rev2cor.pdf>

Table 2. Month Seizure Freedom – sub group analysis by Seizure History (PP Population)

Seizure History	Zonisamide (N=223)		Carbamazepine (N=233)		Adjusted difference[b] (95% CI)[c]	Odds Ratio (95% CI)[a]
	N*	n (%) free	N*	n (%) free		
Simple Partial	47	34 (72.3)	52	39 (75.0)	-0.027 (-0.200, 0.147)	0.872 (0.356, 2.135)
Complex Partial	91	70 (76.9)	86	80 (93.0)	-0.161 (-0.263, -0.059)	0.250 (0.095, 0.654)
All Partial	123	94 (76.4)	129	111 (86.0)	-0.096 (-0.192, -0.000)	0.526 (0.275, 1.006)
Secondary Generalised Tonic-Clonic	137	106 (77.4)	135	108 (80.0)	-0.026 (-0.124, 0.071)	0.855 (0.478, 1.529)
Generalised Tonic-Clonic	28	24 (85.7)	25	23 (92.0)	-0.063 (-0.231, 0.105)	0.522 (0.087, 3.129)
All Generalised Tonic-Clonic	161	127 (78.9)	158	129 (81.6)	-0.028(-0.115, 0.060)	0.840 (0.483, 1.459)

[a] Wald [b] Zonisamide – Carbamazepine [c] Derived
* Total of all Per-Protocol patients with the relevant Seizure History category.
Seizure freedom is modelled with a factor for treatment only. Patients can appear in more than one category

None of the subgroups achieved the preset non-inferiority margin except the combined Generalised Tonic-Clonic subgroups. Viewed separately Complex Partial and Generalised Tonic-Clonic exceeded the modified non inferiority margin, which Simple Partial reached.

Comment: Note that the study was not powered to determine statistically significant differences among subgroups, nor is it clear whether multiplicity effects have been allowed for in the above statistical calculations.

The sponsor's *Clinical Overview* claims Amendment 1 to the protocol modified the entry criteria so that primary generalized seizures were removed as one of the entry criteria in order to align further with the approved indication for Zonegran (ZNS). Such a modification by amendment could not be found in either the Protocol submitted or any of the associated amendments nor was it referred to in the sponsor's Clinical Study Report.

The pivotal Study 304 failed to meet the preset non inferiority margin and as such it has to be considered that efficacy was not shown.

The efficacy shown was greater than anticipated when setting up the study for both carbamazapine and zonisamide with such an event the relevant guideline EMEA/CPMP/EWP/2158/99 *Guideline on the Choice of the Non-Inferiority Margin*[2] states that "*If the performance of the reference product in a trial is very different from what was assumed when defining the non-inferiority margin then the chosen margin may no longer be appropriate*". The sponsor has argued that this being the case the basis of the preset margin, that is, 20% should apply. If this is accepted then efficacy was shown in the population of the study.

[2] <http://www.tga.gov.au/pdf/euguide/ewp215899en.pdf>

Study AN46046-304 added little to the efficacy evaluation outcome.

With regard to once daily dosing which is currently approved for maintenance, but not titration the sponsor has argued[3]:

> *ZNS has a long half-life, which allows for once-daily oral dosing. Convenience of use is expected to result in high patient compliance. Furthermore, because ZNS has a long half-life, plasma concentrations will be reasonably maintained even in the event that a daily dose is missed.*

The evaluator agrees they are not unreasonable statements (terminal elimination half life is approximately 60 h[4])

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

- Study E2090-E044-310 (310).
- StudyE2090-E044-314 (314) from the ongoing double-blind extension of StudyE2090-E044-310 (310), as of the data cut-off of 31 December 2010 (targeted to end in June 2011). No form of study outline was found.
- Study AN46046-304 (304).
- Study ELN46046-355 (355) from the open-label extension of Study ELN46046-304.
- Study ELN46046-108 (108) was not included in the Safety Summary submitted, an evaluation was undertaken.

Monotherapy safety data were not pooled. The sponsor considered it unlikely that a pooling of these data would have resulted in a profile significantly different from the analyses produced from the individual studies.

Overall, a total of 448 subjects were exposed to ZNS in monotherapy studies.

[3] Sponsor's Clinical Overview page 53.
[4] PI

Patient exposure

Table 3. Study 310 Cumulative Extent of Exposure: Time on Trial and Duration of Exposure Safety Population

Extent of Exposure	ZNS (N=281)	CBZ (N=300)
Time on Trial (days)		
n	281	300
Mean	314.5	324.7
SD	159.68	148.26
Median	392.0	393.0
Min	1	1
Max	799	656
Duration of Exposure (days)		
n	281	300
Mean	314.5	324.7
SD	159.68	148.26
Median	392.0	393.0
Min	1	1
Max	799	656

Time on trial = date of last dose before down-titration - date of first dose + 1. CBZ = carbamazepine; ZNS = zonisamide.
Duration of exposure = date of last dose before down-titration – date of first dose + 1 – any drug holidays or dose interruptions.
One patient was randomised to CBZ but received ZNS for the first 2 weeks of study. The patient went on to receive CBZ as randomised and completed the study. The patient was summarized as randomised.

