28 January 2016
EMA/170957/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zonisamide Mylan

International non-proprietary name: zonisamide

Procedure No.: EMEA/H/C/004127/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AEDs	Antiepileptic drugs
ANOVA	Analysis of variance
AS (=API)	Active substance
API (=AS)	Active Pharmaceutical Ingredient
AUC	Area under the concentration- time curve
BE	Bioequivalence
CI	Confidence interval
Cmax	Maximum observed serum concentration
CQA	Critical Quality Attribute
CV	Coefficient of variation
DSC	Differential Scanning Calorimetry
EMA	European Medicines Agency
GABA	Gamma-aminobutyric acid
GC	Gas Chromatography
GCP	Good Clinical Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared spectroscopy
LC/MS/MS	Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
LDPE	Low Density Polyethylene
LLOQ	Lower Limit of Quantitation
NMR	Nuclear Magnetic Resonance
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
QC	Quality Control
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TLSB	Triple Laminate Sunlight Barrier Bag
tmax	Time to achieve Cmax
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
UHPLC	ultra-high performance liquid chromatography
USP/NF	United States Pharmacopoeia/National Formulary
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S. submitted on 6 May 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zonisamide Mylan, through the centralised procedure under Article 3(3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 November 2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Zonisamide Mylan is indicated as:

- monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy
- adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Zonegran instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Zonegran 25 mg, 50 mg, 100 mg, Capsules, hard
- Marketing authorisation holder: Eisai Ltd
- Date of authorisation: 10-03-2005
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/04/307/001-013

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Zonegran 25 mg, 50 mg, 100 mg, Capsules, hard

- Marketing authorisation holder: Eisai Ltd
- Date of authorisation: 10-03-2005
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/04/307/001-013

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Zonegran 100 mg, Capsules, hard
- Marketing authorisation holder: Eisai Ltd
- Date of authorisation: 10-03-2005
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/04/307/004, EU/1/04/307/006, EU/1/04/307/007, EU/1/04/307/008, EU/1/04/307/011
- Bioavailability study number(s): GE/13/ZON/1/13

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Zonisamide Mylan was given a Marketing Authorisation in Australia on 13 June 2006.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Bruno Sepodes

- The application was received by the EMA on 6 May 2015.
- The procedure started on 25 June 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 September 2015.
- During the meeting on 22 October 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 November 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 December 2015.
- During the meeting on 28 January 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zonisamide Mylan.

2. Scientific discussion

2.1. Introduction

This application concerns a marketing authorisation of a generic medicinal product of the centrally authorised product Zonegran. Zonegran was first authorised for use in the European Union on 10 March 2005.

The active substance is zonisamide, a benzisoxazole derivative. Zonisamide is an antiepileptic compound, chemically unrelated to other antiepileptic drugs (AEDs). The exact mechanism of action is not known, but zonisamide has been shown to block voltage sensitive sodium and calcium channels, which is thought to disrupt synchronised neuronal firing, thereby reducing the spread of seizure discharges and disrupting subsequent epileptic activity. Some studies also showed a modulatory effect on Gamma-aminobutyric acid (GABA)-mediated neuronal inhibition as well as a variety of other effects, which may contribute to the pharmacological effects. Furthermore, zonisamide exerts weak carbonic anhydrase activity *in-vitro*.

Zonegran is indicated as:

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

At the time of this report, Zonegran was available as hard capsules (25 mg, 50 mg, and 100 mg) and orodispersible tablets (25 mg, 50 mg, 100 mg and 300 mg).

At treatment initiation of Zonegran in adults it is recommended to titrate the dose of zonisamide on the basis of the clinical effect. In newly diagnosed patients (monotherapy), treatment is started with 100 mg once a day, which is increased by 100 mg/day every 2 weeks. The usual maintenance dose is 300 mg/day. For add-on treatment, zonisamide is recommended to be initiated with a dose of 50 mg/day, which is increased to 100 mg/day after 1 week and thereafter at increments of 100 mg/day until the usual maintenance dose of 300-500 mg/day. In children, dosing recommendations are based on body weight.

Zonegran may be taken with or without food.

The application for Zonisamide Mylan concerns 25 mg, 50 mg and 100 mg hard capsules in the full range of indications approved for the reference product Zonegran. The application is supported by one bioequivalence (BE) study under fasting conditions with the 100 mg capsule strength. A biowaiver has been requested for the remaining strengths.

