

SCIENTIFIC DISCUSSION

1. Introduction

Many patients (30 to 40% of the overall population with epilepsy) continue to have seizures in spite of receiving antiepileptic drug (AED) treatment. The prevalence of active epilepsy, 5-10/1000, is one of the highest among serious neurological disorders with more than 50 million people affected worldwide. Two peaks of incidence are observed, in early childhood and among elderly people. Some patients will have life-long epilepsy.

International classifications, such as the International League Against Epilepsy (ILAE) classification recognise many epileptic diseases or syndromes and each of them can be expressed clinically by one or several seizure groupings. Partial epilepsies (localisation related) are the more frequent, accounting for more than 60% of the epilepsies, and they include most of the difficult-to-treat patients. In terms of seizure types, 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 symptoms are a function of the localisation of the site of seizure onset in the brain (epileptogenic zone) and of the propagation pathways of the abnormal discharge.

Therapeutic management usually follows a staged approach with newly diagnosed patients starting prophylactic treatment with a single drug, and several alternative drugs may be tried in the event of lack of efficacy or poor tolerability. For patients not responding to several attempts of monotherapy, combinations of antiepileptic drugs are generally employed early in the management process.

Uncontrolled epilepsy is associated with cognitive deterioration, psychosocial dysfunction, dependent behaviour, restricted lifestyle, poor quality of life and excess mortality, in particular from sudden unexpected death in epilepsy patients (SUDEP).

Combination therapy is the preferred strategy in the management of difficult-to-control epilepsies and the recent introduction of several new AEDs has considerably increased the number of possible combinations. The rational basis for combining AEDs is largely based upon their modes of action, although these mechanisms are not fully understood for some drugs.

The efficacy of the newer AEDs in adjunctive therapy trials is often evaluated in terms of percentages of responders, a responder being defined as a patient experiencing a $\geq 50\%$ reduction in seizure frequency over a certain period of time. Responder rates on treatment range between 20% and 50% in recent controlled studies; however responder rates obtained on placebo, ranging from 6–18%, should be taken into account when evaluating the actual effect of the drug.

This intended indication of Zonegran was the adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults and adolescents over 12 years with epilepsy.

The development programme

The development of Zonegran is somewhat complicated. Dainippon Pharmaceutical Company Limited (Dainippon) in Japan and Europe and Warner-Lambert/Parke-Davis (WL) in the United States (US) initiated the earliest clinical studies with zonisamide. Subsequently, WL discontinued development of zonisamide in 1987 and Dainippon assumed responsibility for its development in the US and conducted studies during the period up to 1997. Athena Neurosciences (now Elan) acquired rights to zonisamide in 1997. Since 1998, Elan has managed the development programme in Europe and the US.

Zonisamide is currently marketed as Zonegran™ in the US (since 2000) and as Excegran™ in Japan and Korea (since 1989 and 1990, respectively). It received regulatory approval in Mexico in 2002.

A European marketing authorisation application submitted in 1997 was withdrawn and in 1999, the applicant sought scientific advice from the Committee for Proprietary Medical Products (CPMP) on the further development of zonisamide.

Zonegran has been subject of a centralised procedure in 1998. The application was withdrawn due to major deficiencies in that dossier. The studies were not in accordance to the past (adopted in 1989) and revised NfG (adopted end 2000) concerning anti-epileptic agents. Especially, the duration of the two most important studies submitted was too short for an efficacy assessment. Subsequently a new clinical

study has been conducted also in response to the regulatory advice given by the CPMP (scientific advice October 1999). This new study is study 302 which was conducted between 2000-02

Although the current NfG concerning anti-epileptic agents was adopted end 2000 the revised version was in full development at the time (1999) of the scientific advice (1999). Therefore this advice reflected the recommendations of the current revised NfG. In summary, for the add-on indication a randomised, double-blind, placebo-controlled parallel group study design was recommended. The study should include a run-in period, a titration period, a maintenance period of at least 12 weeks and a controlled withdrawal period. Baseline seizure frequency should be sufficiently high, concomitant anti-epileptic therapy should be stable after the titration period. The rationale behind the maintenance period of 12 week is that it generates stable conditions. Such period allows assessment of whether the conditions are indeed stable, to assess the variability of the response, to assess whether efficacy is not short lasting and to assess whether tolerance on the short term does not develop. Endpoint should be the responders' analysis but the (median) percent change in seizure frequency is also considered crucial as both facilitate the assessment of the clinical relevance of the observed effect. After the maintenance period, a controlled withdrawal period is recommended wherein the test and the placebo are gradually phased out and the occurrence of a rebound and withdrawal effects are evaluated. With respect to long-term data, the continuation or extension of add-on studies is necessary in order to assess the maintenance of safety and absence of tolerance in the long term. A one-year duration may be required.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

Many of the pre-clinical studies were performed prior to implementation of the standardised GLP guidelines, or were performed according to older Japanese guidelines. A few pivotal safety studies were performed according to GLP standards. However, the studies are adequate to assess the effects of zonisamide in animals and to estimate the potential effects in human.

There are no GMP concerns; the manufacturing site is within the EEA and is appropriately authorised for the pharmaceutical form.

It is stated that all studies initiated after 1995 were conducted in accordance with Good Clinical Practice (GCP) and since January 1997 have been in compliance with International Conference on Harmonisation (ICH) guidelines on GCP (CPMP/ICH/135/95). Studies initiated prior to the effective date of Good Clinical Practice regulations were conducted in accordance with the relevant standards at the time.

2. Quality aspects

Introduction

Zonegran is presented in the form of hard capsules, and contains 25, 50 and 100 mg of zonisamide as active substance. Other ingredients are microcrystalline cellulose, hydrogenated vegetable oil and sodium laurilsulfate, gelatin, titanium dioxide (E171), Allura red AC (E129) (100 mg only), Sunset yellow FCF (E110) (100 mg only), shellac, propylene glycol, potassium hydroxide, and black iron oxide (E172).

The capsules are packaged in PVC/PCTFE (Aclar)/aluminium blisters.

Drug Substance

Zonisamide is a white to pale yellow crystals or a crystalline powder, which is very slightly soluble in water. Zonisamide does not contain any optically active centres, and therefore, it does not exhibit any optical isomerism. The active substance is not hygroscopic.

- **Manufacture**

Information on zonisamide has been supplied in the form of an active substance master file ("ASMF /EDMF").

- **Specification**

The active substance specification includes test for description, identification (UV, IR), particle size, assay (HPLC, 98.0% - 102.0%), related substances (HPLC), residual solvents (GC), heavy metals, loss on drying, residue on ignition, microbial limit, etc.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance.

Batch analysis data of a number of batches of active substance (n=20) are provided. The results are within the specifications and consistent from batch to batch.

- **Stability**

Three batches made by the original route and three by other route were placed on stability, stored in the packaging described above under both long-term and accelerated conditions. Five years' data on the original lots are available under long-term conditions and 24 months on the new route lots. Six months' data are available on all lots stored under accelerated conditions.

Stress testing was carried out on one batch from the original synthetic route, at 50°C, humidity conditions of 30°C/90 % RH and exposed to 500 lux light. The related substances method differed from that proposed; details of the method are given, as well as validation results for specificity, LOD, LOQ, relative response, linearity, precision, and stability of solutions.

The results show that zonisamide is a very stable compound, with no discernible degradation occurring under the test conditions. The proposed re-test period with no special storage condition is acceptable.

Drug Product

- **Pharmaceutical Development**

The aim of development was to maximise the rate of dissolution by optimising drug particle size, improve wettability and use a suitable diluent. Hard capsules were also developed due to the bitter taste of the active substance. Adequate information has been provided on the development of the capsules. Dissolution results indicate that the aim of the formulation development was achieved.

The capsules have been manufactured by a number of manufacturing sites. The changes in manufacturing site are supported by comparative dissolution testing which showed that the dissolution profiles are equivalent.

Other than the colour of the capsules, the commercial formulation has been used in all Phase III studies. Earlier formulations were also capsules with qualitatively and quantitatively slightly different formulations.

The excipients used in the finished product are microcrystalline cellulose, hydrogenated vegetable oil, sodium laurilsulfate, gelatin, titanium dioxide (E171), Allura red AC (E129) (100 mg only), Sunset yellow FCF (E110) (100 mg only), shellac, propylene glycol, potassium hydroxide, and black iron oxide (E172). Excipients are tested to PhEur monographs or BP in the case of hydrogenated vegetable oil that is not in the Ph. Eur. The only substance of animal origin is gelatin; TSE certificates of suitability were provided. Sodium laurilsulphate is not of animal origin.

The blister material proposed is a two-component thermoformable laminate of PVC and PCTFE. The material complies with PhEur requirements.

- **Manufacture of the Product**

The manufacturing process involves milling of the drug substance, wet mixing, drying, dry mixing, and blending, and encapsulation.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process. The manufacturing process has adequately been validated and is satisfactory. The in process controls are adequate for this pharmaceutical form.

The commercial scale three batch analysis data show that the hard capsules can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation

- **Product Specification**

The specification includes tests by validated methods for appearance, identification (FTIR, HPLC), assay (HPLC, 95.0%-105%), uniformity of content (HPLC), related substances (HPLC), dissolution test (Ph Eur), identification of colours.

The test and limits of the specification for the finished product are appropriate to control the quality of this medicinal product for the intended purpose.

Batch data are provided for pilot and production batches and indicate satisfactory uniformity as well as compliance with the specification.

- **Stability of the Product**

The shelf life specification contains tests for appearance, assay, related substances and dissolution, with limits which are the same as those in the release specification.

A number of batches from pilot-scale to commercial scale and manufactured by different manufacturer sites were placed on stability according to the ICH Guidelines. Supporting stability studies, photostability studies and stress testing studies were also provided.

Results have been generated by validated, stability indicating methods and indicate satisfactory stability. These results support the shelf life and storage conditions stated in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

3. Non-clinical aspects

This application for Zonegran relies heavily on published material. The pharmacodynamic and pharmacokinetic studies are old and fall short of GLP standards, e.g. analytical methods are not well defined, but do give a picture of the disposition of zonisamide.

Introduction

Many of the pharmacology studies presented are in the form of published papers. Many of the toxicology studies were performed prior to implementation of standardised GLP guidelines, others were carried out according to the older Japanese guidelines (e.g. in chronic studies animals were dosed 5 times a week rather than daily). A few pivotal safety studies were done to current GLP standards. Despite these deficiencies, the studies conducted appear adequate to assess the effects of zonisamide in laboratory animals and to support its potential effects in man.

Pharmacology

Zonisamide is an anti-epileptic medicine with weak carbonic anhydrase activity *in-vitro*. It is chemically unrelated to other anti-epileptic agents. It has a blocking action on voltage sensitive sodium and calcium channels, which is thought to disrupt synchronised neuronal firing, and so reduces the spread of seizure discharges and disrupts subsequent epileptic activity. It also has a modulatory effect on GABA-mediated neuronal inhibition as well as a variety of other effects, which may contribute to its pharmacological effects.

- **Primary pharmacodynamics (*in vitro/in vivo*)**

The non-clinical pharmacodynamics and pharmacological activity of zonisamide has been demonstrated in various *in vitro* studies including binding assays screening for a range of receptors and in experimental models using several different animal species. The models include the inhibition of neuro-protective mechanisms, stimulation of cortical and subcortical structures by trauma, irritant substances

or by electrical stimulation (either in the form of maximum electroshock seizures or as kindling) and evaluation in animals genetically predisposed to seizures. The result is the development of motor seizures comparable to those observed in epileptic patients. Experimental models in mice, rats, rabbits, dogs, and cats employed different stimuli leading to convulsions. Results of studies, plus a review of literature, were summarised by the applicant.

Anticonvulsive activity

Based on animal model data, zonisamide appears to possess a broad anticonvulsant profile and thus a broad mechanistic profile. Efficacy was primarily defined as anticonvulsant activity against maximal electroconvulsive seizures (MES), and neurotoxicity (uncoordinated motor function, ataxia, sedation). The results of these studies indicated that the therapeutic window between minimum doses and plasma concentrations required for efficacy and those resulting in toxicity is larger for zonisamide than for a range of other anticonvulsant drugs

Mechanism of action

The mechanism of action of zonisamide is not known, but inhibition of seizure propagation appears to be related at least in part to its ability to both block voltage sensitive sodium and voltage sensitive, T type calcium channels, thus reducing the spread of seizure discharges. This mixture of action is comparable to that of other anticonvulsant drugs, such as phenytoin. The role of GABA in zonisamide induced inhibition of seizures is not clear. There does not seem to be a direct effect of zonisamide on GABA mediated mechanism. Other studies suggest that part of its anticonvulsive effects may be by increasing the inhibitory effects of GABA by either affecting GABA binding to its receptor or increasing GABA release in the hippocampus. The effect of zonisamide on carbonic anhydrase activity does not play a significant role in the anticonvulsant activity of the drug. Zonisamide also appears to increase synaptic concentrations of monoamines.

- Secondary pharmacodynamics

Studies have evaluated secondary pharmacodynamic actions of zonisamide, including the potential for neuroprotection, analgesia and to evaluate its actions as a carbonic anhydrase inhibitor.

Zonisamide appears to have significant neuroprotective effects in various animal models of epilepsy and ischemia, possibly independently of its anticonvulsant effects. Although the mechanism of action is not known, the applicant suggested that zonisamide appears to protect neurons from free radical damage and to stabilise the neuronal membrane. At high doses (≥ 100 in rats, at 300 in mice) slight hypothermia was observed.

Some of the data from animal neuropathic pain models suggest that zonisamide may also have analgesic properties in certain situations, as has been shown for other anticonvulsant drugs. This activity is probably derived from zonisamide's effects on reducing neuronal hyperexcitability.