Table 4. Study 304 Subject Compliance Safety Population

Visit	Statistic	Zonisamide 25 mg/day (N=56)	Zonisamide 100 mg/day (N=52)	Zonisamide 300 mg/day (N=59)
Week 1	N	54	49	56
	≥ 75% Compliant	54 (100.0)	49 (100.0)	56 (100.0)
	< 75% Compliant	0 (0.0)	0 (0.0)	0 (0.0)
Week 2	N	53	48	55
	≥ 75% Compliant	53 (100.0)	48 (100.0)	54 (98.2)
	< 75% Compliant	0 (0.0)	0 (0.0)	1 (1.8)
Week 3	N	52	45	54
	≥ 75% Compliant	52 (100.0)	45 (100.0)	54 (100.0)
	< 75% Compliant	0 (0.0)	0 (0.0)	0 (0.0)
Week 4	N	51	42	51
	≥ 75% Compliant	49 (96.1)	42 (100.0)	51 (100.0)
	< 75% Compliant	2 (3.9)	0 (0.0)	0 (0.0)
Week 5	N	50	40	49
	≥ 75% Compliant	50 (100.0)	40 (100.0)	49 (100.0)
	< 75% Compliant	0 (0.0)	0 (0.0)	0 (0.0)
Week 8	N	45	35	44
	≥ 75% Compliant	45 (100.0)	33 (94.3)	43 (97.7)
	< 75% Compliant	0 (0.0)	2 (5.7)	1 (2.3)

Week 12	N	41	31	43
	≥ 75% Compliant	41 (100.0)	31 (100.0)	43 (100.0)
	< 75% Compliant	0 (0.0)	0 (0.0)	0 (0.0)
Week 24	N	31	25	34
	≥ 75% Compliant	31 (100.0)	25 (100.0)	34 (100.0)
	< 75% Compliant	0 (0.0)	0 (0.0)	0 (0.0)
Week 40	N	49	49	51
	≥ 75% Compliant	48 (98.0)	46 (93.9)	46 (90.2)
	< 75% Compliant	1 (2.0)	3 (6.1)	5 (9.8)

Note: Subjects compliance (≥ 75% or <75%) as recorded on the Drug Dispensing/Return form during clinic visits.
Per protocol, subjects took study medication or placebo from up to 4 bottles per week. Because unblinding data were provided at the subject level rather than at the bottle level, actual daily dose could not be calculated for this study.

Table 5. Study 355 Summary of Exposure to Study Drug (Days) Safety Population

Statistic	Zonisamide 100 mg/day (N=20) (N	Zonisamide 300 mg/day =12) (N	Overall =32)
Exposure Days [1]			
N	20	10	30
Mean (SD)	694.5 (143.52)	553.1 (91.29)	647.3 (143.79)
Median	646	550	627
Min, Max	392, 898	402, 695	392, 898
Study Days [2]			
N	20	10	30
Mean (SD)	396.5 (141.53)	254.3 (87.30)	349.1 (141.90)
Median	350	253	325
Min, Max	99, 576	105, 386	99, 576

[1] Exposure Days = Days on Zonisamide starting with first dose in AN46046-304.
[2] Study Days = Days on Zonisamide starting with first dose in AN46046-355 Study.
Note: The Safety Population and the Evaluable Population are identical in this study.
Per protocol, subjects took study medication or placebo from up to 4 bottles per week. Because unblinding data were provided at the subject level rather than at the bottle level, actual daily dose could not be calculated for this study.

Evaluator's overall conclusions on clinical safety

While the submission does not raise any new concerns regarding safety, any risks of the new once daily regime for titration were not reviewed in the submission.

First round benefit-risk assessment

First round assessment of benefits

The benefits of zonisamide in the proposed usage are:

- The provision of an alternative monotherapy antiepileptic drug, that appears to have a different mode of action. However this was subject to the acceptance of the amended non-inferiority margin in Study 310, and then only applied to the population of that study not that of the proposed Indication.
- The change to a once daily regime for titration.

First round assessment of risks

The risks of zonisamide in the proposed usage are:

- The tolerability of the new once daily regime for titration has not been clarified in that adverse reactions in that period have not been separately reviewed.
- The established risks in the current Indication.

First round assessment of benefit-risk balance

The benefit-risk balance of zonisamide, given the proposed usage, is unfavourable.

First round recommendation regarding authorisation

It is not recommended that authorisation be made without justification by the sponsor of:

- Efficacy in the population in the proposed Indication. The population in the pivotal efficacy study was not the same as the population in whom the monotherapy regimen is proposed. The sponsor should justify the inclusion of subjects with **generalized tonic-clonic seizures** (without clear focal origin) in the study population or this group should be specifically excluded in the indications for monotherapy Zonegran.
- The once daily regime for titration with regard to tolerability.