2.2. Quality aspects

2.2.1. Introduction

Zonisamide Mylan is presented as hard capsules containing 25 mg, 50 mg or 100 mg of zonisamide as active substance.

Other ingredients are: microcrystalline cellulose, sodium laurilsulfate, hydrogenated vegetable oil. The capsule shells contain: titanium dioxide (E171) and gelatin; the printing ink consists of: shellac black iron oxide (E172) and potassium hydroxide, as described in section 6.1 of the SmPC.

The finished product is available in a PVC/PVDC–Aluminium blister, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance zonisamide is 1,2-Benzisoxazole-3-methanesulfonamide, corresponding to the molecular formula $C_8H_8N_2O_3S$ and has a molecular mass 212.23 g/mol. The active substance has the following structure:

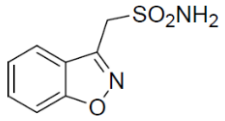

Figure 1: Zonisamide structure.

The structure of the active substance (AS) has been confirmed by means of Mass Spectrometry, Infrared Spectrophotometry (IR), and ^{1}H- and ^{13}C-Nuclear Magnetic Resonance Spectroscopy (NMR), all of which support the chemical structure.

It appears as a white to almost white, non-hygroscopic crystalline powder. It is moderately soluble in water and HCl 0.1 N, practically insoluble in sodium hydroxide 1M, freely soluble in acetone and soluble in ethanol and acetonitrile. Its pKa is 10.2 and its partition coefficient is 0.36.

Zonisamide does not have any chiral centre and is therefore an optical inactive substance. Polymorphism of zonisamide has not been described in literature. A polymorphism study performed the manufacturer using X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC) shows that the same crystalline form is obtained repeatedly under the conditions of the manufacturing process.

Manufacture, characterisation and process controls

The information on the active substance is provided according to the ASMF procedure.

The proposed manufacturing process for zonisamide active substance involves two steps using commercially available starting materials.

Reprocessing of the active substance or intermediate, including the description of the operation that has to be done and has been described. Both steps are considered critical and the critical process parameters were listed together with acceptable justification for each operational margin. The starting material and the intermediate are controlled by appropriate specifications.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were characterised and are well discussed with regards to their origin and fate.

The active substance primary packaging material is of food grade and in compliance with current Ph. Eur. requirements and Commission Regulation 1183/2012.

Specification

The active substance specification includes appropriate tests and limits for: appearance (visual inspection), identity (IR), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), particle size (laser light diffraction).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided.

Batch analysis results for three commercial scale batches manufactured by the proposed manufacturer were presented. The results comply with the proposed specification indicating consistent and robust manufacture.

Stability

Stability data on three commercial scale batches packaged in the proposed container simulating commercial packaging for storage and distribution, stored for up to 24 months at long term condition (30 °C / 65 % RH) and for 6 months under accelerated conditions (40 °C / 75 % RH) were presented. Stability studies were conducted according to the ICH guidelines.

The following parameters were tested: appearance, water, related substances and assay. Water test was performed instead of loss on drying (as in the release specification) because this parameter was specified at the beginning of the stability studies. Also, the control of this parameter is maintained taking into account that water may be increased along the stability studies but not the residual solvents (i.e. ethanol). Particle size is not included in the tested stability parameters because it is not a parameter likely to change with time during storage and does not need to be controlled in stability studies. This has been accepted on the basis of the physicochemical properties of the zonisamide, batch data and considering that no mechanical energy is provided to the substance during storage.

The analytical procedures used in stability studies are the same as described for release which were shown to be stability indicating. Karl-Fischer method was used for water test. After 24 months under long-term conditions or 6 months under accelerated conditions the three batches are within specification showing little or no change over time; the study is on-going.

A stress study on a pilot scale batch was performed under the following conditions: light, high temperature and humidity combined, in solution in neutral, acid and basic medium and in oxidising conditions. Zonisamide was shown to be stable in the solid state under light stress and also at elevated temperatures along with high relative humidity. It is unstable in basic and oxidising solutions only when severe heating conditions are employed. The new impurities generated under extreme conditions are not present in the impurity profile of zonisamide in normal stability conditions.

A photostability study according to the ICH guideline on photostability testing was performed on the same pilot batch of the active substance. The study confirmed that zonisamide is stable against UV/visible light irradiation and therefore that no special storage conditions with respect to light protection are required.

