ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Zonegran 25 mg hard capsules.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each Zonegran hard capsule contains 25 mg of zonisamide.

For excipients, see Section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.

A white opaque body and a white opaque cap printed with a logo and “ZONEGRAN 25” in black.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Zonegran is indicated as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

4.2 **Posology and method of administration**

Zonegran hard capsules are for oral use.

**Adults**

Zonegran must be added to existing therapy and the dose should be titrated on the basis of clinical effect. Doses of 300 mg to 500 mg per day have been shown to be effective, though some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

The recommended initial daily dose is 50 mg in two divided doses. After one week the dose may be increased to 100 mg daily and thereafter the dose may be increased at one weekly intervals, in increments of up to 100 mg.

Use of two weekly intervals should be considered for patients with renal or hepatic impairment and patients not receiving CYP3A4-inducing agents (see Section 4.5).

Zonegran can be administered once or twice daily after the titration phase.

**Elderly**

Caution should be exercised at initiation of treatment in elderly patients as there is limited information on the use of Zonegran in these patients. Prescribers should also take account of the safety profile of Zonegran (see Section 4.8).

**Children and adolescents**

The safety and effectiveness in children and adolescents under 18 years have not been established. Therefore use in these patients is not recommended.

**Patients with renal impairment**

Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients and a slower titration of Zonegran might be required. Since zonisamide and its
metabolites are excreted renally, it should be discontinued in patients who develop acute renal failure or where a clinically significant sustained increase in serum creatinine is observed.

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 < 20 ml/min.

**Patients with hepatic impairment**

Use in patients with hepatic impairment has not been studied. Therefore use in patients with severe hepatic impairment is not recommended. Caution must be exercised in treating patients with mild to moderate hepatic impairment, and a slower titration of Zonegran may be required.

**Effect of food**

Zonegran may be taken with or without food (see Section 5.2).

**Withdrawal of Zonegran**

When Zonegran treatment is to be discontinued, it should be withdrawn gradually. In clinical studies, dose reductions of 100 mg at weekly intervals have been used with concurrent adjustment of other antiepileptic drug doses.

**4.3 Contraindications**

Hypersensitivity to zonisamide, to any of the excipients or to sulphonamides.

**4.4 Special warnings and special precautions for use**

In accordance with current clinical practice, discontinuation of Zonegran in patients with epilepsy must be accomplished by gradual dose reduction, to reduce the possibility of seizures on withdrawal. There are insufficient data for the withdrawal of concomitant antiepileptic medications once seizure control with Zonegran has been achieved in the add-on situation, in order to reach monotherapy with Zonegran. Therefore withdrawal of concomitant anti-epileptic agents must be undertaken with caution.

Zonegran is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune based adverse reactions that have been associated with medicinal products containing a sulphonamide group include rash, allergic reaction and major haematological disturbances including aplastic anaemia.

Serious rashes have occurred in association with Zonegran therapy, including isolated cases of Stevens-Johnson syndrome.

Consideration must be given to discontinuing Zonegran in patients who develop an otherwise unexplained rash. All patients who develop a rash while taking Zonegran must be closely supervised, with additional levels of caution applied to those patients receiving concomitant antiepileptic agents that may independently induce skin rashes.

Isolated cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

Kidney stones have occurred in patients treated with Zonegran. Zonegran should be used with caution in patients who have risk factors for nephrolithiasis, including prior stone formation, a family history of nephrolithiasis and hypercalcuria. 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. 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 patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate, as there are insufficient data to rule out a pharmacodynamic interaction (see Section 4.5).

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. 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.

In patients taking Zonegran who develop the clinical signs and symptoms of pancreatitis, it is recommended that pancreatic lipase and amylase levels are monitored. If pancreatitis is evident, in the absence of another obvious cause, it is recommended that discontinuation of Zonegran be considered and appropriate treatment initiated.

In patients taking Zonegran, in whom severe muscle pain and/or weakness develop either in the presence or absence of a fever, it is recommended that markers of muscle damage be assessed, including serum creatine phosphokinase and aldolase levels. If elevated, in the absence of another obvious cause such as trauma or grand mal seizures, it is recommended that Zonegran discontinuation be considered and appropriate treatment initiated.

Women of child-bearing potential must use adequate contraception during treatment with Zonegran and for one month after discontinuation (see section 4.6). Physicians treating patients with Zonegran should try to ensure that appropriate contraception is used, and should use clinical judgement when assessing whether OCs, or the doses of the OC components, are adequate based on the individual patient’s clinical situation.

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

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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Zonegran on cytochrome P450 enzymes.

In vitro studies using human liver microsomes show no or little (<25%) inhibition of cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4 at zonisamide levels approximately two-fold or greater than clinically relevant unbound serum concentrations. Therefore Zonegran is not expected to affect the pharmacokinetics of other medicinal products via cytochrome P450-mediated mechanisms, as demonstrated for carbamazepine, phenytoin, ethinylestradiol and desipramine in vivo.

Potential for Zonegran to affect other medicinal products

Anti-epileptic drugs
In epileptic patients, steady-state dosing with Zonegran resulted in no clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, or sodium valproate.
**Oral contraceptives**
In clinical studies in healthy subjects, steady-state dosing with Zonegran did not affect serum concentrations of ethinylestradiol or norethisterone in a combined oral contraceptive.

**Carbonic anhydrase inhibitors**
There are insufficient data to rule out possible pharmacodynamic interactions with carbonic anhydrase inhibitors such as topiramate.

**Potential medicinal product interactions affecting Zonegran**

In clinical studies co-administration of lamotrigine had no apparent effect on zonisamide pharmacokinetics. The combination of Zonegran with other medicinal products that may lead to urolithiasis may enhance the risk of developing kidney stones; therefore the concomitant administration of such medicinal products should be avoided.