List of questions

1. ***Please provide for Study E2090-E044-310 an analysis of the primary efficacy parameter (the proportion of subjects seizure-free for 26 weeks) that excludes subjects with generalized tonic-clonic (GTC) seizures that had not been confirmed as local in origin(i.e. as defined in the study: all partial seizures and secondary generalized tonic clonic seizures but not generalized tonic-clonic seizures). The analysis to include calculation of the 95% CI for the difference between treatments.***

   Sponsor response

   The MAH performed the additional sensitivity analysis and the results presented below (Table Subjects with history of GTC seizures without clear focal origin were excluded and the analysis of the 6 month seizure freedom was adjusted by country (as per the primary statistical analysis excluding this subgroup of subjects). For the Per Protocol (PP) population, 78.5% of subjects on ZNS and 82.7% on carbamazepine (CBZ) remained seizure free for 6 months: -4.2% (95% CI -12.4%; 4%). The lower limit of the 95% confidence interval (CI) for the absolute difference for ZNS versus CBZ was -12.4% and the lower difference 15.0% was well within the relative 20% margin that is described for non-inferiority in the International League Against Epilepsy guidelines (ILAE 2006)[5].

[5] <http://www.ilae.org/Visitors/Centre/Guidelines.cfm>

Table 6. Study 310. Six month seizure freedom rates: excluding subjects who had seizure history of Generalized tonic-clonic seizures (PP Population).

N	ZNS n (%) (N=195)	CBZ n (%) (N=208)
Seizure Freedom Rates n (%)	153 (78.5)	172 (82.7)
N	195	208
Odds Ratio	0.770	
Adjusted Difference (ZNS-CBZ) 95% two- sided CI	-0.042 (-0.124; 0.040)	
Lower 95% CI of the Relative Difference (Zonisamide –Carbamazepine)	15.0%	

CBZ = carbamazepine, CI = confidence interval, PP = per-protocol, ZNS = zonisamide

In conclusion, the sensitivity analysis performed on the primary efficacy variable, which excluded subjects with GTC seizures without clear focal origin, does not change the interpretation of the results of Study 310 or the primary conclusion that ZNS could be considered non-inferior to CBZ in accordance with the ILAE guidelines.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the clinical aspects of the safety specifications (SS) by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as shown in Table 7 below.

Table 7. Summary of the Ongoing Safety Concerns

Important Identified Risks	• Hypersensitivity • Skin eruptions • Hematological events • Kidney stones • Disordered body temperature • Pancreatitis and elevated amylase and lipase • Muscle disorders • Weight loss • Metabolic acidosis • Suicide/Suicidal Thoughts
Important Potential Risks	• Seizures following sudden withdrawal • Effects on ability to drive and use machines • Use in patients with renal impairment • Pregnancy issues
Important Missing Information	• Use in impaired liver function • Use in the elderly • Use in children and adolescents

OPR reviewer comment:

Notwithstanding the evaluation of the clinical aspects of the SS, it was recommended that the sponsor include the Important missing information: '*Use in lactating women*' as an Ongoing Safety Concern when this document is next updated.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*, are proposed to monitor all the specified Ongoing Safety Concerns.

The sponsor also refers to *"Monitoring of pregnancy registries"* for the Important potential risk '*Pregnancy issues*' and that such evaluation will be reported as an *"Ongoing periodic review".* No further information was provided about these pregnancy registries.

In addition the Important missing information: '*Use in the elderly*' will be further characterised by pooled safety analysis of data on elderly subjects in all existing clinical studies and by the evaluation of Study E2090-E044-402: *"A randomised, double blind, placebo-controlled study to evaluate the safety, tolerability and explore the efficacy of zonisamide as add-on therapy in elderly patients with refractory partial seizures".* A protocol synopsis for this study, which was terminated 23 November 2010, was provided in Annex 5 of the RMP and the submission of the study report and pooled analysis of elderly clinical trial subjects was stated as August 2011.

The sponsor also proposes to further characterise the Important missing information: '*Use in children and adolescents*' by the evaluation of the following studies:

- Study E2090-E044-312: "*A double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy and safety of adjunctive zonisamide in pediatric partial onset seizures*". A protocol synopsis for this completed study was provided in Annex 5 of the RMP and the submission of the study report was stated as October 2011.
- Study E2090-E044-313: "*An Open-label Extension Study Following a Double-blind, Randomized, Placebo-controlled, Multi-center Study to Assess the Efficacy and Safety of Adjunctive Zonisamide in Pediatric Partial Onset Seizures*". A protocol synopsis for this ongoing study was provided in Annex 5 of the RMP and the submission of the study report was stated as July 2012.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

Table 32: '*Detailed Action Plan for Important Potential Risk (Pregnancy issues)*', Section 2.4: *'Overview of study protocols for the pharmacovigilance plan*' and Section 2.6: '*Summary of outstanding actions, including milestone*s' of the RMP did not provide any information in relation to the stated pregnancy registries. Consequently it is unclear what the status of these actions are and when and how the results of these actions will be reported. The sponsor should correct this oversight when this document is next updated. In addition at least draft protocols for these registries should be provided to the TGA for review if they are not yet ongoing.

The terminated, completed and ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless the stated milestones for these studies have already passed or are imminent. Consequently the sponsor should provide an update on the progress/results/analysis of these studies and describe how this information will be incorporated into the RMP when this document is next updated.

The Australian Specific Annex provided as Annex 9 of the RMP should provide details of the person responsible for the activities in the RMP within the sponsor company and will usually be the Australian pharmacovigilance contact person.