- Safety pharmacology

A series of safety pharmacology studies have been performed, including cardiovascular studies. These studies include both *in vitro* studies and studies conducted *in vivo* as part of repeated dose toxicology studies.

With regard to CNS safety, the median neurotoxic dose for zonisamide was twice that of carbamazepine and three-fold greater than that for phenytoin and phenobarbital. Behavioural studies indicated that carbamazepine was two to 3-fold more potent than zonisamide in causing behavioural disturbances. However, rapid high loading of zonisamide at doses of 10, 25 or 40 mg/kg may inhibit spontaneous activity in the rat, whereas gradual dosing had no unfavourable effects on spontaneous activity. This observation would support the gradual introduction of zonisamide to humans.

As regards the potential for sedation, zonisamide displayed markedly less hypnotic potential in mice than phenytoin, carbamazepine or phenobarbital. Zonisamide was also less effective than these drugs in potentiating barbiturate hypnosis in mice; the potentiating effect of zonisamide was about one-tenth that of phenytoin, carbamazepine or phenobarbital. Overall, the results from these series of evaluations indicate that zonisamide shows little potential to produce adverse effects on the CNS at anticonvulsive doses.

The effect on the cardiovascular system was evaluated by an *in vitro* study of the effects of the drug on the current in the cardiac potassium channel hERG applied to the HEK293 cells expressing hERG.. Zonisamide at 500 µM (approximately equivalent to 100 mg/mL) did not inhibit hERG current.

The lack of cardiovascular effect was also shown in three separate repeated dose GLP safety studies in dogs, ranging in duration from one week to 52 weeks.

- Pharmacodynamic drug interactions

An *in vivo* pharmacodynamic drug interaction study was performed, evaluating the effect of chronic administration of phenobarbital on the anticonvulsant effects of zonisamide. Pharmacodynamic/pharmacokinetic drug interaction studies were performed with zonisamide in MES seizures in rats, indicating that repeated dosing with phenobarbital has fewer effects on the pharmacodynamic response to zonisamide than in the case of phenytoin or carbamazepine. Additional data from other studies evaluating the pharmacokinetic and pharmacodynamic interactions of zonisamide with other drugs are summarized in the Pharmacokinetics.

Pharmacokinetics

The pharmacokinetic profile of zonisamide has been characterised in a series of studies performed by Dainippon and Warner Lambert, as well as by Elan and in published papers from laboratories in Europe, North America and Japan in mice, rats, dogs and monkeys as well as in humans.

- Absorption- Bioavailability

Tmax is about two–four hours in all species, with AUC and Cmax being dose-dependent. Plasma T1/2 in rats, dogs, monkeys, and healthy humans is 8, 15, 24, and 68 hours respectively and the site and route of absorption may influence the rate, but not the extent of absorption. The plasma zonisamide concentration data in mice and rats following dietary administration provide satisfactory evidence of systemic exposure in these species following administration via this route.

- Distribution

Zonisamide distributes evenly throughout the body with maximal tissue concentrations being observed three hours after dosing. Concentrations greater than those in plasma are observed in erythrocytes, brain and to a lesser degree, in most other tissues. In the brain, concentrations are higher in the cortex than in sub-cortical structures. Zonisamide binds in a reversible manner to carbonic anhydrase in blood, brain and to a lesser degree, in other tissues. This accounts for the greater concentrations in these tissues, compared with other tissues and plasma. Plasma protein binding is low. Age does not appear to influence the distribution profile of zonisamide, other than a lower tissue concentration in neonatal rats that correlates with lower carbonic anhydrase protein concentrations. Zonisamide appears to distribute evenly in the foetus, with foetal tissue concentrations comparable to maternal tissues.

- Metabolism (*in vitro/in vivo*)

Zonisamide is readily metabolised following oral administration with little first-pass or pre-systemic metabolism (except possibly increased pre-systemic metabolism in the mouse compared to other species, based on an *in vitro* study performed with gut flora of various species). Zonisamide is metabolised primarily by CYP 3A4 with subsequent ring-opened sulphate and glucuronide conjugates accounting for 34% of urinary radioactivity whereas unchanged zonisamide accounts for 32% and does not induce its own metabolism. Metabolism in younger rats, compared with adult rats is qualitatively similar; the observed quantitative differences are expected given known expression of drug metabolising enzymes in neonates.

- Excretion

The major route of excretion of zonisamide and its metabolites is via urine. Studies in rats, dogs, primates and humans indicate that approximately 85% of the dose is excreted in urine within 96 hours of either single or repeated doses. The remaining 15% is excreted via the faeces. Studies in immature rats indicate age does not influence the route of excretion. No non-clinical studies of the secretion of zonisamide into milk have been performed. Studies in lactating mothers have shown secretion, with concentrations in breast milk approximating those in maternal plasma within a few days of delivery.

- Pharmacokinetic drug interactions

In vitro and *in vivo* drug interaction studies using zonisamide and the common anticonvulsant drugs; phenobarbital, valproic acid, carbamazepine and phenytoin, indicate no alteration in the binding and distribution characteristics of zonisamide to plasma proteins or erythrocytes (Kimura, M et al, 1993, Kimura, M et al, 1992). Drugs that induce cytochrome P450 enzymes, particularly cytochromes of the CYP3A family, may enhance the metabolism of zonisamide in humans as demonstrated by work in rats pre-treated with phenobarbital, valproic acid, or carbamazepine (Kimura, M et al, 1992).

Toxicology

Zonisamide toxicology programme included single dose studies in mice, adults or juvenile rats, dogs and monkeys; repeat-dose studies (diet and gavage) in mice (2, 4 and 13 week treatment), rats (1, 9 and 12 month treatment) and dogs (2 and 12 months); full set of genotoxicity (*in vitro* and *in vivo*); reproductive toxicology (mice, rats, dogs, monkeys) studies; 2-year carcinogenicity evaluation in mice and rats (diet); antigenicity and environmental risk assessment studies. In addition special studies on the potential for dependence were performed.

- Single dose toxicity

In mice, the LD₅₀ was approximately 2000 mg/kg by oral route, and 850 mg/kg by IV. Onset of effects was rapid, 5-15 min depending on route of administration, survivors recovered in 48 hours. Recorded toxic effects were sedation, ataxia, reduced reflexes, coma, respiratory paralysis and death. Post-mortem observations were of distended bladder and gastro-intestinal (petechial haemorrhages). There were no distinct sex differences.

In adult rats the oral LD₅₀ was approximately 2000 mg/kg. In juvenile animals, the oral LD₅₀ was approximately 270 mg/kg at 1 day old, 400 mg/kg at 1 week old, 500 mg/kg at 2 weeks old and 1800 mg/kg at 4 weeks old. Clinical signs were also CNS-related, similar to mice but with a more rapid and marked onset in younger animals.

Non-rodent oral LD₅₀ was approximately 1000 mg/kg in dogs and >1000 mg/kg in monkeys. In dogs onset was in 1-4 hours, recovery in 2-4 days, observations were depression, emesis staggered gait, ataxia, prone position, coma, respiratory depression, loss of corneal reflex, death. In monkeys onset was in 1-4 hours, recovery in 2-6 days, observations were staggered gait, poor co-ordination, nasal mucous discharge, emesis, prone position, loss of pain/corneal reflex, hypothermia, and anorexia.

- Repeat dose toxicity (with toxicokinetics)

In mice, no mortality or drug related clinical signs were seen after 2 week of oral (diet) administration up to 800 mg/kg day. Sedation, ataxia and drowsiness were seen as an initial response, i.e. in the first week only in a 30 day oral toxicity study in females (a dose range finding study for reproductive toxicity tests) at dose levels of 200 and 600 mg/kg/day. In a 13 week study mice given up to 800 mg/kg/day in diet, no behavioural changes nor histopathological changes were noted in contrast to the comparators phenobarbitone, diphenylhydantoin or carbamazepine used in the same study where hepatotoxicity was seen.

In the rat, a 4 week oral (diet) dose range finding/toxicity study at 0-50-100-200-300-600mg/kg/day did not result in mortality or abnormal behaviour patterns. At 600 mg/kg/day there was an increase in relative weight of the brain and liver but no significant drug related pathology. NOAEL was given as 50 mg/kg/day, this would be expected to result in plasma levels of approximately 35 µg/ml, less than 1.5-fold the efficacious plasma levels in man.

In a 9-month oral study, rats were given 0-10-30-100-300 mg/kg/day zonisamide or 300 mg/kg/day diphenylhydantoin, and a 6 week recovery group was included. There was no mortality. At doses of 300 mg/kg/day zonisamide there was mild sedation, reduced muscle tone and slight ataxia. There was a slight increase in the relative weight of the liver and kidney with both zonisamide (at doses over 100 mg/kg/day) and diphenylhydantoin (these animals also had increased pituitary and thyroid weights). There was no abnormal histopathology. The NOAEL was between 30-100 mg/kg/day, i.e. 1-4-fold the expected exposure in man.

In a chronic repeated dose study, rats (20/sex/group) were given 0-2-20-200 mg/kg/day (2ml/kg) orally for 1 year. In life observations included: dose related reduction in body weight gain, associated with reduced food consumption. Fine renal pelvic stones were found in four top dose animals, these were found to contain primarily magnesium phosphate. This effect may be due to inhibition of carbonic anhydrase. Histopathology

of the kidneys was comparable to controls. The NOAEL was given as 20 mg/kg/day, a dose which results in exposure levels equivalent to therapeutic exposure in man.

Animals in the two-month dog study were only dosed on six days per week at 0-10-30-100 mg/kg/day orally (gelatine capsules). There was sporadic emesis at the top dose, and a slight increase in liver and lung weight post-mortem, but no associated pathology. Plasma levels were measured 4 hours after the first (4.9-8.8/21.4-29.6/58.3-77.2 µg/ml) and fourteenth (x1.5 over previous) dose and corresponded to 0.9-3-8-fold the minimum effective plasma level (12.6 µg/ml) or 0.3-1.0-2.7-fold the anticipated mean therapeutic plasma level in man. The NOAEL is given as 30 mg/kg/day.

In a subsequent 1-year oral dosing study, beagle dogs were given 0-10-30-75 mg/kg/day in gelatine capsules. There was no mortality. Occasional emesis and aggressive behaviour was seen from 30 mg/kg/day. Post-mortem there was a trend towards an increase in liver and kidney weight. A diffuse dark brown discoloration of the liver was seen not correlated with microscopic changes. Urinary bladder congestion and/or mucosal thickening or nodularity was seen at the mid- and top-doses. The NOAEL is given as 30 mg/kg/day.

- Genotoxicity in vitro and in vivo (with toxicokinetics)

Zonisamide was not mutagenic in two Ames tests carried out in 5 strains of *Salmonella typhimurium* and in *Escherichia coli* WP2 uvrA), with or without metabolic (S9) activation, an in vitro forward mutation test in mouse lymphoma cells, with or without metabolic activation nor in an in vitro chromosome aberration test in human lymphocytes. The ability of zonisamide to induce sister chromatid exchange (SCE) and cell mutation (at the HGPRT locus) has been investigated in V79 Chinese hamster lung cells. No significant increase in SCE frequency was seen at any test concentration, either with or without activation. A small, but statistically significant, increase in mutation frequency at the HGPRT locus was, however, observed in the absence of metabolic activation. The increase in mutation frequency was, however, very small and there was no dose-response. Whilst the increase was statistically significant, the biological significance is questionable. Therefore, zonisamide did not appear to be mutagenic in this test. Zonisamide was also not mutagenic in a bone-marrow cytogenetic study following administration by oral gavage in mice where systemic exposure was provided. Overall, zonisamide is not considered to pose a mutagenic hazard.

- Carcinogenicity (with toxicokinetics)

Mice (B6C3F1, 50/sex/group) were given zonisamide 0-20-40-80 mg/kg/day as an ad mix in the diet for 104 weeks. There was good survival to terminal sacrifice (80-90% in males, 72-78% in females). There was no increase in non-neoplastic or neoplastic lesions, in treated animals compared to controls.

Rats (Wistar, 50/sex/group) were given zonisamide 0-20-40-80 mg/kg/day as ad mix in diet for 104 weeks. There was good survival to terminal sacrifice (60% in males, 70% in females). There was no increase in non-neoplastic or neoplastic lesions in treated animals compared to controls except for a slightly higher incidence of interstitial cell and uterine tumours in treated vs. control animals, but without dose relationship. Plasma exposures at steady state were extrapolated from a 4-week oral study in rats. This was considered to be acceptable in view of the pharmacokinetic and metabolism of zonisamide in rodents.

- Reproductive and developmental studies

Fertility

Two fertility studies were conducted. In the first one, rats were dosed in the diet at 0-25-50-100 mg/kg for 60 days in males and 14 days prior to mating and up to sacrifice or weaning in females. In the second fertility study, the dosing was given by gavage at 0-20-60-200 mg/kg in males and females. In both studies, there was no apparent dose related effect on fertility and no significant effect on F1 developmental or reproductive capacity. The NOAEL is given as 20 mg/kg/day (second study) for parents and pups. This dose results in systemic exposure equivalent to the therapeutic dose in man.

Embryotoxicity and teratogenicity

In the mouse teratogenicity study, pregnant mice were given zonisamide 0-125-250-500 mg/kg by gavage. Clinical observations and effects on body weight, food intake, and organ weights observed in the F0

generation were consistent with those observed during the repeat-dose gavage studies. Zonisamide evoked maternal and foetotoxicity at 250 mg/kg and was teratogenic at 500 mg/kg.