Zonisamide is metabolised partly by 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:

- **Enzyme Induction:** 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 Zonegran is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing anti-epileptic or other medicinal products are withdrawn, dose adjusted or introduced, an adjustment of the Zonegran dose may be required. Rifampicin is a potent CYP3A4 inducer. If co-administration is necessary, the patient should be closely monitored and the dose of Zonegran and other CYP3A4 substrates adjusted as needed.

- **CYP3A4 Inhibition:** Based upon clinical data, known specific and non-specific CYP3A4 inhibitors appear to have no clinically relevant effect on zonisamide pharmacokinetic exposure parameters. Steady-state dosing of either ketoconazole (400 mg/day) or cimetidine (1200 mg/day) had no clinically relevant effects on the single-dose pharmacokinetics of zonisamide given to healthy subjects. Therefore, modification of Zonegran dosing should not be necessary when co-administered with known CYP3A4 inhibitors.

**4.6 Pregnancy and lactation**

Zonegran must not be used during pregnancy unless clearly necessary and only if the potential benefit is considered to justify the risk to the foetus. The need for anti-epileptic treatment should be reviewed in patients planning to become pregnant. If Zonegran is prescribed, careful monitoring is recommended.

Specialist advice should be given to women who are likely to become pregnant in order to consider the optimal treatment during pregnancy. Women of childbearing potential should be counselled to use contraception during treatment with Zonegran, and for one month after discontinuation.

There are no adequate data from the use of Zonegran in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3).

No sudden discontinuation of anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child.

Zonisamide is excreted in human milk; the concentration in breast milk is similar to maternal plasma. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zonegran therapy. Due to the long retention time of zonisamide in the body, breast-feeding must not be resumed until one month after Zonegran therapy is completed.
4.7 Effects on ability to drive and use machines

Some patients may experience drowsiness or difficulty with concentration, particularly early in treatment or after a dose increase. Patients must be advised to exercise caution during activities requiring a high degree of alertness, e.g., driving or operating machinery.

4.8 Undesirable effects

Zonegran has been administered to over 1,200 patients in clinical studies, more than 400 of whom received Zonegran for at least 1 year. In addition there has been extensive post-marketing experience with zonisamide in Japan since 1989 and in the USA since 2000.

The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Adverse reactions associated with Zonegran obtained from clinical studies and post-marketing surveillance are tabulated below. The frequencies are arranged according to the following scheme:

- very common > 1/10
- common > 1/100 < 1/10
- uncommon > 1/1,000 < 1/100
- rare > 1/10,000 < 1/1,000
- very rare < 1/10,000 including isolated reports

<table>
<thead>
<tr>
<th>System Organ Class (MedDRA terminology)</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Very Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestation</td>
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<td>Pneumonia</td>
<td>Urinary tract infection</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
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<td></td>
<td>Agranulocytosis Aplastic anaemia Leucocytosis Leucopenia Lymphadenopathy Pancytopenia, Thrombocytopenia</td>
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<td>Immune system disorders</td>
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<td>Hypersensitivity</td>
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<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td>Hypokalaemia</td>
<td>Metabolic acidosis</td>
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<td>Psychiatric Disorders</td>
<td>Agitation, Irritability, Confusional state, Depression</td>
<td>Psychotic disorder</td>
<td>Hallucination, Insomnia, Suicidal ideation</td>
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<tr>
<td>Nervous system disorders</td>
<td>Ataxia, Dizziness, Memory impairment, Somnolence</td>
<td>Disturbance in attention, Speech disorder</td>
<td>Convulsion, Amnesia, Coma, Grand mal seizure, Myasthenic syndrome, Neuroleptic malignant syndrome</td>
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<tr>
<td>Eye disorders</td>
<td>Diplopia</td>
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6
<table>
<thead>
<tr>
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<th>Very Common</th>
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</tr>
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<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Dyspnoea</td>
<td>Pneumonia aspiration</td>
<td>Respiratory disorder</td>
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<td><strong>Gastrointestinal disorders</strong></td>
<td>Abnormal pain</td>
<td>Diarrhoea</td>
<td>Nausea</td>
<td>Vomiting</td>
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<td><strong>Hepatobiliary disorders</strong></td>
<td>Cholecystitis</td>
<td>Cholelithiasis</td>
<td>Hepatocellular damage</td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Rash</td>
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<td>Anhidrosis</td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
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<td>Rhabdomyolysis</td>
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<td><strong>Renal and urinary disorders</strong></td>
<td>Calculus urinary</td>
<td>Nephrolithiasis</td>
<td></td>
<td>Hydronephrosis</td>
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<td><strong>General disorders and administration site conditions</strong></td>
<td>Pyrexia</td>
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<td><strong>Investigations</strong></td>
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<td>Blood creatine phosphokinase increased</td>
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<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td></td>
<td></td>
<td>Heat stroke</td>
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</tbody>
</table>

In addition there have been isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP) receiving Zonegran.

### 4.9 Overdose

There have been cases of accidental and intentional overdose in adult and paediatric patients. In some cases, the overdoses were asymptomatic, particularly where emesis or lavage was prompt. In other cases, the overdose was followed by symptoms such as somnolence, nausea, gastritis, nystagmus, myoclonus, coma, bradycardia, reduced renal function, hypotension and respiratory depression. A very high plasma concentration of 100.1 µg/ml zonisamide was recorded approximately 31 hours after a patient took an overdose of Zonegran and clonazepam; the patient became comatose and had respiratory depression, but recovered consciousness five days later and had no sequelae.