It is also recommended that routine pharmacovigilance be used to monitor the Important missing information: '*Use in lactating women*' as a new Ongoing Safety Concern.

Risk minimisation activities

Planned actions

Routine risk minimisation activities will comprise labelling, including contraindications, special warning and precaution statements, interactions with other medicines, instructions for use, and/or notification of undesirable effects for all the specified Ongoing Safety Concerns.

OPR reviewer comment:

The sponsor's proposed application of routine risk minimisation activities would appear to be reasonable and therefore acceptable. It is also acknowledged that routine risk minimisation has already been proposed for the Important missing information: '*Use in lactating women*'.

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft product information document be revised for Important identified risk: 'Weight loss' to provide specific clinical safety information in relation to this Ongoing Safety Concern and is consistent with the EU Summary of product Characteristics.

In regard to the proposed routine risk minimisation activities, the draft consumer medicine information was considered satisfactory.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft product information and consumer medicine information documents should *not* be revised until the Delegates Overview has been received:

1. Safety considerations may be raised by the clinical evaluator through the consolidated section 31 request and/or the Clinical Evaluation Report. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.
2. It is recommended that the sponsor include the Important missing information: '*Use in lactating women*' as an Ongoing Safety Concern within the RMP when this document is next updated.
3. For the Important potential risk: '*Pregnancy issues*', Table 32: '*Detailed Action Plan for Important Potential Risk (Pregnancy issues)*', Section 2.4: '*Overview of study protocols for the pharmacovigilance plan*' and Section 2.6: '*Summary of outstanding actions, including milestones*' of the RMP did not provide any information in relation to the stated pregnancy registries. Consequently it is unclear what the status of these actions are and when and how the results of these actions will be reported. The sponsor should correct this oversight when this document is next updated. In addition at least draft protocols for these registries should be provided to the TGA for review if they are not yet ongoing.
4. The terminated, completed and ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless the stated milestones for these studies have already passed or are imminent. Consequently the sponsor should provide an update on the progress/results/analysis of these studies, and describe

how this information will be incorporated into the RMP when this document is next updated.

5. The Australian Specific Annex provided as Annex 9 of the RMP should provide details of the person responsible for the activities in the RMP within the sponsor company and will usually be the Australian pharmacovigilance contact person.
6. It is recommended that routine pharmacovigilance be used to monitor the Important missing information: '*Use in lactating women*' as a new Ongoing Safety Concern.
7. The sponsor's justification and conclusion that routine risk minimisation activities for all the specified Ongoing Safety Concerns are sufficient is acceptable, as the specified Ongoing Safety Concerns would not appear to warrant additional risk minimisation activities.
8. The sponsor's proposed application of routine risk minimisation activities would appear to be reasonable and therefore acceptable. It is also acknowledged that routine risk minimisation has already been proposed for the Important missing information: '*Use in lactating women*'.
9. In regard to the proposed routine risk minimisation activities, revisions to the draft product information were recommended to the Delegate but these are beyond the scope of this AusPAR.
10. In regard to the proposed routine risk minimisation activities, the draft consumer medicine information was considered satisfactory.

Sponsor response

1. TGA's comment has been noted.
2. The sponsor commits to include *Use in Lactating Women* as an Ongoing Safety Concern within the RMP when this document is next updated.
3. Detailed information has been provided on Important potential risk *Pregnancy issues* in the updated Risk Management Plan (RMP).
4. Updates on terminated, completed and ongoing studies have been included in the updated RMP.
5. The Australian Specific Annex provided as Annex 9 should provide details of the person responsible for the activities in the RMP within the sponsor company and will usually be the Australian pharmacovigilance contact person.

6-8 .The sponsor's justification and conclusion that routine risk management activities for all the specified Ongoing Safety Concerns are sufficient was considered acceptable, as the specified Ongoing Safety Concerns would not appear to warrant additional risk minimisation activities.

9. In regard to the proposed routine risk minimisation activities, a revision of the draft PI was recommended to the Delegate.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacology

A study investigating the PK of a single dose 100 mg dose of zonisamide in 36 White, Black or Asian adults was included in this submission. That study is described in the clinical evaluation report (CER). The results of that study do not suggest that race has a clinically significant effect on the PK of zonisamide.

Efficacy

A dose-ranging study, a pivotal efficacy study and an open, non-randomised extension of the dose-ranging study included efficacy data.

Study 304 was a double-blind, randomised, multicenter study to evaluate 3 dose levels of zonisamide (25, 100, and 300mg/day) as monotherapy in adult subjects with newly diagnosed epilepsy and complex partial seizures. This study is described in the CER. The primary endpoint (reaching the exit criteria) was defined as the time to the occurrence of either of these events after taking the first dose of the study drug:

- 2 complex partial seizures
- generalised tonic-clonic seizure.