Based on presented stability data, the proposed retest period is acceptable.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

Zonisamide Mylan is an immediate release hard gelatin capsule. Zonisamide 25 mg is a white hard capsule size No. 4 printed in black “Z 25”, 50 mg strength is a white hard capsule size No. 3 printed in red “Z 50” and the 100 mg strength is a white hard capsule size No. 1 printed in black “Z 100” to allow strength differentiation.
The objective of pharmaceutical development was to develop a product generic to the reference product Zonegran 25 mg, 50 mg and 100 mg hard capsules. The same pharmaceutical form has been developed as that of the reference product.

The properties of the active substance and the choice of the excipients have been satisfactorily described. All the excipients used in this drug product are referred in the Ph. Eur. or NF.

The compatibility of the active substance with the excipients has been adequately proved. Zonisamide capsules formulations used during development were presented.

Taking into account the pharmaco-technical characteristics of the active substance the development of product was orientated to a granulation process in order to obtain a final mixture with good homogeneity and manufacturability. All three strengths are manufactured from the same blend by proportionally filling the capsules.

Comparative dissolution profiles between the test and reference product used in the bioequivalence study were performed in different media pH 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The results indicate that in all the tested media more than 85% of the drug is released within 15 min. No significant difference between the two products was observed for the comparative dissolution test.

Also, the comparative dissolution profile has been performed in 0.1N HCl, pH 4.5 buffer and pH 6.8 buffer between Zonisamide Mylan different strengths (i.e. 25mg and 50mg) and 100 mg bio-batch. The dissolution profiles show similar profiles with more than 85% of the drug dissolved within 15 minutes in all media.

The influence of the particle size distribution of the Zonisamide drug substance on dissolution behaviour of the final capsules has been investigated and a suitable specification for particle size has been set.

The proposed QC (quality control) dissolution method has been adequately justified concerning the selection of the dissolution medium, apparatus and agitation speed. The discriminatory power of the proposed dissolution test with regard to relevant manufacturing variables and quality attributes of the active substance has been demonstrated.

According to a risk assessment performed to identify the high risk steps of granulation that may affect the Critical Quality Attributes (CQAs) of the final finished product, the critical process parameters that should be controlled were identified .

The initial risk assessment and justifications was provided. Previous experience was used to determine the degree of risk associated with the granulation step and its potential to impact CQAs of the finished drug

product. Once the CQAs were identified, the optimization of the process was focused on studying and establishing the most appropriate process parameters.

The product is packaged n blister PVC/PVDC-Aluminium. The suitability of the selected material as container closure system was confirmed by the stability studies.

Manufacture of the product and process controls

The main steps of the manufacturing process are: blending, granulation, milling, drying, final blending and encapsulation. The final blend is encapsulated proportionally at different weight for each dose and the capsules are packed.

The process is a conventional wet granulation process and subsequent encapsulation. .Critical steps were identified. All provided in-process controls (IPCs) established for the manufacturing process are acceptable and justified and are considered suitable to guarantee the intended quality of the drug product. Details regarding the holding time at various process stages during manufacturing have been established.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Satisfactory validation protocol has been submitted covering all three strengths.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for this kind of dosage form including appearance (organoleptic), uniformity of mass (Ph. Eur.), uniformity of dosage units (Ph. Eur.), identification (IR, UHPLC), dissolution (UHPLC, Ph. Eur.), assay (UHPLC), related substances (UHPLC), water (Ph. Eur.), and microbial contamination (Ph. Eur.).

The specifications were set in line with the requirements of the Ph. Eur. general monographs, the ICH guidelines and available batch data. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of active substance and impurities has been presented.

Batch analysis data were provided on three batches for each strength manufactured at the proposed manufacturing site at a scale smaller than the commercial batch size). Results were in line with proposed specifications and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three commercial scale batches per strength stored under long term conditions (25 ºC / 60% RH) for up to 18 months and under accelerated conditions (40 ºC / 75% RH) for 6 months were provided. The stability studies were carried out in accordance with the ICH guidelines on stability. All the batches were packed in the container closure system proposed for marketing. Samples have been tested for checking the appearance, disintegration, water, dissolution, assay, related substances and microbial contamination (except in photostability studies). The methods used were shown to be stability indicating and were the same as for release with the exception of disintegration (not included in the release specification)

which was done according to the European Pharmacopoeia. No significant changes were observed and the results were found to be well within the specification.