**Treatment**

No specific antidotes for Zonegran overdose are available. Following a suspected recent overdose, emptying the stomach by gastric lavage or by induction of emesis may be indicated with the usual precautions to protect the airway. General supportive care is indicated, including frequent monitoring.
of vital signs and close observation. Zonisamide has a long elimination half-life so its effects may be persistent. Although not formally studied for the treatment of overdose, haemodialysis reduced plasma concentrations of zonisamide in a patient with reduced renal function, and may be considered as treatment of overdose if clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

Zonisamide is benzisoxazole derivative. It is an anti-epileptic medicine with weak carbonic anhydrase activity in-vitro. It is chemically unrelated to other anti-epileptic agents.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, ATC code: N03A X15

Efficacy has been demonstrated with Zonegran in 4 double-blind, placebo-controlled studies of periods of up to 24 weeks with either once or twice daily dosing. These studies show that the median reduction in partial seizure frequency is related to Zonegran dose with sustained efficacy at doses of 300-500 mg per day.

The anticonvulsant activity of zonisamide has been evaluated in a variety of models, in several species with induced or innate seizures, and zonisamide appears to act as a broad-spectrum anti-epileptic in these models. Zonisamide prevents maximal electroshock seizures and restricts seizure spread, including the propagation of seizures from cortex to sub-cortical structures and suppresses epileptogenic focus activity. Unlike phenytoin and carbamazepine however, zonisamide acts preferentially on seizures originating in the cortex.

The mechanism of action of zonisamide is not fully elucidated, but it appears to act on voltage-sensitive sodium and calcium channels, thereby disrupting synchronised neuronal firing, reducing the spread of seizure discharges and disrupting subsequent epileptic activity. Zonisamide also has a modulatory effect on GABA-mediated neuronal inhibition.

5.2 Pharmacokinetic properties

Absorption

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

Zonisamide AUC and C\text{max} values increased almost linearly after single dose over the dose range of 100-800 mg and after multiple doses over the dose range of 100-400 mg once daily. The increase at steady state was 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. Slightly greater than expected accumulation occurs relative to single dosing.

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 – 1.7 l/kg in adults indicating that zonisamide is extensively distributed to tissues. Erythrocyte/plasma ratios are about 15 at low concentrations and about 3 at higher 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. 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 at steady-state after oral administration is about 0.70 l/h and the terminal elimination half-life is about 60 hours in the absence of CYP3A4 inducers. The elimination half-life was independent of dose and not affected by repeat administration. Fluctuation in serum or plasma concentrations over a dosing interval is low (< 30 %). The main route of excretion of zonisamide metabolites and unchanged drug is via the urine. Renal clearance of unchanged zonisamide is relatively low (approximately 3.5 ml/min); about 15 - 30 % of the dose is eliminated unchanged.

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 <20 ml/min (see also section 4.2.).

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 12 mg/kg daily, in divided doses, are similar to those observed in adults, after adjustment for bodyweight.

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

Findings not observed in clinical studies, but seen in the dog at exposure levels similar to clinical use, were liver changes (enlargement, dark-brown discolouration, mild hepatocyte enlargement with concentric lamellar bodies in the cytoplasm and cytoplasmic vacuolation) associated with increased metabolism.

Zonisamide was not genotoxic and has no carcinogenic potential.

Zonisamide caused developmental abnormalities in mice, rats, and dogs, and was embryo lethal in monkeys, when administered during the period of organogenesis at zonisamide dosage and maternal plasma levels similar to or lower than therapeutic levels in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule contents:
Microcrystalline cellulose
Hydrogenated vegetable oil
Sodium laurilsulfate.

Capsule shells:
Gelatin
Titanium dioxide (E171)
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
PVC/PCTFE/aluminium blisters, packs of 14 and 56 hard capsules.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling
No special requirements.

7. MARKETING AUTHORIZATION HOLDER
Eisai Limited
3 Shortlands
London
W6 8EE
United Kingdom

8. MARKETING AUTHORIZATION NUMBER(S)

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

10. DATE OF REVISION OF THE TEXT
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- Enzyme Induction: 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 Zonegran is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing anti-epileptic or other medicinal products are withdrawn, dose adjusted or introduced, an adjustment of the Zonegran dose may be required. Rifampicin is a potent CYP3A4 inducer. If co-administration is necessary, the patient should be closely monitored and the dose of Zonegran and other CYP3A4 substrates adjusted as needed.

- CYP3A4 Inhibition: Based upon clinical data, known specific and non-specific CYP3A4 inhibitors appear to have no clinically relevant effect on zonisamide pharmacokinetic exposure parameters. Steady-state dosing of either ketoconazole (400 mg/day) or cimetidine (1200 mg/day) had no clinically relevant effects on the single-dose pharmacokinetics of zonisamide given to healthy subjects. Therefore, modification of Zonegran dosing should not be necessary when co-administered with known CYP3A4 inhibitors.

4.6 Pregnancy and lactation
Zonegran must not be used during pregnancy unless clearly necessary and only if the potential benefit is considered to justify the risk to the foetus. The need for anti-epileptic treatment should be reviewed in patients planning to become pregnant. If Zonegran is prescribed, careful monitoring is recommended.

Specialist advice should be given to women who are likely to become pregnant in order to consider the optimal treatment during pregnancy. Women of childbearing potential should be counselled to use contraception during treatment with Zonegran, and for one month after discontinuation.

There are no adequate data from the use of Zonegran in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3).

No sudden discontinuation of anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child.

Zonisamide is excreted in human milk; the concentration in breast milk is similar to maternal plasma. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zonegran therapy. Due to the long retention time of zonisamide in the body, breast-feeding must not be resumed until one month after Zonegran therapy is completed.
4.7 Effects on ability to drive and use machines

Some patients may experience drowsiness or difficulty with concentration, particularly early in treatment or after a dose increase. Patients must be advised to exercise caution during activities requiring a high degree of alertness, e.g., driving or operating machinery.