A total of 169 subjects were randomised with 67 subjects continuing to EOS at Week 42. The percentage of subjects who reached a predefined exit criterion was lower in the 300-mg/day group (22.0%) than in the 25 mg and 100 mg/day groups (41.1% and 40.4%, respectively). However, this difference was not statistically significant in the safety population. A separate efficacy population was not defined. This study gave a general indication that 300 mg zonisamide would be more effective that the 25 mg and 100 mg daily doses in monotherapy for partial epilepsy. The extension of this study is discussed in the CER.

Study 310 is the pivotal study and is described the CER. This was a multicentre study to assess the efficacy of zonisamide compared to carbamazepine when given as monotherapy to newly diagnosed adult subjects with partial seizures by assessment of the 26 week seizure-free rate. Study 310 was a non-inferiority study with the non-inferiority margin (delta) a *relative* difference of 20% difference for the primary efficacy endpoint of the proportion of subjects that were seizure free for 26 weeks during the maintenance dose period. The *absolute* difference that was to be accepted as non-inferior was dependent on the proportion of subjects who were seizure-free for 26 weeks in the comparator group. Sample sizes were determined based on an assumed 60% of subjects given carbamazepine being seizure free for 26 weeks, giving an estimated absolute non-inferiority margin of 12%. The primary analysis was of the per-protocol population.

The study consisted of:

- A maximum 2-week screening period.
- A 4 week Titration Period: The starting dose was 100 mg/day zonisamide or 200 mg/day carbamazapine once daily in the evening. The dose was up-titrated every 2 weeks; to 200 mg/day zonisamide given once daily plus a daily placebo or 400 mg/day carbamazapine, given twice daily, and after 4 weeks to 300 mg/day zonisamide or 600 mg/day carbamazapine.

- A 26 to 78 week Flexible Dosing Period during which, if subjects experienced a seizure, their dose could be up-titrated a maximum of 2 times (up to a maximum dose of 400 mg/day zonisamide or 800 mg/day carbamazepine initially, then to a maximum of 500 mg/day zonisamide or 1200 mg/day carbamazapine. Down titration for AEs etc. was possible. \
- A 26 week Maintenance Period: Subjects seizure-free for 26 weeks entered the Maintenance Period and continued on a stable dose for a further 26 weeks.
- Subjects who completed the study (seizure-free for 26 weeks during the Maintenance Period) could continue randomised treatment with either zonisamide or carbamazepine in extension study E2090-E044-314. \

Otherwise:

- Up to 6 weeks Down-titration Period at a rate of 100 mg/week zonisamide or 200 mg/week carbamazepine until a zero dose was reached.

A total of 583 subjects were randomised and received treatment with 161 (57.1%) given zonisamide and 192 (63.8%) given carbamazepine completing the study. The groups were comparable with a mean of 2.6 months and 3.0 months respectively for since diagnosis for subjects given zonisamide or carbamazepine respectively. The majority of subjects in both groups had 2 or 3 seizures in the 12 months preceding study entry. Each group included similar proportions of subjects with simple partial seizures with or without motor signs, complex partial seizures, secondary generalized tonic-clonic seizures and generalized tonic-clonic seizures. Although subjects with generalized tonic-clonic seizures were permitted to enter the study, a documented EEG within 12 months of the Screening Visit, compatible with localization-related epilepsy (to exclude primary generalized epilepsy) was required. A total of 37 (13.2%) and 38 (12.7%) subjects given zonisamide and carbamazepine respectively with generalized tonic-clonic seizures were randomised. Mean doses of study medication given to subjects who had seizure-free periods of 26 weeks during the maintenance period are shown in the CER.

In the PP Population the proportion of subjects seizure-free for 6 months was 79.4% for ZNS and 83.7% for CBZ; the adjusted treatment difference was –4.5%, (95% CI: –12.2, 3.1). The lower limit of the CI narrowly exceeded the –12% margin prespecified in the protocol. For the ITT population the proportion of subjects seizure-free for 6 months was 69.4% for ZNS and 74.7% for CBZ; the adjusted treatment difference was –6.1% and the lower limit of the CI for the absolute difference for ZNS versus CBZ was −13.6%.

Secondary analyses included calculation of odds ratio for the seizure-free period and the 12 month seizure-free period. Subgroup analyses of seizure-free period by seizure type were also performed. These were not powered to determine non-inferiority however there was a consistent trend favouring carbamazepine in the majority of secondary efficacy assessments.

An additional subgroup analysis of the proportion of subjects seizure-free for 26 weeks that excluded subjects with generalized tonic-clonic seizures that had not been confirmed as local in origin was performed at the request of the TGA. Results were similar to that of the primary analysis group. For the PP population with confirmed local in origin seizures, the seizure freedom rates were 78.5% (153/195) for ZNS and 82.7% (172/208) for CBZ with adjusted difference -0.042 (95%CI -0.124; 0.040). The lower CI for the Relative Difference was 15%. This relative difference is accepted as not being of clinical significance by the ILAE. The sponsor did not provide results for the Intent-to-Treat (ITT) population with confirmed local in origin seizures.

Safety

The safety of the once daily regime has not been directly compared with the current twice daily regimens however given the half-life of zonisamide is about 60 hours, the evaluator did not consider that this is likely to alter the safety profile. The proposed monotherapy dose regimen gives a similar exposure to zonisamide as occurs with the approved adjuvant indication.