In the rat teratogenicity and development studies, pregnant rats were given zonisamide by gavage at up to 200 mg/kg/day. The clinical signs observed in treated dams, as well as the effects on body weight, food intake, and organ weights were consistent with the effects seen during the repeat-dose studies. Visceral abnormalities such as ventricular septal defects of the heart were seen at doses of 200 mg/kg. Developmental effects such as delayed ossification and reduced foetal weight were observed at around 60 mg/kg and above, however these effects are likely to be secondary to effects on maternal body weight gain and are, consequently, not considered to be significant. Zonisamide was, therefore, maternally toxic at 60 mg/kg and higher and teratogenic at 200 mg/kg. Slight delays in foetal development also occurred at 60 mg/kg and higher, although these are considered secondary to maternal toxicity.

In the dog teratogenicity study, zonisamide was given at 0-10-30-60 mg/kg/day in capsules on days 14-35 of gestation, followed by caesarean delivery on day 55 of gestation. There was an increased occurrence of short/kinky tails, due mainly to fusion/deformity of the caudal vertebrae, at 60 mg/kg. Cardiovascular abnormalities, hypoplasia/dysplasia of the spleen and thymus, umbilical hernia and higher incidence of eight lumbar vertebrae were seen at doses over 30 mg/kg. Therefore zonisamide was teratogenic in dogs at doses of 30 mg/kg or higher and materno-toxic at 60 mg/kg as characterised by reduction in body weight gain and food consumption.

In the primate teratogenicity study, cynomolgus monkeys were given 0-10-20 mg/kg by gavage on days 21-45 of gestation, followed by caesarean delivery on day 100 of gestation. There was some emesis in treated animals and reduced food consumption. Zonisamide was abortifacient at from the lowest tested dose (10 mg/kg). It cannot be ruled out that abortion was a secondary effect consequent to teratogenicity. Zonisamide was, therefore, maternally toxic and abortifacient at 10 mg/kg and higher.

Pre- and post- natal

Pregnant rats were given 0-10-30-60 mg/kg/day by gavage from day 17 of gestation to day 20 of lactation. No effect was noted on pregnancy or delivery, there were no maternal deaths. Body weight gain and food consumption were reduced at the top dose. There were no adverse effects on F1 pups at delivery and no increase in pup mortality to weaning. Physical and behavioural development was normal in all groups. Reproductive performance and F2 pups were also normal. The NOAEL is given as 30 mg/kg/day, a dose which gives about 1.5-times the expected exposure in man.

• **Other toxicity studies**

Special toxicity studies

Antigenicity studies were carried out by immunising mice, guinea pigs and rabbits with a BSA-zonisamide conjugate given for up to 5 weeks. Zonisamide conjugates, but not zonisamide alone, induced positive responses in PHA tests and the PCA test in naive guinea pigs. The observations suggest that zonisamide is not likely to be antigenic when administered as a free haptent.

Dependence

The potential for dependence have been studied in 3 animal models.

In a model of physical dependence on pentobarbital (PTB) induced in rats, zonisamide did not prevent the loss of body weight associated with PTB abstinence which suggests that zonisamide is unlikely to produce barbiturate-like physical dependence, even at doses well in excess of those intended for clinical use. Zonisamide substitution did, however, produce a partial but significant ($p < 0.05$) suppression of behavioural withdrawal signs of hyperexcitability associated with PTB abstinence, suggesting sedative or depressant activity of zonisamide.

In a drug discrimination model in the rat (SN2; $n=6$), zonisamide was tested at up to 176 mg/kg/day IP, for its ability to induce diazepam (DZP)-like discriminative stimulus effects. At these doses, zonisamide failed to substitute for DZP (2.5 mg/kg IP), suggesting that it should not produce benzodiazepine-like intoxication if taken at high doses.

In a similar substitution procedure in monkeys zonisamide at doses in excess of the human therapeutic range lacked reinforcing effects on trained monkeys for self-administration of methohexital, a known

drug reinforcer. These data confirm that zonisamide lacks potential for abuse since results of drug self-administration testing in monkeys is usually predictive of abuse liability.

Whilst zonisamide treatment did appear to suppress some of the behavioural signs associated with withdrawal from pentobarbital, it is considered that this represents the depressant effect of zonisamide and it is considered unlikely that zonisamide has a dependence liability. Zonisamide also appears to lack potential for abuse.

Environmental risk assessment

The ERA of zonisamide was performed based on the most recent draft CPMP Note for Guidance (24 July 2003). The Phase I assessment indicated that a Phase II assessment is needed. Phase II A studies to determine the PNEC (predicted no effect concentration) value and fate studies have been performed, although not to the OECD standard. However, the justification for these studies was considered to be acceptable. Based on the default Fpen value (1%) the PEC/PNEC is lower than 1 (ratio=0.2). It is therefore concluded that the use of zonisamide does not pose a risk to the environment.

Discussion on the non-clinical aspects

Pharmacodynamic studies have demonstrated that zonisamide can reduce the extent of induced seizures. The mechanism of action remains unclear, although it appears to be similar to phenytoin, phenobarbitone and carbamazepine, the main comparators.

Following oral dosing the drug is rapidly absorbed, widely distributed and metabolised, and excreted in the urine. Metabolites are similar across the species tested but vary in relative amount. Foetal exposure is high, similar to that of the dam.

The main adverse observations following a single high dose of zonisamide appear to be linked to the CNS effects of the drug. In repeat dose toxicity, transient clinical signs of toxicity such as sedation and ataxia, which are in line with its pharmacological action, have been induced when zonisamide was administered as bolus doses (i.e. gavage) at 200 mg/kg/day or greater; such effects were, however, not seen when higher doses (800 mg/kg/day) were administered via dietary admixture, suggesting a Cmax basis of these observations rather than overall exposure (AUC/Css). Adverse effects in CNS, kidney and liver were observed in animals at doses leaving no safety margin for human therapeutic use. Juvenile toxicity was only investigated in acute studies.

In reproductive/developmental toxicity studies in rodents and dogs, no evidence of effects on fertility of zonisamide were seen. Zonisamide was embryotoxic and teratogenic (reduced pup weight, increase in cardiac and major blood vessel defects, delayed ossification) and induced maternal toxicity at high doses. In monkeys zonisamide acted as an abortifacient. The suggested NOAELs are 20 mg/kg in rats, 10 mg/kg in dogs and <10 mg/kg in monkeys, all of which produce plasma levels within human efficacious levels. Therefore, it cannot be excluded that the adverse effects observed in animals might also occur in humans. Pregnancy is contra-indicated and potential interference between zonisamide and the chosen method of avoiding pregnancy should be ruled out.

Based on *in vitro* and *in vivo* genotoxic tests, zonisamide is not considered to pose a genotoxic hazard for humans. The results of the two year studies in rodents suggest that zonisamide does not possess carcinogenic potential.

No antigenic potential was observed when tested in mice, guinea pigs and rabbits.

No environmental risk is anticipated from the use of zonisamide.

It is considered unlikely that zonisamide could have a dependence liability or potential for abuse.

4. Clinical aspects

Introduction

The indication originally submitted for Zonegran (zonisamide) was the adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults and adolescents over 12

years with epilepsy. The pharmaceutical form is a hard capsule for oral use containing 25 mg, 50 mg or 100 mg of zonisamide.

Pharmacokinetics

38 pharmacokinetic studies were submitted. In addition, one population pharmacokinetic analysis was submitted, and 2 in vitro studies.

- Methods**

The analysis of zonisamide in plasma (urine and erythrocytes) is performed by validated HPLC methods. The first method (Dainippon/WARS) was replaced from 1988 by a new HPLC method (KCAS/AAI).

Pharmacokinetic variables, e.g. AUC_{0-t} , AUC_{inf} , AUC_{τ} , C_{max} , C_{min} , t_{max} , C_t and $t_{1/2}$ were calculated according to standard procedures.

For statistical analysis, the significance level used in most trials was 5%, and accordingly 95% confidence intervals were calculated. The 90% confidence intervals were calculated for bioequivalence trials and when testing for equivalence.

- Absorption – Bioavailability**

Bioavailability

After oral administration, zonisamide is slowly absorbed with peak plasma concentrations 2.5 – 4.5 h after administration. Based upon excretion data in faeces, and plasma radioactivity after administration of ^{14}C labelled drug, the absolute bioavailability is considered to be close to 100%.

Bioequivalence

The initial capsule formulation (the IND formulation) containing 100 mg zonisamide was used only in 4 biopharmaceutic and clinical pharmacology studies conducted prior to 1984. This formulation was compared to the intended formulation for marketing (Market formulation) containing also 100 mg zonisamide.

The IND formulation proved to be bioequivalent with the 100 mg Market formulation . (see table below).

Table PK 1. Pharmacokinetics of zonisamide after administration of the 100 mg IND capsule formulation and the 100 mg Market capsule formulation to healthy volunteers (fasting).

n=17	100 mg IND capsule	100 mg Market capsule	ratio (90% CI)
AUC_{inf} ($\mu g \cdot h/ml$)	71 \pm 24	77 \pm 20	0.90 (0.84 – 0.96)
C_{max} ($\mu g/ml$)	1.1 \pm 0.6	1.0 \pm 0.3	1.03 (0.89 – 1.17)
t_{max} (h)	4 (1 – 12)	4 (1 – 12)	--
$t_{1/2}$ (h)	54 \pm 13	56 \pm 12	--

More recently, 25 and 50 mg strength capsules have been formulated. A further bioequivalence study showed that after once daily dosing, the 100 mg Market capsule formulation, the 25 mg Market capsule formulation (as 4x25 mg) and the 50 mg Market capsule formulation (as 2x 50 mg) were bioequivalent at steady state.

Influence of food

Food interaction studies have shown that the rate and extent of zonisamide absorption was not influenced by a high fat breakfast, a standard breakfast or in case the dose was administered as sprinkle in apple sauce. Therefore zonisamide can be administered with and without food

- **Distribution**

Animal data indicate that zonisamide is widely distributed over the body, and that zonisamide crosses the blood-brain barrier, and the placenta. In addition, animal data indicate that zonisamide is excreted into mother milk, which is also confirmed in humans. Human data regarding penetration or distribution of zonisamide within the central nervous system is lacking. Animal studies of brain uptake suggest that zonisamide is well distributed to the brain and that the carrier mechanism is probably carbonic anhydrase elated.

In vitro and in vivo studies show that plasma protein binding is about 40 – 50% at clinically relevant plasma concentrations of 10 – 100 µg/ml. No interactions on drug-protein displacement are expected, based on in vitro studies with phenytoin, phenobarbital or sulthiame.

The volume of distribution (Vd/F) was estimated to be about 1.6 l/kg

A major distribution compartment of zonisamide are the erythrocytes. The binding to erythrocytes is non linear, due to a combined saturable binding to erythrocyte carbonic anhydrase at concentrations below 3 µg/ml, and to a non saturable binding (passive diffusion) at higher concentrations. Consequently, erythrocytes/plasma ratio's are about 15 at low concentrations and about 3 at higher concentrations. Possible displacement from the carbonic anhydrase binding site at erythrocytes by other sulphonamide agents is not expected to be clinically relevant as their affinity is comparable to zonisamide.

- **Elimination**

Metabolism-Excretion

In vitro studies using human liver microsomes indicate that zonisamide is metabolised to 2-(sulphamoylacetyl)-phenol (SMAP). The metabolism of zonisamide to SMAP was almost completely inhibited by anti-P450 3A4 antibody but not by anti-P450 2D6 antibody showing the involvement of cytochrome CYP3A4.

In vivo, metabolism of zonisamide was studied after administration of ¹⁴C-labelled zonisamide (300 mg) to 6 healthy male volunteers. Pharmacokinetic variables obtained for zonisamide are shown in table below:

Table PK 4. Pharmacokinetics of zonisamide after administration of 300 mg ¹⁴C-zonisamide to healthy male volunteers.

n=6	zonisamide plasma, day 1	zonisamide plasma, day 14
AUC _{0-24h} (µg.h/ml)	60 ± 7	393 ± 74
AUC _{inf} (µg.h/ml)	246 ± 67	--
C _{max} (µg/ml)	3.2 ± 0.4	20 ± 3
t _{max} (h)	3.2 ± 1.3	2.8 ± 1.3
Cl/F (ml/min)	22 ± 8	13 ± 2
Clr (ml/min)	3.5 ± 1.2	1.9 ± 0.6
t _{1/2} (h)	56 ± 16	58 ± 13
Ae _{240h} (%)	15 ± 3	15 ± 4

Recovery data indicate that zonisamide is almost completely absorbed, without pre-systemic metabolism. Zonisamide is almost completely but slowly excreted into urine, mainly as metabolites and no metabolites could be detected in plasma. Recoveries of zonisamide and its metabolites over a 240 h collection time in urine was about 62% including two inactive metabolites (N-acetyl zonisamide (10 – 20%), and glucuronide conjugates of 2-(sulphamoylacetyl)-phenol (SMAP, 50 - 60%) and 3% in faeces.

The elimination half-life of about 60 h was independent of dose and not affected by repeat administration. The total body clearance is about 20 ml/min after single dosing and about 11 ml/min

after multiple dosing. Renal clearance covered 15% of the total clearance, which was indicated by the excretion of only 14% of the dose as intact zonisamide in the urine.

Zonisamide is not subject to interconversion as zonisamide has no chiral centre.

- **Dose proportionality and time dependencies**

Dose proportionality

AUC and C_{max} values increased almost linear with dose after single dose over the dose range of 100 – 800 mg and after multiple dose over the dose range of 100 – 400 mg once daily. The increase was slightly more than expected on base of dosing, probably due to the saturable binding of zonisamide to erythrocytes.

In line with the almost linear pharmacokinetics, the total daily exposure was only 10% lower in case the total daily dose was administered as a single dose compared to twice daily, with about 10% lower C_{max} values and 20% lower trough levels for the once daily treatment.