4.8 Undesirable effects

Zonegran has been administered to over 1,200 patients in clinical studies, more than 400 of whom received Zonegran for at least 1 year. In addition there has been extensive post-marketing experience with zonisamide in Japan since 1989 and in the USA since 2000.

The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Adverse reactions associated with Zonegran obtained from clinical studies and post-marketing surveillance are tabulated below. The frequencies are arranged according to the following scheme:

- very common > 1/10
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<td>Suicidal ideation</td>
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<td>Blood creatine phosphokinase increased Blood urea increased Liver function tests abnormal</td>
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<tr>
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</table>

In addition there have been isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP) receiving Zonegran.

### 4.9 Overdose

There have been cases of accidental and intentional overdose in adult and paediatric patients. In some cases, the overdoses were asymptomatic, particularly where emesis or lavage was prompt. In other cases, the overdose was followed by symptoms such as somnolence, nausea, gastritis, nystagmus, myoclonus, coma, bradycardia, reduced renal function, hypotension and respiratory depression. A very high plasma concentration of 100.1 µg/ml zonisamide was recorded approximately 31 hours after a patient took an overdose of Zonegran and clonazepam; the patient became comatose and had respiratory depression, but recovered consciousness five days later and had no sequelae.

**Treatment**

No specific antidotes for Zonegran overdose are available. Following a suspected recent overdose, emptying the stomach by gastric lavage or by induction of emesis may be indicated with the usual precautions to protect the airway. General supportive care is indicated, including frequent monitoring
of vital signs and close observation. Zonisamide has a long elimination half-life so its effects may be persistent. Although not formally studied for the treatment of overdose, haemodialysis reduced plasma concentrations of zonisamide in a patient with reduced renal function, and may be considered as treatment of overdose if clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

Zonisamide is benzisoxazole derivative. It is an anti-epileptic medicine with weak carbonic anhydrase activity in-vitro. It is chemically unrelated to other anti-epileptic agents.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, ATC code: N03A X15

Efficacy has been demonstrated with Zonegran in 4 double-blind, placebo-controlled studies of periods of up to 24 weeks with either once or twice daily dosing. These studies show that the median reduction in partial seizure frequency is related to Zonegran dose with sustained efficacy at doses of 300-500 mg per day.

The anticonvulsant activity of zonisamide has been evaluated in a variety of models, in several species with induced or innate seizures, and zonisamide appears to act as a broad-spectrum anti-epileptic in these models. Zonisamide prevents maximal electroshock seizures and restricts seizure spread, including the propagation of seizures from cortex to sub-cortical structures and suppresses epileptogenic focus activity. Unlike phenytoin and carbamazepine however, zonisamide acts preferentially on seizures originating in the cortex.

The mechanism of action of zonisamide is not fully elucidated, but it appears to act on voltage-sensitive sodium and calcium channels, thereby disrupting synchronised neuronal firing, reducing the spread of seizure discharges and disrupting subsequent epileptic activity. Zonisamide also has a modulatory effect on GABA-mediated neuronal inhibition.

5.2 Pharmacokinetic properties

Absorption

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

Zonisamide AUC and C\text{max} values increased almost linearly after single dose over the dose range of 100-800 mg and after multiple doses over the dose range of 100-400 mg once daily. The increase at steady state was 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. Slightly greater than expected accumulation occurs relative to single dosing.

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 – 1.7 l/kg in adults indicating that zonisamide is extensively distributed to tissues. Erythrocyte/plasma ratios are about 15 at low concentrations and about 3 at higher 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. 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 at steady-state after oral administration is about 0.70 l/h and the terminal elimination half-life is about 60 hours in the absence of CYP3A4 inducers. The elimination half-life was independent of dose and not affected by repeat administration. Fluctuation in serum or plasma concentrations over a dosing interval is low (< 30 %). The main route of excretion of zonisamide metabolites and unchanged drug is via the urine. Renal clearance of unchanged zonisamide is relatively low (approximately 3.5 ml/min); about 15 - 30 % of the dose is eliminated unchanged.

**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 <20 ml/min (see also section 4.2.).

*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 12 mg/kg daily, in divided doses, are similar to those observed in adults, after adjustment for bodyweight.

**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

Findings not observed in clinical studies, but seen in the dog at exposure levels similar to clinical use, were liver changes (enlargement, dark-brown discolouration, mild hepatocyte enlargement with concentric lamellar bodies in the cytoplasm and cytoplasmic vacuolation) associated with increased metabolism.

Zonisamide was not genotoxic and has no carcinogenic potential.

Zonisamide caused developmental abnormalities in mice, rats, and dogs, and was embryo-lethal in monkeys, when administered during the period of organogenesis at zonisamide dosage and maternal plasma levels similar to or lower than therapeutic levels in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule contents:
Microcrystalline cellulose
Hydrogenated vegetable oil
Sodium laurilsulfate.

Capsule shells:
Gelatin
Titanium dioxide (E171)
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
PVC/PCTFE/aluminium blisters, packs of 56 hard capsules.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Eisai Limited
3 Shortlands
London
W6 8EE
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

Zonegran 100 mg hard capsules.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each Zonegran hard capsule contains 100 mg of zonisamide.

For excipients, see Section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.

A white opaque body and a red opaque cap printed with a logo and “ZONEGRAN 100” in black.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Zonegran is indicated as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

4.2 **Posology and method of administration**

Zonegran hard capsules are for oral use.