Adverse events associated with ZNS and CBZ in the pivotal study are shown in the CER. There were similar percentages of subjects with total adverse events (AEs), serious AEs and AEs leading to study withdrawal in subjects given either medication. There was one death on study, in a subject taking zonisamide. The cause of death was unexplained.

The major safety issues associated with zonisamide are:

- Central nervous system-related adverse events such as depression and psychosis, psychomotor slowing, difficulty with concentration, and speech or language problems and somnolence or fatigue. These include, as with other AEDs, an increased likelihood of suicidal thoughts.
- Serious immune based adverse reactions including rash, allergic reaction and major haematological disturbances including aplastic anaemia.
- Metabolic acidoisis
- Kidney stones
- Hyperthermia associated with oligohydrosis
- Pancreatitis
- Muscle pain and weakness
- Weight loss.

Zonisamide causes hyperchloremic, non-anion gap, metabolic acidosis, that is, decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase. Metabolic acidosis appears to be dose-dependent and can occur at doses as low as 25 mg daily.

The following information concerning metabolic acidosis was extracted from the US PI for Zonegran but has not to date been included in the Australian PI:

Some manifestations of acute or chronic metabolic acidosis include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated, metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis. Nephrolithiasis has been observed in the clinical development program in 4 % of adults treated with Zonegran, has also been detected by renal ultrasound in 8 % of paediatric treated patients who had at least one ultrasound prospectively collected, and was reported as an adverse event in 3 % (4/133) of paediatric patients.

Chronic, untreated metabolic acidosis may result in osteomalacia (referred to as rickets in paediatric patients) and/or osteoporosis with an increased risk for fracture. Of potential relevance, zonisamide treatment was associated with reductions in serum phosphorus and increases in serum alkaline phosphatase, changes that may be related to metabolic acidosis and osteomalacia. Chronic, untreated metabolic acidosis in paediatric patients may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of zonisamide on growth and bone-related sequelae has not been systematically investigated.

The US PI also notes the bicarbonate results from three clinical trials for indications which have not been approved in the USA*:*

a placebo-controlled trial for migraine prophylaxis in adults, a controlled trial for monotherapy in epilepsy in adults, and an open label trial for adjunctive treatment of epilepsy in paediatric patients (3-16 years). In adults, mean serum bicarbonate reductions ranged from approximately 2 mEq/L at daily doses of 100 mg to nearly 4 mEq/L at daily doses of 300 mg. In paediatric patients, mean serum bicarbonate reductions ranged from approximately 2 mEq/L at daily doses from above 100 mg up to 300 mg, to nearly 4 mEq/L at daily doses from above 400 mg up to 600 mg.

In two controlled studies in adults, the incidence of a persistent treatment-emergent decrease in serum bicarbonate to less than 20 mEq/L (observed at 2 or more consecutive visits or the final visit) was dose-related at relatively low zonisamide doses. In the monotherapy trial of epilepsy, the incidence of a persistent treatment-emergent decrease in serum bicarbonate was 21% for daily zonisamide doses of 25 mg or 100 mg, and was 43% at a daily dose of 300 mg. In a placebo-controlled trial for prophylaxis of migraine, the incidence of a persistent treatment-emergent decrease in serum bicarbonate was 7% for placebo, 29% for 150 mg daily, and 34% for 300 mg daily. The incidence of persistent markedly abnormally low serum bicarbonate (decrease to less than 17 mEq/L and more than 5 mEq/L from a pretreatment value of at least 20 mEq/L in these controlled trials was 2% or less.

In the paediatric study, the incidence of persistent, treatment-emergent decreases in serum bicarbonate to levels less than 20 mEq/L was 52% at doses up to 100 mg daily, was 90% for a wide range of doses up to 600 mg daily, and generally appeared to increase with higher doses. The incidence of a persistent markedly abnormally low serum bicarbonate value was 4 % at doses up to 100 mg daily, was 18% for a wide range of doses up to 600 mg daily, and generally appeared to increase with higher doses. Some patients experienced moderately severe serum bicarbonate decrements down to a level as low as 10 mEq/L. The relatively high frequencies of varying severities of metabolic acidosis observed in this study of paediatric patients (compared to the frequency and severity observed in various clinical trial development programs in adults) suggest that paediatric patients may be more likely to develop metabolic acidosis than adults.

There is insufficient detail in the US PI to determine if the studies reported in the US PI were among those included with this submission. The reporting of serum bicarbonate levels is somewhat different. In the pivotal study (310) supporting this submission, the incidence of patients with reductions from baseline in serum bicarbonate of >3.5 mmol/L was 121/237 (51.1%) for patients given zonisamide and 45/259 (17.4%) for patients given carbamazepine. Reductions from baseline of ≥ 6 mmol/L or to ≤ 16 mmol/L were seen in 9 (3.8%) of subjects given zonisamide and in 1 (0.4%) given carbamazepine.