Time dependency

Exposure at steady state is slightly greater than predicted from single dose data. The cause of this time dependency has not been identified but saturation of one or more metabolic pathways is the most likely explanation. Elimination half-life was independent of dose and not affected by repeated administration. Steady state was achieved by day 13.

Intra- and inter-individual variability

Inter-individual variability in zonisamide pharmacokinetics (AUC, C_{max} and Cl) is estimated to be 15 – 25%. Intra-individual variability in zonisamide pharmacokinetics was not evaluated, however taking into account the inter-individual variability, the intra-individual variability is considered less than 25%.

- **Special populations**

Impaired renal function

A clinical pharmacokinetic study of zonisamide in patients with varying degrees of renal function was performed. Patients received a single 300mg oral dose of zonisamide. Plasma and urine were assayed for zonisamide using HPLC procedure. Mean plasma concentration-time data and the relationship between zonisamide total plasma clearance and creatinine clearance were measured.

In subjects with renal impairment receiving a single 300 mg dose, AUC rose by 36% and C_{max} by 12%. In those with creatinine clearance of less than 20 mL/min, renal clearance was reduced by 35%.

Therefore, zonisamide should be discontinued in patients who develop acute renal failure or where a clinically significant sustained increase in serum creatinine is observed. Zonisamide should not be used in patients with renal failure, as there has been insufficient experience concerning drug dosing and toxicity.

Impaired liver function

Pharmacokinetics data of zonisamide in patients with an impaired liver function is very limited and considered to be insufficient to support the use in this patient group.

The SPC states that the use of zonisamide in hepatic impaired patients have not been adequately studied, and therefore the use of zonisamide in these patients is not recommended.

Gender, weight, and target population (including population pharmacokinetics)

A prospectively planned population pharmacokinetic analysis of Study 302 was carried out; the primary objectives of which were to describe the pharmacokinetics of zonisamide from serum samples obtained at steady state from subjects participating in this study and to identify the influence of demographic factors and concomitant medication with other anti-epileptic drugs on zonisamide pharmacokinetics. Zonisamide concentration data were obtained from 208 subjects (1023 samples, mean age was 35.5 years, range 12–77 years), which reflect the fixed dose assessment phase.

Steady state zonisamide concentration data were used for non-linear mixed effects modelling by extended least squares regression using the NONMEM program with first order estimation.

The population pharmacokinetic analysis did not reveal any unexpected issues.

Gender: gender did not influence the pharmacokinetics of zonisamide (after incorporation of body weight into the model).

Weight: for each evaluated dose level, high total body weight was one of the combinations of subject factors producing the largest decrease in steady state concentration (up to 32% lower), relative to the reference subject. Although the magnitude of these increases could be clinically relevant (i.e. potential impact on safety), the fact that patients are typically titrated to an effective and tolerable dose reduces the safety concerns. Furthermore, the relatively small magnitude of these changes is unlikely to be clinically relevant (i.e. little or no expected impact on efficacy).

Target population: mean zonisamide steady state concentrations in subjects receiving zonisamide, 100, 300 or 500 mg daily, concomitantly with CYP 3A4-inducing anti-epileptic drugs (phenytoin, phenobarbital and/or carbamazepine) were 35.7%, 18.0% and 25.7% lower, respectively, than in subjects receiving zonisamide concomitantly with other (non-inducing) anti-epileptic drugs.

The mean observed steady state apparent oral clearance of zonisamide decreased approximately 37% with an increase in daily zonisamide dose from 100 mg to 500 mg, both in subjects receiving concomitant treatment with inducers of CYP 3A4 and in subjects receiving treatment with other anti-epileptic drugs. However, in general, only slightly non-linear increases in steady state zonisamide concentrations were observed or predicted over the dose range evaluated.

Elderly

The pharmacokinetics of zonisamide were evaluated a study in subjects aged between 21 – 40 years (n=11) and subjects aged between 65 – 71 years (n=11). Subjects received a single 300 mg dose zonisamide. No clinically significant differences were observed in the pharmacokinetics between young and elderly. As there is limited clinical information, the SPC states that elderly should be treated with caution.

Children

No specific studies were carried out in adolescents patients aged 12 -18 years. Only a few reports (literature, translated) were submitted dealing with pharmacokinetics in children. Thus in general data is limited. The data available indicate that adolescents aged 12 – 18 years, on daily dose add on therapy or receiving 6 mg/kg day, have comparable serum level/dose values compared with young subjects (aged > 18 years).

Taking into account that the dose is titrated to clinical effect, the risk of eventual differences in pharmacokinetics may be limited. However, clinical safety and efficacy data should thoroughly support the use of zonisamide in adolescents (see clinical part).

- **Interaction studies**

In vitro

In vitro studies showed that zonisamide is a substrate for CYP3A4. The ability of zonisamide to inhibit 7 major cytochrome P450 enzymes, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 (table PK 12), which mediate drug metabolism in humans, was investigated.

No evidence of significant inhibition was observed for the cytochrome P450 isoforms CYP1A2 and CYP2D6. Zonisamide inhibited CYP2A6, 2C9, 2C19 and 2E1 in a concentration-dependent manner, but inhibition was less than 25% at a concentration of 42 µg/ml, a concentration which is 2-fold higher than clinical relevant zonisamide plasma concentrations. The K_i for inhibition of CYP3A4 appeared to be ca. 1.1 µM (230 µg/ml). These results suggest that a metabolically-based clinical interaction between zonisamide and some other drugs whose clearance is dependent upon one of the P450s tested is unlikely at therapeutic concentrations of zonisamide.

In vivo

Zonisamide (steady state, 200 mg twice daily, gradual titrated or 300 mg for phenobarbital) did not influence the pharmacokinetics of valproate (a CYP 2C9 inhibitor enzyme inhibitor), lamotrigine (a

drug mainly metabolised by glucuronidation), phenytoin, carbamazepine, and phenobarbital (enzyme inducers), and ethinyl estradiol/levonorgestrel, and ethinyl estradiol/norethindrone.

Zonisamide metabolism can be affected by the enzyme inducers (CYP3A4) phenytoin, carbamazepine, and phenobarbital which increase the clearance of zonisamide, resulting in a decrease in AUC (25 – 50%) and the elimination half-life (up to 50%). Valproate (at steady state) apparently increased zonisamide oral steady state clearance.

Consequently, if co-administration is necessary, the patient should be closely monitored and the dose of Zonegran and other CYP3A4 substrates adjusted as needed. This is stated in the SPC (4.5)

CYP3A4 inhibitors 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.

Overall conclusions on pharmacokinetics

The absolute bioavailability of zonisamide is estimated to be approximately 100%, and C_{max} values increased almost linear with dose after single dose over the dose range of 100 – 800 mg and after multiple dose over the dose range of 100 – 400 mg once daily. The increase at steady state was slightly more than expected on base of dosing, probably due to the saturable binding of zonisamide to erythrocytes. Peak plasma concentrations were reached 2.5 – 4.5 h after administration. Steady state was achieved within 13 days, and no unexpected accumulation occurs (once daily or twice daily dosing)

The capsule formulations used in the clinical trial program and intended for marketing are considered bioequivalent, based upon in vivo bioequivalence data.

In vitro protein binding studies using human plasma indicate that protein binding is about 40 – 50%. A major distribution compartment are the erythrocytes, which is in common with other sulphonamides. Erythrocytes/plasma ratios are about 15 at low concentrations and about 3 at higher concentrations.

Zonisamide is metabolised partly by CYP3A4 (reductive cleavage), and also by N-acetyl-transferases and conjugation with glucuronic acid. 3% is excreted in faeces and about 62% in urine as zonisamide (20 – 30%), and two inactive metabolites (N-acetyl zonisamide (10 – 20%), and glucuronide conjugates of 2-(sulphamoylacyl)-phenol (SMAP, 50 - 60%).

The total body clearance is about 20 ml/min after single dosing. The elimination half-life of about 60 h was independent of dose and not affected by repeat administration.

Zonisamide should not be used in patients with renal failure, as there has been insufficient experience concerning drug dosing and toxicity. Data in patients with an impaired liver function are very limited. Therefore the use of zonisamide in these patients is not recommended.

Limited data indicate that pharmacokinetics in adolescents aged between 12 – 18 years is comparable to adults. However, the numbers are too low to draw firm conclusions. No data are available in children aged <12.

Concomitant use of CYP450 inducers, like carbamazepine, phenytoin and phenobarbital, decrease the exposure to zonisamide (up to 50% as shown in vivo) due to an increase in the metabolism of zonisamide.

Pharmacodynamics

No pharmacodynamic studies in humans have been submitted. Only two published studies investigating the effects of zonisamide on cognitive function are available. (see clinical section on cognitive function)

- **Mechanism of action**

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.

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.

- **Primary and Secondary pharmacology**

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.

Clinical efficacy

Four placebo-controlled studies are included in this application to demonstrate efficacy: the primary study (Study 302) the more recent, performed after seeking scientific advice, and three studies 922, 912 US, and 912 EUR which are considered to provide supporting rather than primary data because the treatment duration at steady state of these studies was shorter than required by the current CPMP/EWP/566/98 guideline.

In the four studies, a total of 498 subjects received zonisamide and 350 subjects received placebo over a treatment period of up to 24 weeks, excluding down titration (a period of up to 18 weeks at steady state).

Five open-label extension (OLE) studies are provided to document long-term efficacy over a seven-year period (including base study period). In the five OLE studies, a total of 667 subjects received zonisamide. In addition several other uncontrolled studies were performed.

The “All Zonisamide Population” was defined as all subjects who received at least one dose of zonisamide, including patients randomised to placebo in the placebo-controlled studies and who later switched to zonisamide.

Ten epilepsy studies are currently ongoing or are in the process of being completed: these include a long-term extension to Study 302 (Study 353) and a monotherapy study in newly diagnosed patients (Study 304).

- **Dose response studies**

Study 922 assessed different zonisamide doses (100, 200, 400 mg/day), although the assessment periods were not consistent and of shorter duration than 12 weeks at steady state. Subjects in earlier studies (912-US and 912-EUR) received a range of zonisamide doses (median final dose 400 mg/day), but dose-response was not specifically assessed.

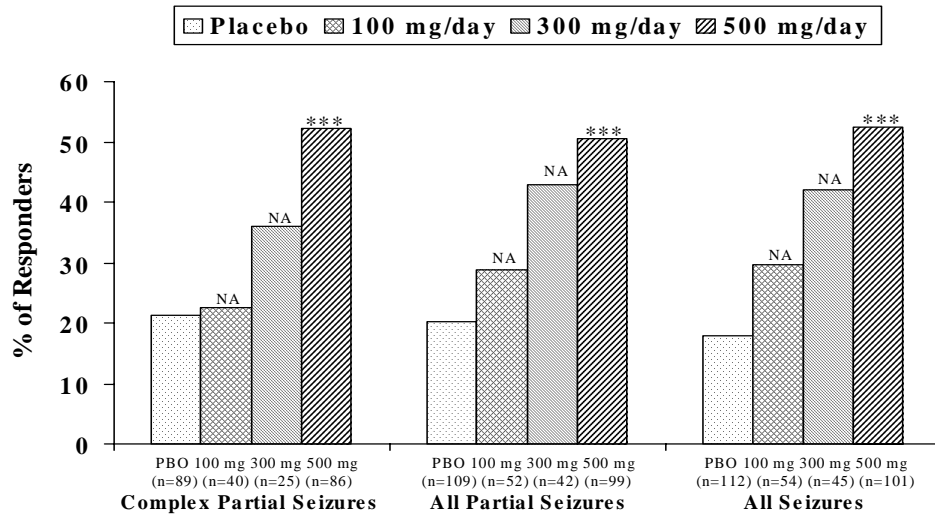
Dose-response was in fact addressed by Study 302, which assessed the efficacy and safety of a range of fixed doses (100, 300, 500 mg/day) at steady state over 18 weeks (following a titration period of six weeks). Use of a titration to fixed dose design was considered appropriate as zonisamide has a relatively long $t_{1/2}$.

Study 302 showed a dose-response relationship in terms of the median percentage reduction in seizure frequency from baseline for each seizure grouping in the primary efficacy population.

There was a statistically significant difference in median percentage reduction in seizure frequency from baseline between the 500 mg/day group and placebo for each seizure grouping. There was also a statistically significant difference between the 300 mg/day group and placebo for all partial and all seizures.

Study 302 showed also a dose-response relationship in terms of the percentage of responders for each seizure grouping in the primary efficacy population (see table below).

Study 302: Percentage of Subjects with $\geq 50\%$ Reduction in Seizure Frequency from Baseline (Responders) by Dose (Weeks 19-36) (Primary Efficacy Population)



Source: Clinical Study Report 302: In-text tables 12, 21, 23.
 Partial seizures without secondary generalisation.
 n = number of subjects with assessable data.
 p values are for comparison between zonisamide 500 mg/day and placebo only.
 *** p<0.001; NA Not assessed, only highest dose was assessed as per analysis plan; PBO Placebo.

A linear trend test of the percentage of responders (all seizures) across the three-zonisamide doses was performed using the intended to treat (ITT) population. This analysis showed that subjects were 1.95 times as likely to show a response to treatment whilst receiving zonisamide 500 mg/day compared with 100 mg/day, and were 1.18 times as likely to show a response whilst receiving zonisamide 300 mg/day compared with 100 mg/day. The linear association between dose level and the percentage of responders was statistically significant (p=0.0357).

A linear trend analysis of the percentage of responders (all seizures) including the placebo group was also performed using the ITT population. Results from this test showed that the odds ratios for response compared with placebo in the 100 mg/day, 300 mg/day and 500 mg/day zonisamide groups were 2.09, 2.46 and 4.07, respectively. The observed linear trend was statistically significant (p<0.0001).