**Adults**

Zonegran must be added to existing therapy and the dose should be titrated on the basis of clinical effect. Doses of 300 mg to 500 mg per day have been shown to be effective, though some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

The recommended initial daily dose is 50 mg in two divided doses. After one week the dose may be increased to 100 mg daily and thereafter the dose may be increased at one weekly intervals, in increments of up to 100 mg.

Use of two weekly intervals should be considered for patients with renal or hepatic impairment and patients not receiving CYP3A4-inducing agents (see Section 4.5).

Zonegran can be administered once or twice daily after the titration phase.

**Elderly**

Caution should be exercised at initiation of treatment in elderly patients as there is limited information on the use of Zonegran in these patients. Prescribers should also take account of the safety profile of Zonegran (see Section 4.8).

**Children and adolescents**

The safety and effectiveness in children and adolescents under 18 years have not been established. Therefore use in these patients is not recommended.

**Patients with renal impairment**

Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients and a slower titration of Zonegran might be required. Since zonisamide and its
metabolites are excreted renally, it should be discontinued in patients who develop acute renal failure or where a clinically significant sustained increase in serum creatinine is observed.

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 < 20 ml/min.

**Patients with hepatic impairment**

Use in patients with hepatic impairment has not been studied. Therefore use in patients with severe hepatic impairment is not recommended. Caution must be exercised in treating patients with mild to moderate hepatic impairment, and a slower titration of Zonegran may be required.

**Effect of food**

Zonegran may be taken with or without food (see Section 5.2).

**Withdrawal of Zonegran**

When Zonegran treatment is to be discontinued, it should be withdrawn gradually. In clinical studies, dose reductions of 100 mg at weekly intervals have been used with concurrent adjustment of other antiepileptic drug doses.

### 4.3 Contraindications

Hypersensitivity to zonisamide, to any of the excipients or to sulphonamides.

### 4.4 Special warnings and special precautions for use

In accordance with current clinical practice, discontinuation of Zonegran in patients with epilepsy must be accomplished by gradual dose reduction, to reduce the possibility of seizures on withdrawal. There are insufficient data for the withdrawal of concomitant antiepileptic medications once seizure control with Zonegran has been achieved in the add-on situation, in order to reach monotherapy with Zonegran. Therefore withdrawal of concomitant anti-epileptic agents must be undertaken with caution.

Zonegran is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune based adverse reactions that have been associated with medicinal products containing a sulphonamide group include rash, allergic reaction and major haematological disturbances including aplastic anaemia.

Serious rashes have occurred in association with Zonegran therapy, including isolated cases of Stevens-Johnson syndrome.

Consideration must be given to discontinuing Zonegran in patients who develop an otherwise unexplained rash. All patients who develop a rash while taking Zonegran must be closely supervised, with additional levels of caution applied to those patients receiving concomitant antiepileptic agents that may independently induce skin rashes.

Isolated cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

Kidney stones have occurred in patients treated with Zonegran. Zonegran should be used with caution in patients who have risk factors for nephrolithiasis, including prior stone formation, a family history of nephrolithiasis and hypercalcuria. 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. 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 patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate, as there are insufficient data to rule out a pharmacodynamic interaction (see Section 4.5).

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. 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.

In patients taking Zonegran who develop the clinical signs and symptoms of pancreatitis, it is recommended that pancreatic lipase and amylase levels are monitored. If pancreatitis is evident, in the absence of another obvious cause, it is recommended that discontinuation of Zonegran be considered and appropriate treatment initiated.

In patients taking Zonegran, in whom severe muscle pain and/or weakness develop either in the presence or absence of a fever, it is recommended that markers of muscle damage be assessed, including serum creatine phosphokinase and aldolase levels. If elevated, in the absence of another obvious cause such as trauma or grand mal seizures, it is recommended that Zonegran discontinuation be considered and appropriate treatment initiated.

Women of child-bearing potential must use adequate contraception during treatment with Zonegran and for one month after discontinuation (see section 4.6). Physicians treating patients with Zonegran should try to ensure that appropriate contraception is used, and should use clinical judgement when assessing whether OCs, or the doses of the OC components, are adequate based on the individual patient’s clinical situation.

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

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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Zonegran on cytochrome P450 enzymes.

*In vitro* studies using human liver microsomes show no or little (<25%) inhibition of cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4 at zonisamide levels approximately two-fold or greater than clinically relevant unbound serum concentrations. Therefore Zonegran is not expected to affect the pharmacokinetics of other medicinal products via cytochrome P450-mediated mechanisms, as demonstrated for carbamazepine, phenytoin, ethinylestradiol and desipramine *in vivo*.

Potential for Zonegran to affect other medicinal products

Anti-epileptic drugs
In epileptic patients, steady-state dosing with Zonegran resulted in no clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, or sodium valproate.
Oral contraceptives
In clinical studies in healthy subjects, steady-state dosing with Zonegran did not affect serum concentrations of ethinylestradiol or norethisterone in a combined oral contraceptive.

Carbonic anhydrase inhibitors
There are insufficient data to rule out possible pharmacodynamic interactions with carbonic anhydrase inhibitors such as topiramate.

Potential medicinal product interactions affecting Zonegran
In clinical studies co-administration of lamotrigine had no apparent effect on zonisamide pharmacokinetics. The combination of Zonegran with other medicinal products that may lead to urolithiasis may enhance the risk of developing kidney stones; therefore the concomitant administration of such medicinal products should be avoided.

Zonisamide is metabolised partly by 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:

- Enzyme Induction: 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 Zonegran is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing anti-epileptic or other medicinal products are withdrawn, dose adjusted or introduced, an adjustment of the Zonegran dose may be required. Rifampicin is a potent CYP3A4 inducer. If co-administration is necessary, the patient should be closely monitored and the dose of Zonegran and other CYP3A4 substrates adjusted as needed.