The incidence of nephrolithiasis reported in the US PI is considerably more specific than the figure presented in the current Australian PI. The current PI notes that >1% of subjects given zonisamide in open label clinical trials developed nephrolithiasis. The US PI notes the following:

Among 991 patients treated during the development of ZONEGRAN, 40 patients (4.0%) with epilepsy receiving ZONEGRAN developed clinically possible or confirmed kidney stones (e.g. clinical symptomatology, sonography, etc.), a rate of 34 per 1000 patient-years of exposure (40 patients with 1168 years of exposure). Of these, 12 were symptomatic, and 28 were described as possible kidney stones based on sonographic detection. In nine patients, the diagnosis was confirmed by a passage of a stone or by a definitive sonographic finding. The rate of occurrence of kidney stones was 28.7 per 1000 patient-years of exposure in the first six months, 62.6 per 1000 patient-years of exposure between 6 and 12 months, and 24.3 per 1000 patient-years of exposure after 12 months of use.

Weight loss was noted in the monotherapy clinical trial. The RMP evaluator recommended amending the PI to include the incidences of weight loss ≥10% and ≥ 20% of baseline were 13.2% and 0.7% respectively. These figures have been included in the draft PI.

Zonisamide is metabolised partly by cytochrome P450 isozyme CYP3A4 (reductive cleavage) and also by N-acetyl-transferases and conjugation with glucuronic acid; therefore, substances that can induce or inhibit these enzymes may affect the pharmacokinetics of zonisamide. Exposure to zonisamide is lower in epileptic patients receiving CYP3A4-inducing agents such as phenytoin, carbamazepine and phenobarbitone. These effects are unlikely to be of clinical significance when zonisamide is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing antiepileptic or other medicinal products are withdrawn, dose adjusted or introduced, an adjustment of the zonisamide dose may be required.

Risk management plan

The RMP evaluator considered the RMP was supportive to the submission and the implementation of a RMP satisfactory to the stage be imposed as a condition of registration. Amendments to the PI and RMP were requested.

Risk-benefit analysis

Delegate considerations

The choice of non-inferiority margin for the difference in proportion of subjects with at least a 26 week seizure free period on maintenance therapy was required to be justified by the sponsor. The sponsor initially selected an absolute margin of -12%, that is, the 95%CI for the between treatment group difference had to be no greater than 12% favouring carbamazepine. That margin was chosen assuming that the proportion seizure-free to 26 weeks would be in the region of 60%. The basis of selection of this margin was an International League Against Epilepsy (ILAE) paper in which a *relative* difference of ≤ 20% in proportion seizure-free to 26 weeks was considered not to be clinically significant. The sponsor also sought regulatory advice. The lower bound of the 95% CI of the relative difference (−14.7%) for the PP population was within the relative 20% margin that has been previously accepted as a noninferiority margin in publications supported by the ILAE.

The Delegate considered that efficacy of zonisamide as a monotherapy agent for newly diagnosed individuals with partial seizures has been adequately demonstrated. The efficacy studies in this submission also support once daily dosing for monotherapy zonisamide. The dose regimen, including the titration schedule, used in the pivotal efficacy study was the same as has been proposed for registration. The dosage schedule incorporated titration and the additive value of increasing the dose to efficacy was examined, supporting the proposed dose range.

The primary issue for this submission is whether a medicine with the safety profile of zonisamide is acceptable as a first line treatment for newly diagnosed individuals with partial epilepsy.

Of particular concern is the extent to which mild persistent metabolic acidosis may increase the likelihood of osteoporosis and/or osteomalacia and nephrolithiasis. This has not been adequately examined.

The Delegate considered that would be possible to manage the risks of many of the adverse effects associated with zonisamide with regular assessments of serum bicarbonate and bone density and by advising patients to report symptoms consistent

with nephrolithiasis, fevers, skin rashes and psychiatric symptoms. Adjustments to the zonisamide dose may also be required if patients are given concomitant medicines that inhibit or induce CYP3A4. Newly diagnosed patients being considered for zonisamide treatment would require careful selection. Individuals in whom compliance with monitoring may be an issue, those with renal impairment, a history of unexplained rashes, hypersensitivity, osteoporosis or nephrolithiasis would be poor candidates for this treatment.

The general advice of the ACPM was requested. The Committee was also requested to provide advice on the following specific issues:

- Please advice on the clinical importance of definitely excluding patients with generalized epilepsy from calculations of efficacy, noting that the sponsor did not provide efficacy results for the ITT population with confirmed local in origin seizures.
- Does the Committee consider the relative difference of 20% is an acceptable non-inferiority margin for the 26 week seizure free period used in the pivotal study?
- Does the Committee consider that the 26 week seizure free interval is an acceptable primary endpoint for the pivotal study?
- Zonisamide has many safety issues associated with its use. Does the Committee consider these issues are of sufficient concern such that other AEDs with fewer and/or different safety issues should be trialled and found to be unsatisfactory due to intolerance or safety reasons prior to use of zonisamide as monotherapy? If that is the case, can the Committee identify these alternative AEDs? Note that the efficacy of monotherapy zonisamide has not been examined in a population with inadequate control of seizures with alternative AEDs.
- The sponsor has not proposed routine monitoring of serum bicarbonate or bone density. Does the Committee consider this is required for all patients or for a subgroup of patients taking zonisamide? If this is the case can the Committee recommend a monitoring regimen?