- **Main studies**

The primary efficacy study in the development programme is study 302 that was designed to conform with CPMP guidelines as well as incorporating regulatory advice and recommendations from internationally recognised guidelines for the treatment of epilepsy, in particular Draft 6 of the Committee for Proprietary Medicinal Products (CPMP) Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders.

However, it is noted that the analysis plan of study 302 does not fully adhere to the guidelines in respect of the recommendation to analyse partial seizures in terms of separate analyses of simple, complex and secondarily generalised seizures. The applicant selected the reduction in complex partial seizures as primary efficacy parameter as these seizure types were considered to be of primary concern, could be reliably recorded by subjects/caregivers and were of sufficient frequency to be analysed alone. Other seizure types were recorded and in all studies analysed by appropriate groupings of seizure types.

Studies 922, 912 US, and 912 EUR are considered to provide supporting rather than primary data because the treatment duration at steady state of these studies was shorter than required by the current CPMP/EWP/566/98 guideline.

Methods

• Study Participants

The subject population in the four placebo-controlled studies was chosen to assess the efficacy of zonisamide as adjunctive therapy in subjects with refractory partial epilepsy.

History of partial seizures was defined in study 302 as least 12 partial seizures during the 12-week baseline period, as recorded in the daily seizure diary, with no more than a 3-week seizure free interval during this time. In studies 912-US and 912 EUR as at least four complex partial seizures per month over the four months preceding the study and no more than eight primary or secondary generalised tonic, clonic or tonic-clonic seizures while awake during those four months.

Baseline seizure frequency was established during an 8–12-week period, depending on the patient's seizure frequency: an 8-week period for patients who had ≥ 15 seizures in the first 4 weeks or ≥ 30 seizures in the first 8 weeks and a 12-week period for patients who had fewer seizures.

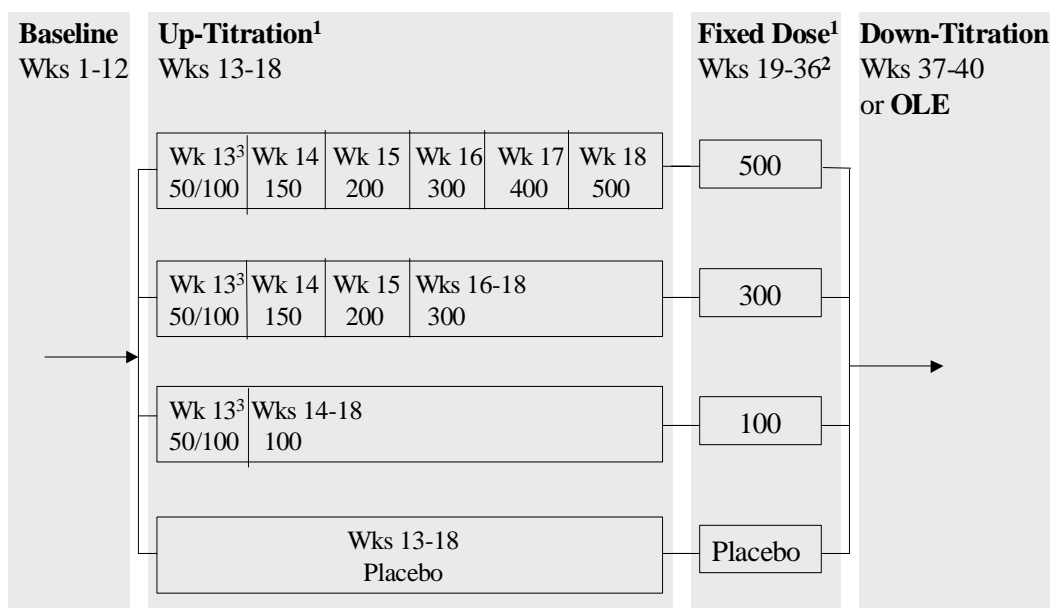
Unsatisfactory seizure control or sub-optimal treatment was either due to poor seizure control or unacceptable side effects. Only subjects with a documented history of partial seizures despite treatment with other anti-epileptic drugs (AEDs) were included. The frequency of seizures was assessed during the baseline periods of 12 weeks during which only the concomitant AED regimen was used. All subjects were refractory to previous treatment and were receiving at least one, and up to three, concomitant AEDs at doses in the usual ranges for epilepsy treatment.

Exclusion criteria included mainly a history or evidence of a progressive central nervous system (CNS) disease or lesion (all studies), progressive encephalopathy or progressive ophthalmologic disease; patients with a history of absence seizures, myoclonic or atonic seizures or non-epileptic seizures, any clinically significant organic disease or laboratory abnormality.

• Treatments

Following Screening (Week 0) and a 12 week prospective baseline phase (Weeks 1–12), subjects were randomised to receive one of four treatments – zonisamide 500 mg/day, 300 mg/day or 100 mg/day or placebo - in the ratio 2:1:1:2.

The design of this study is shown in the figure below.



¹Zonisamide doses are in mg/day.

²Fixed dose assessment phase, includes the two-week stabilisation phase (Weeks 19-20).

³During Week 13, zonisamide-treated subjects received 50 mg/day on Days 1-3 and 100 mg/day on Days 4-7.
Wk week. OLE Open-label extension.

- **Objectives**

The efficacy of zonisamide was compared with placebo and assessed by measuring the median percentage reduction from baseline in seizure frequency, expressed as seizures per 28-day period and the percentage of subjects with a 50% or greater reduction in seizure frequency, expressed as seizures per 28-day period (responders).

Investigator and subject global assessments of improvement relative to baseline were also assessed.

Secondary objectives of Study 302 were to assess the dose-effect relationship of zonisamide, to evaluate the efficacy of total daily zonisamide doses of 100mg and 300mg versus placebo; to evaluate the safety and tolerability of zonisamide 50mg/day (25mg twice daily) when used at the initiation of therapy (days 1-3); to assess investigator evaluation of subject's response and also patient's rating.

- **Outcomes/endpoints**

The primary efficacy variable was a comparison of change in seizure frequency from baseline (expressed as seizures per 28 day period) between the 500 mg/day zonisamide and placebo groups and was assessed by:

- Median percentage changes from baseline in frequency of seizures during the fixed dose assessment phase (Weeks 19-36).
- Proportion of subjects with $\geq 50\%$ reduction in seizure frequency from baseline (responders) (Weeks 19-36).

Secondary efficacy variables were: median percentage change in seizure frequency from baseline in all partial seizures without secondary generalisation and all seizures; the percentage of subjects responding to treatment for all partial seizures and all seizures; number of seizure-free days and subject and investigator Global Evaluations of Improvement.

Safety evaluations included treatment-emergent adverse events (TEAEs), and changes in laboratory evaluations, physical and neurological examinations, vital signs, concomitant medications and electrocardiogram (ECG).

- **Sample size**

Sample size was based on the proportion of responders during the assessment phase in the primary efficacy analysis population.

- **Randomisation**

An unequal randomisation (2:1:1:2) was used because the primary analysis of interest was the comparison of the zonisamide 500 mg/day group with placebo

- **Blinding (masking)**

Blinding was achieved by using a double dummy technique.

- **Statistical methods**

Analyses were conducted in three of the following subject populations: for study 302:

Intent-to-treat (ITT): Randomised subjects who took at least one dose of study medication and that had some post-baseline partial seizure frequency data collected.

Modified intent-to-treat (MITT) studies 922, 912-US and EUR: All ITT subjects who took at least one dose of study medication during the assessment phase (Weeks 8-12 in study 922; Weeks 5-12 in Studies 912-US and 912 EUR).

Primary efficacy analysis: All ITT subjects with some partial seizure frequency data collected during the fixed-dose assessment phase (Weeks 19-36)

Efficacy evaluable:

All ITT subjects who had an average of four seizures per month during the baseline phase and who took study medication for at least 10 weeks.

For Study 302, the efficacy analyses were conducted on the primary efficacy population and, for the three supporting studies the efficacy analyses were conducted on the MITT population.

Results

- **Participant flow**

Summary of Subject Numbers by Study

Subject Population	Study 302				Study 922		Study 912-US		Study 912-EUR	
	Plac ebo	ZNS			Plac ebo	ZNS 400 mg/d	Plac ebo	ZNS <200- ≥600 mg/da	Plac ebo	ZNS <200- ≥600 mg/day
		100 mg/d	300 mg/d	500 mg/d						
Subjects randomised	120	57	56	118	85	118	74	78	71	73
ITT population	119	55	55	118	85	118	74	78	71	73
Excluded from ITT population ¹	1	2	1	0	0	0	0	0	0	0
Primary efficacy ² or MITT population	112	54	45	101	72	98	71	69	66	67
Excluded from primary efficacy ² or MITT population ¹	8	3	11	17	13	20	3	9	5	6
Efficacy evaluable population	109	54	43	88	70	94	70	65	66	65
Excluded from efficacy evaluable population ¹	11	3	13	30	15	24	4	13	5	8
Withdrawn	23	4	16	39	13	24	7	14	3	11
Completed evaluation	97	52	39	79	72	94	67	64	68	62
Entered open-label extension phase	88	46	38	71	145		123		115	

¹ Number of randomised subjects who were excluded from the analysis population. Four randomised subjects were excluded from the ITT population of Study 302; two did not receive any study medication and two did not have any post-baseline partial seizure frequency data.

² For Study 302, the principal population upon which efficacy analyses were performed was the primary efficacy population, not the MITT population. ITT Intent-to-treat. MITT Modified intent-to-treat. ZNS Zonisamide.

Recruitment

In study 302 and including the 3 supportive studies, 444 subjects were screened and 93 patients failed screening; 351 patients were randomised; 321 patients completed titration; 82 were terminated prematurely; 267 completed steady state and 243 entered the follow-up study.

It is of note that in study 302 the inclusion criteria is based upon all seizure types whereas the primary efficacy variable is based upon the seizure frequency of complex partial seizures.

It is noted that the preferred primary endpoint in the NfG on anti-epileptic agents is 50% responders.

- **Conduct of the study**

Major protocol deviations were noted in 1.8% of patients administered 100mg/day; 21.8% patients administered 300mg/day and 25.4% of 500mg/day versus 8.3% of the placebo group. 58.2% of the major deviations related to compliance (less than 80% compliance) and this occurred more frequently in the zonisamide groups.

- **Baseline data**

Treatment groups were comparable for age, height, weight and race.

The most commonly used antiepileptic drug (AED) at baseline and during the study was carbamazepine for all treatment groups.

The subject population in the placebo-controlled study is considered appropriate and representative of patients with partial epilepsy refractory to other AEDs. Despite receiving other AEDs before study entry, subjects had a median baseline seizure frequency of greater than 9 seizures per 28 days.

- **Outcomes and estimation**

The median percentage reduction in seizure frequency from baseline in this study was compared between zonisamide and placebo using a two-way analysis of variance (ANOVA) model, using rank-transformed data containing the main effects of treatment and study centre. Analyses commenced with the 500 mg/day dose group and, if found to be statistically significant, continued in a step-down procedure comparing each active treatment group with placebo in turn. No corrections were made for multiple statistical comparisons.

The results are summarised in the table below:

Study 302 Reduction in Seizure Frequency from Baseline (Weeks 19-36)

Analysis Seizure Grouping		Population	&	Placebo	Zonisamide		
					100 mg/day	300 mg/day	500 mg/day
Primary Efficacy Population				N = 112	N = 54	N = 45	N = 101
Complex partial	n with assessable data ¹			89	40	25	86
	Median % reduction			16.3	11.4	40.1	51.2
	p-value				NA	0.3160	<0.0001
All partial ²	n with assessable data ¹			109	52	42	99
	Median % reduction			19.4	18.3	46.4	50.6
	p-value				0.7204	0.0007	<0.0001
All seizures	n with assessable data ¹			112	54	45	101
	Median % reduction			18.1	18.6	41.8	51.3
	p-value				0.4452	0.0005	<0.0001
ITT Population				N = 119	N = 55	N = 55	N = 118
Complex partial	n with assessable data ¹			94	40	33	102
	Median % reduction			16.9	11.4	32.4	44.1
	p-value				NA	0.4648	0.0017
All partial ²	n with assessable data ¹			114	53	52	115
	Median % reduction			19.0	18.7	41.4	45.1
	p-value				0.6828	0.0060	0.0001
All seizures	n with assessable data ¹			119	55	55	118
	Median % reduction			17.4	18.7	38.5	46.1
	p-value				0.4134	0.0034	<0.0001

Analysis Seizure Grouping	Population	& Placebo	Zonisamide		
			100 mg/day	300 mg/day	500 mg/day
Efficacy Evaluable Population		N = 109	N = 54	N = 43	N = 88
Complex partial	n with assessable data ¹	86	39	25	74
	Median % reduction	16.3	11.5	40.1	49.8
	p-value		NA	0.3299	0.0004
All partial ²	n with assessable data ¹	106	52	40	86
	Median % reduction	19.0	19.7	44.7	48.9
	p-value		0.5693	0.0015	<0.0001
All seizures	n with assessable data ¹	109	54	43	88
	Median % reduction	18.7	19.7	40.9	50.4
	p-value		0.3959	0.0016	<0.0001

¹ Number of assessable subjects. Analysis can only be performed on subjects with seizure frequency data for baseline and assessment phase and a baseline seizure frequency greater than zero.

² All partial seizures without secondary generalisation. p-values are for comparison between zonisamide and placebo, starting with 500 mg/day versus placebo and, if found to be statistically significant, continuing in a step-down procedure comparing each active treatment group with placebo in turn. No corrections were made for multiple statistical comparisons. ITT Intent-to-treat. NA Not assessed.

The percentage of responders ($\geq 50\%$ Reduction in Seizure Frequency from Baseline) was compared between the 500 mg/day group and placebo using the Cochran-Mantel-Haenszel (CMH) test, with study centre group as the stratification variable. Statistical comparisons between other dose groups and placebo were not made. The results demonstrate a statistically significant effect for the 500mg/day dose.