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There are no adequate data from the use of Zonegran in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3).

No sudden discontinuation of anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child.

Zonisamide is excreted in human milk; the concentration in breast milk is similar to maternal plasma. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zonegran therapy. Due to the long retention time of zonisamide in the body, breast-feeding must not be resumed until one month after Zonegran therapy is completed.
4.7 Effects on ability to drive and use machines

Some patients may experience drowsiness or difficulty with concentration, particularly early in treatment or after a dose increase. Patients must be advised to exercise caution during activities requiring a high degree of alertness, e.g., driving or operating machinery.

4.8 Undesirable effects

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<td>Hallucination Insomnia Suicidal ideation</td>
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<td></td>
<td>Irritability</td>
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<td>Confusional state</td>
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<td>Depression</td>
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<td>Nervous system disorders</td>
<td>Ataxia</td>
<td>Disturbance in attention Speech disorder</td>
<td>Convulsion Amnesia Coma Grand mal seizure Myasthenic syndrome Neuroleptic malignant syndrome</td>
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<td></td>
<td>Dizziness</td>
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<td>Memory</td>
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<td>impairment</td>
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<td></td>
<td>Somnolence</td>
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<tr>
<td>Eye disorders</td>
<td>Diplopia</td>
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</tbody>
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24
In addition there have been isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP) receiving Zonegran.

### 4.9 Overdose

There have been cases of accidental and intentional overdose in adult and paediatric patients. In some cases, the overdoses were asymptomatic, particularly where emesis or lavage was prompt. In other cases, the overdose was followed by symptoms such as somnolence, nausea, gastritis, nystagmus, myoclonus, coma, bradycardia, reduced renal function, hypotension and respiratory depression. A very high plasma concentration of 100.1 µg/ml zonisamide was recorded approximately 31 hours after a patient took an overdose of Zonegran and clonazepam; the patient became comatose and had respiratory depression, but recovered consciousness five days later and had no sequelae.

**Treatment**

No specific antidotes for Zonegran overdose are available. Following a suspected recent overdose, emptying the stomach by gastric lavage or by induction of emesis may be indicated with the usual precautions to protect the airway. General supportive care is indicated, including frequent monitoring of vital signs and close observation. Zonisamide has a long elimination half-life so its effects may be persistent. Although not formally studied for the treatment of overdose, haemodialysis reduced plasma concentrations of zonisamide in a patient with reduced renal function, and may be considered as treatment of overdose if clinically indicated.
5. PHARMACOLOGICAL PROPERTIES

Zonisamide is benzisoxazole derivative. It is an anti-epileptic medicine with weak carbonic anhydrase activity in-vitro. It is chemically unrelated to other anti-epileptic agents.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, ATC code: N03A X15

Efficacy has been demonstrated with Zonegran in 4 double-blind, placebo-controlled studies of periods of up to 24 weeks with either once or twice daily dosing. These studies show that the median reduction in partial seizure frequency is related to Zonegran dose with sustained efficacy at doses of 300-500 mg per day.

The anticonvulsant activity of zonisamide has been evaluated in a variety of models, in several species with induced or innate seizures, and zonisamide appears to act as a broad-spectrum anti-epileptic in these models. Zonisamide prevents maximal electroshock seizures and restricts seizure spread, including the propagation of seizures from cortex to sub-cortical structures and suppresses epileptogenic focus activity. Unlike phenytoin and carbamazepine however, zonisamide acts preferentially on seizures originating in the cortex.

The mechanism of action of zonisamide is not fully elucidated, but it appears to act on voltage-sensitive sodium and calcium channels, thereby disrupting synchronised neuronal firing, reducing the spread of seizure discharges and disrupting subsequent epileptic activity. Zonisamide also has a modulatory effect on GABA-mediated neuronal inhibition.

5.2 Pharmacokinetic properties

Absorption

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

Zonisamide AUC and C_max values increased almost linearly after single dose over the dose range of 100-800 mg and after multiple doses over the dose range of 100-400 mg once daily. The increase at steady state was 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. Slightly greater than expected accumulation occurs relative to single dosing.

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 – 1.7 l/kg in adults indicating that zonisamide is extensively distributed to tissues. Erythrocyte/plasma ratios are about 15 at low concentrations and about 3 at higher 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. 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 at steady-state after oral administration is about 0.70 l/h and the terminal elimination half-life is about 60 hours in the absence of CYP3A4 inducers. The elimination half-life was independent of dose and not affected by repeat administration. Fluctuation in serum or plasma concentrations over a dosing interval is low (< 30 %). The main route of excretion of zonisamide metabolites and unchanged drug is via the urine. Renal clearance of unchanged zonisamide is relatively low (approximately 3.5 ml/min); about 15 - 30 % of the dose is eliminated unchanged.

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 <20 ml/min (see also section 4.2.).

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 12 mg/kg daily, in divided doses, are similar to those observed in adults, after adjustment for bodyweight.

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

Findings not observed in clinical studies, but seen in the dog at exposure levels similar to clinical use, were liver changes (enlargement, dark-brown discolouration, mild hepatocyte enlargement with concentric lamellar bodies in the cytoplasm and cytoplasmic vacuolation) associated with increased metabolism.

Zonisamide was not genotoxic and has no carcinogenic potential.