Response from sponsor

Sponsor's comment on evaluations

Clinical trial

Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy: Add a more comprehensive description of the patients enrolled in this study to the first paragraph and both the PP & ITT results for the primary efficacy endpoint included in Table 1.

The sponsor agreed with the recommendations and has included additional information with respect to 12-month seizure freedom data and also 6-month seizure freedom data for the seizure sub-types (6-month seizure freedom-PP population) analysed. This brings the Australian product information into line with section 5.1 of the EU Summary of Product Characteristics. The additional information is underlined.

Efficacy of zonisamide as monotherapy was established in a double-blind, parallel group, noninferiority comparison to carbamazepine prolonged release (PR) in 583 adult subjects with newly diagnosed partial seizures with or without secondary generalized tonic-clonic seizures. Subjects were randomised to carbamazepine PR (N=301; 600 to 1200 mg/day, twice-daily) or zonisamide (N=282; 300 to 500 mg/day, once-daily), and received treatment for a duration of up to 24 months depending on response.

Subjects were titrated to the initial target dose of 600 mg carbamazepine or 300 mg of zonisamide. Subjects who experienced a seizure were titrated to the next target dose, that

is, 800 mg carbamazepine or 400 mg of zonisamide. Subjects who experienced a further seizure were titrated to the maximal target dose of 1200 mg carbamazepine or 500 mg zonisamide. Subjects who were seizure-free for 26 weeks at a target dose level continued on this dose for another 26 weeks. Six-month seizure freedom was achieved in 79.4% of zonisamide-treated subjects and 83.7% of carbamazepine PR treated subjects (in the per protocol population). The adjusted absolute difference between treatments was -4.5% (95% CI: -12.2%, 3.1%). More than half of the subjects remained seizure-free at 12 months (67.6%% zonisamide versus 74.7%). Main outcomes of this study are presented in Table 8 below.

Table 8. Efficacy results for Monotherapy Study 310

	Zonisamide	Carbamazepine		
n (ITT population)*	281	300		
Six months seizure freedom			Diff	$CI_{95\%}$
PP-population**	79.4%	83.7%	-4.5%	-12.2% ; 3.1%
ITT-population	69.4%	74.7%	-6.1%	-13.6% ; 1.4%
≤ 4 seizures during 3 month baseline period	71.7%	75.7%	-4.0%	-11.7% ; 3.7%
> 4 seizures during 3 month baseline period	52.9%	68.9%	- 15.9%	-37.5% ; 5.6%
Twelve months seizure freedom				
PP-population	67.6%	74.7%	-7.9%	- 17.2% ; 1.5%
ITT-population	55.9%	62.3%	-7.7%	- 16.1% ; 0.7%
≤ 4 seizures during 3 month baseline period	57.4%	64.7%	-7.2%	-15.7% ; 1.3%
> 4 seizures during 3 month baseline period	44.1%	48.9%	-4.8%	-26.9% ; 17.4%
Seizure Sub-type (6 month seizure freedom-PP population)				
All partial	76.4%	86.0%	-9.6%	-19.2% ; 0.0%
Simple partial	72.3%	75.0%	-2.7%	-20.0% ; 14.7%
Complex partial	76.9%	93.0%	- 16.1%	-26.3% ; -5.9%
All generalized Tonic-Clonic	78.9%	81.6%	-2.8	-11.5% ; 6.0%
Secondary Tonic-Clonic	77.4%	80.0%	-2.6%	-12.4% ; 7.1%
Generalized Tonic-Clonic	85.7%	92.0%	-6.3%	-23.1% ; 10.5%

PP = Per Protocol Population; ITT = Intent To Treat Population
**Two subjects withdrew consent after randomization and before taking study medication. The Safety Population therefore comprised 581 subjects.*
***Primary endpoint*

Other changes to the draft PI

With respect to other changes to the draft PI proposed by the TGA, the sponsor generally agreed with the recommendations proposed by the Delegate and submitted revised text.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered these products to have an overall marginal positive benefit–risk profile only for the revised indication;

> *Zonisamide is indicated as monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy who are intolerant to other agents or where other agents are contraindicated.*

In making this recommendation the ACPM noted that the clinical trial data were based on establishing efficacy and safety for the population of treatment naïve patients.

The ACPM expressed concern about the significant adverse reaction profile for these products, specifically in the potential interactions with other products, the incidence of metabolic acidosis and kidney stones and the importance for baseline and routine monitoring in the management and safe use of these products. The ACPM therefore did not support the use of these products as first line therapy and has recommended a revised indication.

The ACPM recommended amendments to the Product Information (PI) and Consumer Medicine Information (CMI) which are beyond the scope of this AusPAR.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zonegran (zonisamide) 25 mg, 50 mg and 100 mg capsule blister packs for oral administration, indicated for:

> *Zonisamide is indicated as monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy who are intolerant to other agents or where other agents are contraindicated.*

Specific conditions applying to these therapeutic goods

The European Risk management Plan identified as Version 7.0, dated 30 March 2012, to be revised as specified in the sponsor's correspondence dated 9 November 2012 including an updated Australian Specific Annex (ASA), must be implemented.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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Reference/Publication #