These results are summarised in the table below:

Study 302: Percentage of Subjects with $\geq 50\%$ Reduction in Seizure Frequency from Baseline (Responders) (Weeks 19-36)

Analysis Population & Seizure Grouping		Placebo	Zonisamide		
			100 mg/day	300 mg/day	500 mg/day
Primary Efficacy Population		N = 112	N = 54	N = 45	N = 101
Complex partial	n with assessable data ¹	89	40	25	86
	n of responders	19	9	9	45
	%	21.3	22.5	36.0	52.3
	p-value		NA	NA	<0.001
All partial ²	n with assessable data ¹	109	52	42	99
	n of responders	22	15	18	50
	%	20.2	28.8	42.9	50.5
	p-value		NA	NA	<0.001
All seizures	n with assessable data ¹	112	54	45	101
	n of responders	20	16	19	53
	%	17.9	29.6	42.2	52.5
	p-value		NA	NA	<0.001

Analysis Population & Seizure Grouping		Placebo	Zonisamide		
			100 mg/day	300 mg/day	500 mg/day
ITT Population		N = 119	N = 55	N = 55	N = 118
Complex partial	n with assessable data ¹	94	40	33	102
	n of responders	21	9	10	46
	%	22.3	22.5	30.3	45.1
	p-value		NA	NA	<0.001
All partial ²	n with assessable data ¹	114	53	52	115
	n of responders	23	16	18	51
	%	20.2	30.2	34.6	44.3
	p-value		NA	NA	<0.001
All seizures	n with assessable data ¹	119	55	55	118
	n of responders	21	17	19	55
	%	17.6	30.9	34.5	46.6
	p-value		NA	NA	<0.001
Complex partial	n with assessable data ¹	86	39	25	74
	n of responders	18	9	9	37
	%	20.9	23.1	36.0	50.0
	p-value		NA	NA	<0.001
All partial ²	n with assessable data ¹	106	52	40	86
	n of responders	21	16	16	42
	%	19.8	30.8	40.0	48.8
	p-value		NA	NA	<0.001
All seizures	n with assessable data ¹	109	54	43	88
	n of responders	20	17	17	45
	%	18.3	31.5	39.5	51.1
	p-value		NA	NA	<0.001

¹ Number of assessable subjects. Analysis can only be performed on subjects with seizure frequency data for baseline and assessment phase and a baseline seizure frequency greater than zero.

² All partial seizures without secondary generalisation. Responders = Subjects with $\geq 50\%$ reduction in seizure frequency from baseline. p-values are for comparison between zonisamide 500 mg/day and placebo only. ITT Intent-to-treat NA Not assessed.

- **Ancillary analyses**

Seizure-Free Days

In the ITT population, in both the 300 mg/day and 500 mg/day zonisamide groups, the median number of seizure-free days per 28 days increased by 2.8 days and 3.0 days, respectively in the fixed-dose assessment phase compared with baseline.

Clinical studies in special populations

There were no specific studies in the elderly or in adolescents or children although patients from these groups were recruited in study 302.

Use in patients with hepatic and renal impairment might be dealt with in the SPC. There were relatively few adolescents or elderly in study 302; caution could be advised in the elderly.

Supportive studies

In order to have some indication of the maintenance of effect three open label studies (studies 920, 921, and 912-39) and five open label extension studies (studies 922 ext, 912-US ext, 912-EUR ext, 921 ext, and 912-ext) are referred to by the applicant.

Discussion on clinical efficacy

Zonisamide, in comparison with placebo in study 302, over a period of up to 24 weeks, statistically significantly reduced the median frequency of complex partial seizures at 500 mg/day. The effective dose range claimed in the SPC is 300 – 500 mg per day.

The reduction in complex partial seizure frequency was numerically greater at 300 mg/day compared with placebo but was not statistically significant. The lack of statistical significance is probably due to a lack of power due to the limited number of patients with complex partial seizures due to an unlucky distribution of patients with simple and complex partial seizures in the 300 mg study arm. The median percentage change in seizure frequency in the 300 mg arm however, is twice of that under placebo and for the 100 mg arm. Moreover, if all partial seizures are considered, the dose response is clear-cut.

Zonisamide demonstrated a responder rate (patients with a $\geq 50\%$ reduction in seizure frequency) of over 50% for each seizure grouping at the 500 mg/day dose in study 302, compared with a placebo rate of around 20%. The percentage of responders showed an apparent dose-response relationship for each seizure grouping. An analysis of all seizures across all four-treatment groups (i.e., including placebo), showed a statistically significant dose-response relationship between increasing dose of zonisamide and proportion of responders ($p < 0.0001$).

The improvement in number of seizure free days and global assessment raises doubt with respect to the clinical relevance of the observed effect.

There were however limited data in adolescents or in the elderly.

The high number of drop-outs (30%-40%) due to lack of efficacy in the open label studies raised concern with respect to the maintenance of effect. The applicant has reviewed the withdrawal rates in extension studies and open label extension studies and notes that withdrawal rates varied, but were usually higher with longer studies. Some degree of lack of efficacy is not unexpected in a population with refractory disease.

The titration schedule initially recommended was not justified by the data. The applicant has proposed a titration schedule which is more consistent with that used in study 302, and where it differs from that used in study 302, has appropriately justified the proposal on the basis of the pharmacokinetic data. Specific instructions are provided for patients with renal impairment or for patients who are not being administered concurrent CYP3A4 inducing agents. An adequate dose de-escalation is also provided.

Efficacy in secondary generalised seizures was not evaluated in a separate pooled analysis. The applicant has presented data on seizures leading to secondary generalisation and secondary generalised seizures, and median and mean percent reductions were seen for the 300 and 500mg doses. The applicant acknowledges that the limited numbers make it difficult to draw firm conclusions.

The applicant has reviewed the withdrawal rates in extension studies and open label extension studies and notes that withdrawal rates varied, but were usually higher with longer studies.

The choice of complex partial seizures as primary endpoint in study 302 is uncommon. The applicant has provided the rationale for the primary endpoint and how it was defined as those subjects for whom a 50% or greater reduction in complex partial seizure frequency relative to baseline was demonstrated in the fixed dose assessment period. The applicant has also confirmed that the endpoint was defined in the original protocol and was not driven by a protocol amendment. However, inclusion criteria and endpoint should be consistent. Study 302 is affected by the inclusion of subject with no complex partial seizures who do not add to primary efficacy.

Concern was raised as to whether the way seizure frequency was normalised and whether different definitions of patient populations did not introduce, at least partly, artificial results. The applicant indicates that missing data with regard to seizures were imputed from the up-titration period. An analysis was conducted with respect to the week 19-36 fixed dose period that does not impute missing

data and there were no significant differences in the results compared to those where missing data had been imputed.

The definition of three population data sets ITT-, Primary Efficacy Analysis -, and the efficacy evaluable – population) also raised concern with respect to the manner how missing values were dealt with. The applicant performed the analysis requested by the CHMP demonstrating statistically significant reductions in all partial seizure frequency for the 300 and 500mg doses. For the responder analysis the P-values for both analyses for the 500mg/day versus placebo showed statistical significance $p < 0.0001$.

The extension of the fixed dose period in study 302 from week 19-36 because of the number of subject dropouts that had occur prior to week 36, raised concern. The applicant has performed the analysis requested by CHMP and the results suggest that the inclusion of data from weeks 19 and 20 did not impact the statistical significance observed in the percentage change from baseline for all partial seizures for any of the treatment groups in Study 302 for the ITT and ITT completer populations.

Clinical safety

Patient exposure

In clinical studies, 1207 subjects aged 12 years or more, with refractory partial epilepsy received zonisamide as adjunctive therapy. Doses ranged from <100–>600 mg/day; 744 subjects received a modal (most-frequently used) dose of zonisamide in the range >200–500 mg/day.

The most frequent modal doses in the subjects who had received at least one dose of zonisamide were >300-400 mg/day (324/1207 [26.8%] subjects) and >400-500 mg/day (283/1207 [23.4%] subjects). Over half of the All Zonisamide population received a modal dose of zonisamide in the ranges >200-300, >300-400 and >400-500 mg/day.

Approximately 65% of the All Zonisamide population received treatment for a period of >3-24 months. The most frequent dosing period was >6-12 months. Fewer than 9% of subjects received treatment for ≤two months and approximately 7% of subjects received treatment for >five years.

Overall exposure to zonisamide, irrespective of dose, was more than 1500 patient years.

In the placebo-controlled studies, the zonisamide and placebo groups were well balanced in terms of demographic characteristics. In each treatment group, there were slightly more males than females; the ratio of male to female subjects was greater in the zonisamide group compared with placebo. The majority of subjects were aged between 18 and 65 years and the mean age at screening was approximately 35.5 years in each treatment group. More than 90% of subjects in each of the treatment groups were White.

As in the placebo-controlled studies, the All Zonisamide population contained more males than females, more than 93% of subjects were aged between 18 and 65 years and more than 90% of subjects were White. There are limited data on use in adolescents (12-16 years), the elderly (over 65 years) and in non-Caucasians.

There were no major differences in demographic characteristics between dose groups when subjects were categorised according to their most frequently used (modal) dose except that the highest dose group had a higher proportion of males (72.9%). This may reflect the generally greater body weight of males.

Adverse events

In placebo-controlled studies, the incidence of treatment emergent adverse events (TEAEs), defined as any event reported on or after the randomisation date, was 77.9% with zonisamide and 67.7% with placebo. Treatment-related TEAEs occurred in 61.0% of zonisamide subjects and 48.6% of placebo subjects. In the All Zonisamide population, the incidence of TEAEs was 89.1% of subjects.

For all doses combined, the highest incidence of TEAEs by body system was in the nervous system. The most frequently reported TEAEs in the zonisamide group were somnolence (16.1%), dizziness (15.5%) and headache (12.4%). The most frequently reported TEAEs in the placebo group were headache

(12.6%), accidental injury (8.9%), somnolence and dizziness (8.3% for each event). Similar findings were reported for the all zonisamide population

Analysis of adverse event incidence by dose group in the placebo-controlled studies and 'All Zonisamide' population showed a greater incidence with zonisamide >300-400 mg/day and >400-500 mg/day than with lower doses. However, incidence increased further with higher doses.

In order to evaluate the appropriateness of the proposed dosage regimen, the safety and tolerability of zonisamide were assessed separately in the dose-escalation phase and the steady-state phase.

The data suggest that adverse reactions occur more often in the dose escalation phase but less frequently if dose escalation is slower as in study 302 (see table below)

Overview of Treatment-Emergent Adverse Events by Treatment Phase (Placebo-Controlled Studies and Study 302)

Adverse Event Category	Number (%) of Subjects			
	Dose-Escalation Phase		Steady-State Phase	
	Zonisamide	Placebo	Zonisamide	Placebo
Placebo-Controlled Studies	N = 498	N = 350	N = 467	N = 336
Any adverse event	308 (61.8)	189 (54.0)	277 (59.3)	149 (44.3)
Treatment-related adverse events	235 (47.2)	135 (38.6)	190 (40.7)	84 (25.0)
Serious adverse events	14 (2.8)	8 (2.3)	11 (2.4)	9 (2.7)
Treatment-related serious adverse events	9 (1.8)	2 (0.6)	3 (0.6)	1 (0.3)
Adverse events leading to discontinuation	61 (12.2)	27 (7.7)	50 (10.7)	15 (4.5)
Study 302	N = 229	N = 120	N = 211	N = 118
Any adverse event	127 (55.5)	55 (45.8)	125 (59.2)	61 (51.7)
Treatment-related adverse events	83 (36.2)	27 (22.5)	64 (30.3)	19 (16.1)
Serious adverse events	4 (1.7)	4 (3.3)	6 (2.8)	5 (4.2)
Treatment-related serious adverse events	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to discontinuation	23 (10.0)	4 (3.3)	19 (9.0)	7 (5.9)

Serious adverse events and deaths

Placebo-Controlled Studies

In the placebo-controlled studies, the incidence of serious TEAEs was similar between the zonisamide group (4.8%) and the placebo group (4.6%).

The highest incidence of serious TEAEs by body system was in the nervous system for both treatment groups. The most frequently reported serious TEAE was convulsion (reported as a TEAE) in both the zonisamide group (0.6%) and the placebo group (0.9%).

There were no reports of kidney calculus, irrespective of seriousness, in the placebo-controlled studies.

All Zonisamide Population

The incidence of serious TEAEs was higher in the All Zonisamide population (19.0%) than in the zonisamide group of the placebo-controlled studies (4.8%), which probably reflects the much longer treatment duration in the uncontrolled studies.

In the All Zonisamide population, the highest incidence of serious TEAEs by body system was in the nervous system. The most frequently reported serious TEAEs were convulsion (4.6%) and kidney calculus (3.3%).

The serious TEAEs of convulsion and kidney calculus were considered to be treatment-related in 1.2% and 3.2% of subjects, respectively.

Death

A total of 24 subjects died as a result of TEAEs: 3 placebo-treated subjects and no zonisamide-treated subjects in the placebo-controlled studies and 24 subjects in the All Zonisamide population. All of them were unrelated to the study treatment.

Serious adverse events occurred more frequently in those on treatment. Convulsions, which could represent a failure of treatment, are recorded both as serious adverse events and causes of death.

Paranoid behaviour, suicidal behaviour and psychosis occurred in the All Zonisamide Group although only confusion is noted as an SAE in the placebo- controlled group.

A total of 19 subjects died as a result of TEAEs after receiving treatment with zonisamide and narratives are provide on these and a number of other deaths in a supplemental database. There were a number of falls, drowning and shootings which could have been accidental although it is not possible to rule out an effect from either the underlying condition or zonisamide.