Zonisamide caused developmental abnormalities in mice, rats, and dogs, and was embryoletal in monkeys, when administered during the period of organogenesis at zonisamide dosage and maternal plasma levels similar to or lower than therapeutic levels in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Microcrystalline cellulose
Hydrogenated vegetable oil
Sodium laurilsulfate.
Capsule shells:
Gelatin
Titanium dioxide (E171)
Allura red AC (E129)
Sunset yellow FCF (E110)
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PCTFE/aluminium blisters, packs of 56 hard capsules.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORITY

Eisai Limited
3 Shortlands
London
W6 8EE
United Kingdom

8. MARKETING AUTHORITY NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER  
RESponsible FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Elan Pharma Ltd
Monksland, Athlone, County Westmeath
Republic of Ireland

B CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

• OTHER CONDITIONS

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON – BOX OF 14

1. NAME OF THE MEDICINAL PRODUCT

Zonegran 25 mg hard capsules
zonisamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 25 mg zonisamide

3. LIST OF EXCPIENTS

Colouring agents E171, E172

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Ltd., 3 Shortlands, London W6 8EE, UK
12. MARKETING AUTHORISATION NUMBER

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS FOR USE
OUTER CARTON – BOX OF 56

1. NAME OF THE MEDICINAL PRODUCT

Zonegran 25 mg hard capsules
zonisamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 25 mg zonisamide

3. LIST OF EXCIPIENTS

Colouring agents E171, E172

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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Eisai Ltd., 3 Shortlands, London W6 8EE, UK
12. MARKETING AUTHORISATION NUMBER

EU/00/0000/000

13. MANUFACTURER’S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS FOR USE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Zonegran 25 mg hard capsules
zonisamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai Ltd.

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Lot: {number}
1. **NAME OF THE MEDICINAL PRODUCT**

Zonegran 50 mg hard capsules
zonisamide

2. **STATEMENT OF ACTIVE SUBSTANCE**

Each hard capsule contains 50 mg zonisamide

3. **LIST OF EXCIPIENTS**

Colouring agents E171, E172

4. **PHARMACEUTICAL FORM AND CONTENTS**

56 hard capsules

5. **METHOD AND ROUTE OF ADMINISTRATION**

Oral use
Read the package leaflet before use

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

7. **OTHER SPECIAL WARNINGS, IF NECESSARY**

8. **EXPIRY DATE**

EXP (MM/YYYY)

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 30°C

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Ltd., 3 Shortlands, London W6 8EE, UK

12. MARKETING AUTHORISATION NUMBER

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS FOR USE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Zonegran 50 mg hard capsules</td>
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<tr>
<td>zonisamide</td>
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<td>Lot: {number}</td>
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Zonegran 100 mg hard capsules</td>
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<tr>
<td>zonisamide</td>
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</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE</th>
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<tbody>
<tr>
<td>Each hard capsule contains 100 mg zonisamide</td>
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<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
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<tbody>
<tr>
<td>Colouring agents sunset yellow FCF (E110), E171, E129 and E172. See leaflet for further information.</td>
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<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
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<tr>
<td>56 hard capsules</td>
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<tr>
<th>5. METHOD AND ROUTE OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Oral use</td>
</tr>
<tr>
<td>Read the package leaflet before use</td>
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</tbody>
</table>

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<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN</th>
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<tbody>
<tr>
<td>Keep out of the reach and sight of children</td>
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<tr>
<th>7. OTHER SPECIAL WARNINGS, IF NECESSARY</th>
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<th>8. EXPIRY DATE</th>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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<tbody>
<tr>
<td>Do not store above 30°C</td>
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<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
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<td>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
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<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
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<tbody>
<tr>
<td>Medicinal product subject to medical prescription</td>
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<tr>
<th>15. INSTRUCTIONS FOR USE</th>
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MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

<table>
<thead>
<tr>
<th></th>
<th>NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>1</td>
<td>Zonegran 100 mg hard capsules</td>
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<tr>
<td></td>
<td>zonisamide</td>
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<th>NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tr>
<td>4</td>
<td>Lot: {number}</td>
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</table>
B. PACKAGE LEAFLET
Zonegran 25 mg hard capsules
Zonegran 50 mg hard capsules
Zonegran 100 mg hard capsules
(zonisamide)

Read all of this leaflet carefully before you start taking this medicine.
1. Keep this leaflet. You may need to read it again.
2. If you have further questions, please ask your doctor or your pharmacist.
3. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

IN THIS LEAFLET
1. What Zonegran is and what it is used for
2. Before you take Zonegran
3. How to take Zonegran
4. Possible side effects
5. Storing Zonegran
6. Further information

The active substance in Zonegran hard capsules is zonisamide. Zonegran 25 mg hard capsules contain 25 mg of zonisamide. Zonegran 50 mg hard capsules contain 50 mg zonisamide. Zonegran 100 mg hard capsules contain 100 mg zonisamide.

• The other ingredients that are present in the capsule contents are: microcrystalline cellulose, hydrogenated vegetable oil and sodium laurilsulfate.

• The capsule shell contains: gelatin, titanium dioxide (E171), shellac, propylene glycol, potassium hydroxide, black iron oxide (E172). Additionally the 100 mg capsule shell contains sunset yellow FCF (E110) and allura red (E129).

MARKETING AUTHORISATION HOLDER
Eisai Ltd., 3 Shortlands, London W6 8EE, UK.

MANUFACTURER
Elan Pharma Ltd, Monksland, Athlone, County Westmeath, Ireland

1. WHAT ZONEGRAN IS AND WHAT IT IS USED FOR

• Zonegran 25 mg hard capsules have a white opaque body and a white opaque cap and are printed with a logo and “ZONEGRAN 25” in black.

• Zonegran 50 mg hard capsules have a white opaque body and a grey opaque cap and are printed with a logo and “ZONEGRAN 50” in black.

• Zonegran 100 mg hard capsules have a white opaque body and a red opaque cap and are printed with a logo and “ZONEGRAN 100” in black.