Laboratory findings

Zonisamide does not appear to have a clinically or statistically significant effect on hepatic function although there were individual cases of raised enzymes.

There does appear to be an effect on urea and creatinine, which is consistent, but probably not of clinical significance.

There is no evidence from clinical studies of a clinically significant adverse effect of zonisamide on clinical chemistry parameters although the lowered potassium might reflect an underlying metabolic acidosis.

No clinically relevant haematological findings have been reported.

Vital Signs

There was no clinically significant change in median systolic blood pressure, diastolic blood pressure or heart rate in the zonisamide group or placebo group.

ECGs

Zonisamide did not demonstrate any significant cardiovascular effects. In particular, the ECG data did not show any an increase in QT/QTc interval.

Safety in special populations

There were no apparent differences in the incidence of TEAEs between adolescents, adults and elderly subjects. However, the numbers of adolescent and elderly subjects were low (61 subjects and 13 subjects, respectively).

The percentage of subjects reporting at least one TEAE was similar between adolescents (86.9%), adults (89.2%) and elderly subjects (92.3%). Dizziness, infection and headache were among the most frequently reported TEAEs in each age group. The most frequently reported treatment-related TEAEs were anorexia (19.7%) for adolescents, somnolence (22.7%) for adults and confusion (23.1%) for elderly subjects.

The adolescent subgroup generally reported each TEAE at a similar or lower frequency compared with the adult subgroup, except for vomiting and rhinitis that were reported at a frequency $\geq 5.0\%$ higher in the adolescent subgroup compared with other age groups. The 12- 16-year-old group had higher incidences of emotional lability (11.5%), ataxia (13.1%), convulsion (14.8%), difficulty in concentrating, and in verbal expression (9.8%)

The elderly subgroup generally reported each TEAE at a similar or lower frequency compared with the adult subgroup. However, headache, infection, pain, constipation, diarrhoea, confusion, insomnia and amblyopia were reported at a frequency $\geq 5.0\%$ higher in the elderly subgroup compared with the adult subgroup.

Serious TEAEs were reported slightly more frequently in elderly subjects (23.1%) compared with adolescents (18.0%); 19.0% of adults reported serious TEAEs. However, no serious TEAEs in elderly

subjects were considered to be treatment-related, compared with 11.5% of adolescents and 8.8% of adult subjects.

In summary, data on tolerability in adolescents, and elderly are limited. Adolescents had higher incidences of ataxia, emotional lability, convulsion, and difficulties with concentrating and verbal ability. There was a higher incidence of serious TEAEs in the elderly and the elderly experienced a higher incidence of insomnia and confusion.

Safety related to drug-drug interactions and other interactions

Zonisamide does not significantly affect the pharmacokinetics of other AEDs (valproate, lamotrigine, phenytoin and carbamazepine). However, AEDs that induce hepatic metabolising enzymes (phenytoin, carbamazepine and phenobarbital) increase the clearance of zonisamide significantly.

The CYP inhibitor, cimetidine, does not significantly affect the pharmacokinetics of zonisamide. Zonisamide does not significantly affect the pharmacokinetics of ethinyloestradiol or norethindrone (norethisterone) in oral contraceptives or substrates of CYP 2D6 (e.g., desipramine). These data are reported in the SPC.

Discontinuation due to adverse events

Withdrawals in both placebo- and zonisamide-treated groups in Study 302 were generally higher than other studies, possibly reflecting the longer treatment period (24 weeks) in this study.

In all studies, the percentage of subjects withdrawing from study treatment was greater in the zonisamide groups compared with the placebo groups except in the 100mg/day zonisamide group in Study 302, which had a lower withdrawal rate than placebo.

The incidence of withdrawal because of adverse events was greater in the 500 mg/day and 300 mg/day zonisamide groups of Study 302 and in the zonisamide groups of Studies 912-US and EUR, compared with the placebo groups.

Of the 108 zonisamide-treated subjects who withdrew from treatment, 63 (58.3%) withdrew because of adverse events. Of the 46 placebo-treated subjects who withdrew from treatment, 17 (37.0%) withdrew because of adverse events.

Placebo Controlled Studies

The most frequently reported treatment-related TEAEs leading to discontinuation in the zonisamide group were agitation/irritability (2.8%), dizziness (2.6%) and anorexia (2.4%). The most frequently reported treatment-related TEAEs leading to discontinuation in the placebo group were tiredness (1.4%), dizziness (1.1%) and somnolence (0.9%). Analysis by treatment phase showed that TEAEs leading to discontinuation occurred more frequently with zonisamide than with placebo in each phase. The most frequently reported TEAEs leading to discontinuation with zonisamide were agitation/irritability and somnolence (3.0% for each event in placebo-controlled studies). In the All Zonisamide population, the incidence of TEAEs leading to discontinuation was 24.6% and the most frequently reported TEAEs leading to discontinuation were anorexia, agitation/irritability (3.1% each) and somnolence (3.0%). See table below.

Treatment-Emergent Adverse Events Leading to Discontinuation Reported by ≥1.0% of Subjects, by Dose at Onset in the Double-Blind Period (Placebo-Controlled Studies)

Body System and COSTART Preferred Term ¹	Number (%) of Subjects ²								
	Zonisamide Dose at Onset (mg/day)								Placebo
	≤100 N=448	>100-200 N=417	>200-300 N=370	>300-400 N=361	>400-500 N=193	>500-600 N=43	>600 N=12	All Doses ³ N=498	
Any adverse event	9 (2.0)	15 (3.6)	20 (5.4)	26 (7.2)	31 (16.1)	5 (11.6)	1 (8.3)	99 (19.9)	39 (11.1)
Body as a whole									
Headache	3 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.4)	2 (0.6)
Digestive									
Anorexia	0 (0.0)	0 (0.0)	1 (0.3)	5 (1.4)	5 (2.6)	0 (0.0)	0 (0.0)	12 (2.4)	0 (0.0)
Nausea	1 (0.2)	1 (0.2)	3 (0.8)	1 (0.3)	3 (1.6)	0 (0.0)	0 (0.0)	10 (2.0)	1 (0.3)
Nervous system									
Agitation/irritability	2 (0.4)	2 (0.5)	3 (0.8)	3 (0.8)	3 (1.6)	0 (0.0)	0 (0.0)	15 (3.0)	1 (0.3)
Anxiety	1 (0.2)	1 (0.2)	1 (0.3)	0 (0.0)	3 (1.6)	0 (0.0)	0 (0.0)	7 (1.4)	1 (0.3)
Ataxia	0 (0.0)	1 (0.2)	1 (0.3)	1 (0.3)	3 (1.6)	1 (2.3)	0 (0.0)	10 (2.0)	1 (0.3)
Confusion	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)	8 (1.6)	1 (0.3)
Depression	1 (0.2)	2 (0.5)	0 (0.0)	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)	8 (1.6)	3 (0.9)
Difficulty concentrating	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)	3 (1.6)	0 (0.0)	0 (0.0)	7 (1.4)	3 (0.9)
Difficulty with memory	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.8)	3 (1.6)	1 (2.3)	0 (0.0)	11 (2.2)	1 (0.3)
Dizziness	2 (0.4)	3 (0.7)	0 (0.0)	4 (1.1)	4 (2.1)	0 (0.0)	0 (0.0)	13 (2.6)	4 (1.1)
Emotional lability/moodiness	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)	1 (0.5)	0 (0.0)	1 (8.3)	5 (1.0)	1 (0.3)
Somnolence	1 (0.2)	2 (0.5)	2 (0.5)	4 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)	15 (3.0)	4 (1.1)
Tiredness	0 (0.0)	1 (0.2)	3 (0.8)	3 (0.8)	2 (1.0)	0 (0.0)	0 (0.0)	11 (2.2)	5 (1.4)
Special senses									
Diplopia	0 (0.0)	1 (0.2)	1 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	7 (1.4)	1 (0.3)

¹. Only serious treatment-emergent adverse events leading to discontinuation with a frequency ≥1.0% in the zonisamide all doses or placebo groups are shown. Treatment-emergent adverse events leading to discontinuation are counted by subject in the double-blind period following initiation of randomised treatment. Subjects are counted uniquely per adverse event and per indicated dose.

2. The denominator is the number of subjects who ever received treatment at the indicated dose level during the double-blind period. Subjects may be counted in more than one dose group.
3. Events with unknown zonisamide dose at onset are included only in the 'All Doses' column.

COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

In the All Zonisamide population, the incidence of TEAEs leading to discontinuation was 24.6%. The highest incidence of TEAEs leading to discontinuation by body system was in the nervous system. The most frequently reported TEAEs leading to discontinuation were anorexia and agitation/irritability (3.1% for each event) and somnolence (3.0%).

As in the placebo-controlled studies, the most frequently reported treatment-related TEAEs leading to discontinuation were anorexia (3.0%), agitation/irritability (2.9%) and dizziness (2.7%). The incidence of TEAEs leading to discontinuation did not increase with increasing duration of treatment, either for the percentage of subjects reporting any adverse event or any COSTART preferred term.

Kidney Stones

Renal calculus, which was reported only in the All Zonisamide group, does appear to be a definite association and case reports suggest that this may be associated with carbonic anhydrase inhibition producing alkaline urine.

As renal stones were considered to be possibly related to zonisamide, renal ultrasound examinations were performed at baseline and during treatment in several studies and all stones found on the renal ultrasounds and clinical symptoms of renal stones in these studies were to be recorded as serious adverse events.

Of the 59 reported stones, only 15 of these events in 12 subjects were considered to be symptomatic (diagnosis based on either passing a stone or clinical symptoms). At the time of the symptomatic event, six of the 12 subjects were receiving zonisamide 600-800 mg/day. The mean time following initiation of treatment to the first report of symptomatic stones was 22 months (range 3-69 months). Renal stones may be related to an effect on carbonic anhydrase.

Oligohidrosis

The primary safety database was searched for TEAEs related to oligohidrosis (dehydration and heat stroke). These events were reported in four subjects while receiving zonisamide. Dehydration was reported in three subjects; one of these events was reported as serious. In addition, one subject had a non-serious heat stroke on Study Day 857 that was rated as mild in intensity. None of the four subjects discontinued study drug because of these events. Oligohidrosis and renal stones may be related to an effect on carbonic anhydrase

Cognitive Function

Patients withdrew from both placebo controlled and All zonisamide groups for difficulty in concentrating, difficulty with memory, somnolence, emotional lability, confusion and depression.

In a small study in nine patients, at mean steady state plasma concentrations of approximately 30 mcg/ml, zonisamide appeared to affect specific cognitive functions such as acquisition and consolidation of new information. There was no effect on previously learned material such as vocabulary and psychomotor performance. Verbal learning was affected but visual-perceptual learning was not. Clinical signs and symptoms of toxicity were not observed.

In the placebo controlled trials, within the Nervous System body system, commonly reported events included fatigue, somnolence and tiredness; somnolence occurred more frequently with zonisamide (16.1%) than with placebo (8.3%). There were reports coded as agitation/irritability, confusion, difficulty concentrating and difficulty with memory. All these occurred slightly more frequently with zonisamide than with placebo but the differences were less marked than for somnolence.

Rash and hypersensitivity

A total of 30 subjects had TEAEs that met the search criteria for hypersensitivity. Twenty subjects had an allergic reaction, seven had urticaria and four subjects had ulcerative stomatitis. One of the

urticarial events was considered serious (severe intensity); this event started on Study Day 2 and ended on Day 50. The study drug was temporarily discontinued, but the subject did not discontinue treatment. One subject with a non-serious allergic reaction (mild intensity and possibly related to study drug) that started on Day 25 was discontinued from the study on Day 28 due to this adverse event.

A total of 101 subjects had TEAE that met the criteria for rash-like events. The occurrence of the rash-like events resulted in discontinuation of 10 of the other 98 subjects.

Post marketing experience

From approval in 2000 until March 2003, subject exposure for zonisamide capsules in the US is estimated to be 59,667 patient-years (total prescriptions per year) based upon retail and mail order prescriptions. Hospital patient data are not available and US exposure information is based upon US prescription data provided by Scott-Levin. From approval (March 2000) until December 2002, the number of unique subjects was estimated to be 37,276.

Based upon prescription data provided by Intercontinental Marketing Services (IMS) through Dainippon, cumulative Japanese zonisamide exposure is estimated to be 2,230,460 patient-years from approval in Japan in April 1989 until March 2003, which represents approximately 1,229,881 unique subjects.

In total, 632 cases containing adverse events cases, that indicate a possible relationship between the event and the use of zonisamide, were identified from US and Japanese post-marketing sources. Of these, 257 cases contained 602 SAEs.

Overall, based on the combined incidence of cases from the US and Japan, all events listed below have occurred in isolated cases (<1:10000).

Neurological Events: Convulsion, grand mal convulsion, psychosis, hallucinations, confusion, somnolence, depression, thinking abnormal, amnesia, coma.

Gastrointestinal Events: Nausea, vomiting, gastrointestinal disorder, diarrhoea, pancreatitis.

Haematologic Events: Agranulocytosis, thrombocytopenia, leucopenia, aplastic anaemia, pancytopenia, leucocytosis.

Hepatic Events: Liver damage, liver function tests abnormal.

Hypersensitivity Reactions: Allergic reactions, including rash, pruritus, Stevens Johnson Syndrome, erythema multiforme.

Renal Events: Urolithiasis, kidney calculus, urinary tract infection, hydronephrosis, urine abnormality, kidney failure.

Respiratory Events: Pneumonia, aspiration pneumonia, respiratory disorder, dyspnoea

Skin and Appendages Events: Rash.

In addition, isolated cases of fever, metabolic acidosis, myasthenia, hypokalaemia, non-protein nitrogen increase, creatine phosphokinase increase, rhabdomyolysis, abnormal vision, lymphadenopathy, neuroleptic malignant syndrome, oligohidrosis, including decreased sweating and heat stroke, and SUDEP have been reported.

- **Discussion on clinical safety**

Data from clinical trials were supplemented with data from extensive post marketing experience in the United States and Japan. The safety profile of zonisamide is more or less the expected profile for an anti-epileptic given in the add-on setting and sulphonamides.

In the placebo-controlled studies, the incidence of TEAEs was 77.9% with zonisamide and 67.7% with placebo whilst treatment-related TEAEs occurred in 61.0% of zonisamide subjects and 48.6% of placebo subjects. The incidence of TEAEs was greater with zonisamide than with placebo for both the dose-escalation phase and the steady-state treatment phase. The incidence of treatment-related TEAEs was higher in the dose-escalation phase than in the steady-state phase in both treatment groups. In the All Zonisamide population, the incidence of TEAEs was 89.1% of subjects.

The incidence of serious TEAEs was similar for the zonisamide group (4.8%) and the placebo group (4.6%) (placebo-controlled studies). The incidence of serious TEAEs was higher in the All Zonisamide population (19.0%) reflecting the longer treatment duration in the uncontrolled studies. The most frequently reported serious TEAEs in the All Zonisamide population were convulsion reported as an adverse event (4.6%) and kidney calculus (3.3%). There were no reports of kidney calculus, irrespective of seriousness, in the placebo-controlled studies.

The high incidence of CNS events is not unexpected for anti-epileptics. There does however appear to be an association between zonisamide and the occurrence of kidney stones, dehydration and heat stroke. Zonisamide may also lead to a substantial decrease in weight. Clinically significant effects on blood pressure and ECG's were not observed.

Certain aspects of the safety profile appear to be related to the fact that it is a benzisoxazole derivative containing a sulphonamide group and is also a carbonic anhydrase inhibitor. Post marketing experience raised concern with respect to the occurrence of the Steven Johnson syndrome and other serious skin reactions, heat stroke, neuroleptic malignant syndrome, rhabdomyolysis and kidney failure. These should be subject of continued pharmacovigilance activities.

Reports of skin rash and hypersensitivity may reflect a sulphonamide like effect.

Safety was not demonstrated in children, adolescents and the elderly. The small numbers of patients in these age-categories do not allow benefit risk assessment. Studies in children and adolescent are lacking and are to be part of an ongoing developmental plan for zonisamide.

With respect to elderly, special attention should be drawn to the impact of zonisamide on other CNS function especially sedation and cognition as elderly subjects are more sensitive to CNS adverse events. In order to establish the optimal dose in the elderly more safety data are required

5. Overall conclusions, benefit/risk assessment and recommendation

In this application the main efficacy study (study 302) was designed and performed after the applicant had sought scientific advice from the CPMP. Other previously performed studies were supportive and the overall impression is that the dose used in these latter studies is in the lower effective dose range.

Safety data from clinical trials were supplemented with data from extensive post marketing experience in the United States and Japan. The safety profile of zonisamide is more or less the expected profile for an anti-epileptic given in the add-on setting.

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

Pharmacodynamic studies have demonstrated that zonisamide can reduce the extent of induced seizures. The mechanism of action remains unclear, although it appears to be similar to phenytoin, phenobarbitone and carbamazepine, the main comparators.

Following oral dosing the drug is rapidly absorbed, widely distributed and metabolised, and excreted in the urine. Metabolites are similar across the species tested but vary in relative amount. Foetal exposure is high, similar to that of the dam.

The main adverse observations following a single high dose of zonisamide appear to be linked to the CNS effects of the drug. In repeat dose toxicity, transient clinical signs of toxicity such as sedation and ataxia, which are in line with its pharmacological action, have been induced when zonisamide was administered as bolus doses (i.e. gavage) at 200 mg/kg/day or greater; such effects were, however, not seen when higher doses (800 mg/kg/day) were administered via dietary admixture, suggesting a C_{max} basis of these observations rather than overall exposure (AUC/C_{ss}). Adverse effects in CNS, kidney and liver were observed in animals at doses leaving no safety margin for human therapeutic use. Juvenile toxicity was only investigated in acute studies.

In reproductive/developmental toxicity studies in rodents and dogs, no evidence of effects on fertility of zonisamide were seen. Zonisamide was embryotoxic and teratogenic (reduced pup weight, increase in cardiac and major blood vessel defects, delayed ossification) and induced maternal toxicity at high doses. In monkeys zonisamide acted as an abortifacient. The suggested NOAELs are 20 mg/kg in rats, 10 mg/kg in dogs and <10 mg/kg in monkeys, all of which produce plasma levels within human efficacious levels. Therefore, it cannot be excluded that the adverse effects observed in animals might also occur in humans. Pregnancy is contra-indicated and potential interference between zonisamide and the chosen method of avoiding pregnancy should be ruled out.

Based on *in vitro* and *in vivo* genotoxic tests, zonisamide is not considered to pose a genotoxic hazard for humans. The results of the two-year studies in rodents suggest that zonisamide does not possess carcinogenic potential.

No antigenic potential was observed when tested in mice, guinea pigs and rabbits.

No environmental risk is anticipated from the use of zonisamide.

It is considered unlikely that zonisamide could have a dependence liability or potential for abuse.

Efficacy

Zonisamide, in comparison with placebo in study 302, over a period of up to 24 weeks, statistically significantly reduced the median frequency of complex partial seizures at 500 mg/day. The effective dose range claimed is in the SPC (300 – 500 mg per day).

The reduction in complex partial seizure frequency was numerically greater at 300 mg/day compared with placebo but was not statistically significant. The median percentage change in seizure frequency in the 300 mg arm however, is twice of that under placebo and for the 100 mg arm. Moreover, if all partial seizures are considered, the dose response is clear-cut.

Zonisamide demonstrated a responder rate (patients with a $\geq 50\%$ reduction in seizure frequency) of over 50% for each seizure grouping at the 500 mg/day dose in study 302, compared with a placebo rate of around 20%. The percentage of responders showed an apparent dose-response relationship for each seizure grouping. An analysis of all seizures across all four-treatment groups (i.e., including placebo), showed a statistically significant dose-response relationship between increasing dose of zonisamide and proportion of responders ($p < 0.0001$).

There were however limited data in adolescents or in the elderly.

The high number of drop-outs (30%-40%) due to lack of efficacy in the open label studies raised concern with respect to the maintenance of effect. The applicant has reviewed the withdrawal rates in extension studies and open label extension studies and notes that withdrawal rates varied, but were usually higher with longer studies. Some degree of lack of efficacy is not unexpected in a population with refractory disease.

The titration schedule initially recommended was not justified by the data. The applicant has proposed a titration schedule which is more consistent with that used in study 302, and where it differs from that used in study 302, has appropriately justified the proposal on the basis of the pharmacokinetic data. Specific instructions are provided for patients with renal impairment or for patients who are not being administered concurrent CYP3A4 inducing agents. An adequate dose de-escalation is also provided.

Efficacy in secondary generalised seizures was not evaluated in a separate pooled analysis. The applicant has presented data on seizures leading to secondary generalisation and secondary generalised seizures, and median and mean percent reductions were seen for the 300 and 500mg doses. The applicant acknowledges that the limited numbers make it difficult to draw firm conclusions.

The choice of complex partial seizures as primary endpoint in study 302 is uncommon. The applicant has provided the rationale for the primary endpoint and how it was defined as those subjects for whom a 50% or greater reduction in complex partial seizure frequency relative to baseline was demonstrated in the fixed dose assessment period. The applicant has also confirmed that the endpoint was defined in the original protocol and was not driven by a protocol amendment. However, inclusion criteria and endpoint

should be consistent. Study 302 is affected by the inclusion of subject with no complex partial seizures who do not add to primary efficacy.

Concern was raised as to whether the way seizure frequency was normalised and whether different definitions of patient populations did not introduce, at least partly, artificial results. The applicant indicates that missing data with regard to seizures were imputed from the up-titration period. An analysis was conducted with respect to the week 19-36 fixed dose period that does not impute missing data and there were no significant differences in the results compared to those where missing data had been imputed.

The definition of three population data sets ITT-, Primary Efficacy Analysis -, and the efficacy evaluable – population) also raised concern with respect to the manner how missing values was dealt with. The applicant has performed the requested analysis that demonstrates statistically significant reductions in all partial seizure frequency for the 300 and 500mg doses. For the responder analysis the P-values for both analyses for the 500mg/day versus placebo showed statistical significance $p < 0.0001$.

The extension of the fixed dose period in study 302 from week 19-36 is agreed.

Safety

The safety profile of zonisamide in adults is acceptable. The safety profile is more or less the expected profile for an anti-epileptic given in the add-on setting and sulphonamides.

In the placebo-controlled studies, the incidence of TEAEs was 77.9% with zonisamide and 67.7% with placebo whilst treatment-related TEAEs occurred in 61.0% of zonisamide subjects and 48.6% of placebo subjects. The incidence of TEAEs was greater with zonisamide than with placebo for both the dose-escalation phase and the steady-state treatment phase. The incidence of treatment-related TEAEs was higher in the dose-escalation phase than in the steady-state phase in both treatment groups. In the All Zonisamide population, the incidence of TEAEs was 89.1% of subjects.

The incidence of serious TEAEs was similar for the zonisamide group (4.8%) and the placebo group (4.6%) (placebo-controlled studies). The incidence of serious TEAEs was higher in the All Zonisamide population (19.0%) reflecting the longer treatment duration in the uncontrolled studies. The most frequently reported serious TEAEs in the All Zonisamide population were convulsion reported as an adverse event (4.6%) and kidney calculus (3.3%). There were no reports of kidney calculus, irrespective of seriousness, in the placebo-controlled studies.

Safety in children, adolescents and the elderly could not be assessed due to insufficient data.

Certain aspects of the safety profile appear to be related to the fact that it is a benzisoxazole derivative containing a sulphonamide group and is also a carbonic anhydrase inhibitor. Post marketing experience raised concern with respect to the occurrence of the Steven Johnson syndrome and other serious skin reactions, heat stroke, neuroleptic malignant syndrome, rhabdomyolysis and kidney failure.

Benefit/risk assessment

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Zonisamide is of low acute oral toxicity ($LD_{50} \geq 1000$ mg/kg) in mice, rats, dogs and monkeys. The main effects are CNS-related. There is no apparent gender-related difference. Neonatal rats are of increased sensitivity. In repeated dose studies, zonisamide induces adverse effects on the CNS, kidney and liver. Reproduction toxicology studies indicated that zonisamide has abortifacient and teratogenic potential. The safety margin for these effects is low to absent. Therefore, it cannot be excluded that the adverse effects observed in animals might also occur in humans. Adverse eye effects were not observed in the repeated dose studies. Zonisamide does not possess genotoxic or carcinogenic potential. No antigenic potential was observed when tested in mice, guinea pigs and rabbits. It is considered unlikely that zonisamide contains potential for dependence liability. Juvenile toxicity was not investigated. An expert report has been submitted on the environmental risk. The conclusion that there is no concern for environmental pollution is endorsed.

Zonisamide, in comparison with placebo in study 302, over a period of up to 24 weeks, statistically significantly reduced the median frequency of complex partial seizures at 500 mg/day. The effective dose range claimed is in the SPC (300 – 500 mg per day).

The reduction in complex partial seizure frequency was numerically greater at 300 mg/day compared with placebo but was not statistically significant. The median percentage change in seizure frequency in the 300 mg arm however, is twice of that under placebo and for the 100 mg arm. Moreover, if all partial seizures are considered, the dose response is clear-cut.

Zonisamide demonstrated a responder rate (patients with a $\geq 50\%$ reduction in seizure frequency) of over 50% for each seizure grouping at the 500 mg/day dose in study 302, compared with a placebo rate of around 20%. The percentage of responders showed an apparent dose-response relationship for each seizure grouping.

There is limited data in adolescents and elderly. Therefore the indication is restricted to adults.

The applicant has proposed a titration schedule on the basis of the pharmacokinetic data. Specific instructions are provided for patients with renal impairment or for patients who are not being administered concurrent CYP3A5 inducing agents. An adequate dose de-escalation is also provided.

Efficacy in secondary generalised seizures was not evaluated in a separate pooled analysis and the limited numbers make it difficult to draw firm conclusions.

In clinical safety, the high incidence of CNS events is not unexpected for anti-epileptics. There does however appear to be an association between zonisamide and the occurrence of kidney stones, dehydration and heat stroke. Zonisamide may also lead to weight loss. Clinically significant effects on blood pressure and ECG's were not observed.

Certain aspects of the safety profile appear to be related to the fact that zonisamide is a benzisoxazole derivative containing a sulphonamide group and is also a carbonic anhydrase inhibitor. Post marketing experience raised concern with respect to the occurrence of the Steven Johnson syndrome and other serious skin reactions, heat stroke, neuroleptic malignant syndrome, rhabdomyolysis and kidney failure. The applicant committed in a letter of undertaking to ensure a close pharmacovigilance monitoring.

Safety was not demonstrated in children, adolescents and the elderly. The small numbers of patients in these age-categories do not allow benefit risk assessment. Studies in children and adolescent are lacking and are to be part of an ongoing developmental plan for zonisamide.

With respect to elderly, special attention should be drawn to the impact of zonisamide on other CNS function especially sedation and cognition as elderly subjects are more sensitive to CNS adverse events. In order to establish the optimal dose in the elderly more safety data are required. A post-marketing surveillance focusing on the CNS effects of zonisamide use in the elderly is planned as a follow-up measure.

Overall, zonisamide is considered to have a positive benefit risk ratio as adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults with epilepsy.

Recommendation

”Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Zonégren in the adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation, was favourable and therefore recommended the granting of the marketing authorisation