Zonegran hard capsules contain zonisamide, which is an antiepileptic medicine. It is used to treat partial seizures, with or without secondary generalisation, for patients who are already taking other antiepileptic medicines.

Zonegran capsules are packaged in blister packs supplied in boxes containing 14 (25 mg capsules only) or 56 hard capsules. Not all pack sizes may be available.

2. BEFORE YOU TAKE ZONEGRAN

Do not take Zonegran:
• if you are hypersensitive (allergic) to zonisamide or to any of the other ingredients of Zonegran
• you are pregnant, think you might be pregnant or are breast feeding
Take special care with Zonegran:

- if you are younger than 18 years, because the use of Zonegran is not recommended for this age group.
- if you are a woman of childbearing age. You must use adequate contraception while taking Zonegran and for one month after you stop taking Zonegran.
- if you are elderly, because there is limited information on the use of Zonegran in this age group and the dose of your medicine may need to be adjusted.
- if you suffer from liver problems, because there is limited information on the use of Zonegran in this group and the dose of your medicine may need to be changed or increased more slowly.
- if you suffer from kidney problems, because there is limited information on the use of Zonegran in this group and the dose of your medicine may need to be changed or increased more slowly.
- if you get a sudden pain in your back or stomach, have pain on urinating (passing water) or notice blood in your urine, as this may be a sign of kidney stones. Always try to drink plenty of water to reduce the risk of kidney stones. If you have suffered from kidney stones in the past, please tell your doctor.
- if the weather is particularly warm. You must take care to drink plenty of water and try to keep cool.
- if you get a skin rash. See your doctor immediately as very occasionally this may become serious.
- if you have lost a lot of weight, or weigh less than 40 kg. Tell your doctor as this may need to be monitored.
- if you feel unusually tired or have had a sore throat for a few days or notice that you are bruising easily. See your doctor as this may mean you have a blood disorder.
- if you have pains in your muscles or a feeling of weakness. Tell your doctor.
- when you are stopping your treatment. Follow your doctor’s instructions concerning the gradual reduction of Zonegran.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

Pregnancy

If you are pregnant, or think you might be pregnant, or are planning to get pregnant, tell your doctor. You must only take Zonegran during your pregnancy if your doctor tells you to.

Breast-feeding

You must not breast-feed while taking Zonegran, or for one month after you stop taking Zonegran.

Driving and using machines

Special care is required while driving or operating machinery, because Zonegran may affect your concentration and your ability to react/respond, and may make you feel sleepy, particularly at the beginning of your treatment or after your dose is increased.

Important information about some of the ingredients of Zonegran

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

Taking other medicines

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines – even those not prescribed. The effect of zonisamide can be reduced by other medicines you are taking. This may require an adjustment of your dose of Zonegran.

3. HOW TO TAKE ZONEGRAN

Always take Zonegran exactly as your doctor has instructed. You must check with your doctor or pharmacist if you are unsure.
The usual starting dose is 50 mg daily taken in two equal doses. The dose will be adjusted for you by your doctor and may be increased by up to 100 mg at intervals of one to two weeks, to a daily dose of between 300 mg and 500 mg. Some patients may respond to lower doses. The dose may be increased more slowly if you experience unwanted effects or if you already suffer from a kidney problem.

Zonegran capsules must be swallowed whole with water. Do not chew the capsules. The capsules must be taken once or twice daily, as instructed by your doctor. If you take the capsules twice a day, half the daily dose should be taken in the morning and half in the evening. Zonegran can be taken with or without food.

If you feel that the effect of Zonegran is too strong or too weak, talk to your doctor or pharmacist.

Zonegran is meant to be taken as a long-term medicine. Do not reduce your dose or stop your medicine unless your doctor tells you to.

**If you take more Zonegran than you should**
If you may have taken more Zonegran than you should, tell a carer (relative or friend), your doctor or pharmacist immediately, or contact your nearest hospital casualty department, taking your medicine with you. You may become sleepy and could lose consciousness. Do not drive at this time.

**If you forget to take Zonegran**
If you forget to take a dose, continue taking your medicine as normal. Do not take a double dose to make up for any forgotten doses.

**Effects when treatment with Zonegran is stopped**
If your doctor advises you to stop treatment, the Zonegran dose will be reduced gradually in order to lower the risk of an increase in seizures.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Zonegran can have side effects.

The most commonly reported side effects are all mild effects. They are more common during the first month of treatment and often decrease with continued treatment. Tell your doctor if you have any of the following effects and if they are too uncomfortable for you:
- drowsiness, loss of appetite, loss of weight, dizziness, loss of concentration, nausea, agitation or irritability, double vision, depression, poor muscle coordination, confusion, poor memory, stomach pains, diarrhoea (loose stools), speech abnormalities, skin rashes, fever and allergic reactions.

Uncommon side effects of Zonegran are:
- strange or unusual thoughts, vomiting, gall bladder inflammation or gallstones, kidney or urinary stones, pneumonia and urinary tract infections, low blood potassium levels and convulsions/seizures.

Very rarely the following side effects have been seen with Zonegran:
- blood disorders, swollen glands, hallucinations, memory loss, insomnia, thoughts of suicide, coma, neuroleptic malignant syndrome (inability to move, sweating, fever, incontinence), breathing disorders, shortness of breath, inflammation of the lungs, inflammation of the pancreas, liver problems, itching, severe rashes, decreased sweating and heat stroke, muscle pain, muscle weakness, kidney failure, or other kidney problems.

Tell your doctor immediately if you notice any of these side effects.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.
5. **STORING ZONEGRAN**

Keep Zonegran out of the reach and sight of children.

Do not store above 30°C.

Do not use Zonegran after the expiry date stated on the blister and the carton.

6. **FURTHER INFORMATION**

This leaflet was last updated on