A photostability study was performed on one batch of Zonisamide Mylan 25 mg and 100 mg capsules according ICH Q1 B. Based on the results of this study, it can be concluded that the Zonisamide Mylan is photostable.
The forced degradation study (neutral medium, acidic medium, basic medium, oxidative medium, light stress (simulated sun light, temperature and humidity and temperature) has shown that Zonisamide Mylan capsules are stable under neutral medium, acid medium, light stress and high temperature and humidity and that the product is less stable under basic medium, oxidative medium and high temperature (150 ºC).

Base on the overall results, the proposed shelf-life of 30 months without any special storage conditions is acceptable as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

Hard gelatin capsules are the only excipients from animal origin and corresponding Certificates of Suitability (CEPs) of monograph of the European Pharmacopoeia for Gelatin have been presented.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has 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 clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided by the applicant. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Zonisamide Mylan is considered unlikely to result in any significant increase in the combined sales volumes for all zonisamide containing products and the exposure of the environment to the active substance. Thus, any risk for the environment is expected to be similar and not increased.

2.3.3. Discussion and conclusion on the non-clinical aspects

The CHMP was of the view that the non-clinical overview provided in support of this application was based on up-to-date and adequate scientific literature. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a generic product consisting of hard capsules containing 25 mg, 50 mg and 100 mg zonisamide. To support the marketing authorisation application the applicant conducted a bioequivalence study with the 100 mg strength based on a cross-over design under fasting conditions. This study was the pivotal study for the assessment.

The applicant also provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of zonisamide based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Good Clinical Practice (GCP)

The applicant confirmed that the clinical trial was performed in accordance with GCP.

The applicant has provided a statement to the effect that the clinical trial conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant requested a biowaiver for the remaining hard capsule strengths (25 and 50 mg). According to the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) the following general requirements must be met where a waiver for additional strength(s) is claimed:

a) the pharmaceutical products are manufactured by the same manufacturing process,

b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

d) appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Although, for the reference product Zonegran, dose proportionality was only demonstrated for the dose range from 100 to 800 mg following single dose administration, proportionality is also expected at doses lower than 100 mg due to the pharmacokinetic profile and metabolism of zonisamide. Thus, upon fulfilment of the general biowaiver criteria, it was considered sufficient to establish bioequivalence with the highest strength applied for, i.e. 100 mg.

All hard capsule strengths for Zonisamide Mylan are produced by the same manufacturing process. The qualitative composition of Zonisamid Mylan hard capsules is the same for all strengths and the quantitative composition is proportional. Thus, conditions, a, b, and c were considered fulfilled.

The applicant furthermore conducted comparative dissolution tests comparing the dissolution profile of Zonisamide Mylan 100 mg hard capsules with the profile for Zonisamide Mylan 25 and 50 mg hard capsules at three pH values (pH 1.2, pH 4.5 and pH 6.8) and the following conditions:

Apparatus: Paddle
RPM: 75
Medium: HCl 0.1 N
Volume: 900 ml
Temperature: 37 ± 0.5ºC
Surfactant: NA

Table 1 – *In-vitro* dissolution data for biowaiver request

Dissolution medium		**Collection Times (minutes or hours)**					
		5	10	15	30	45	f2
100 mg 12 capsules Batch:H003	pH= HCl 0.1N	89.13	93.71	95.86	98.87	100.32	NA
	pH= 4.5 buffer	91.31	95.94	97.50	100.00	101.17	NA
	pH= 6.8 buffer	90.31	94.23	96.33	98.94	100.28	NA
50 mg 12 capsules Batch:H002	pH= HCl 0.1N	89.95	94.70	96.66	99.29	101.07	NA
	pH= 4.5 buffer	91.70	95.44	96.60	99.05	100.66	NA
	pH= 6.8 buffer	91.41	95.84	97.38	99.64	101.23	NA
25 mg 12 capsules Batch:H002	pH= HCl 0.1N	92.20	95.99	98.30	101.98	103.52	NA
	pH= 4.5 buffer	97.93	101.17	103.17	105.60	106.71	NA
	pH= 6.8 buffer	93.72	97.67	99.62	103.45	104.68	NA

As more than 85% of the drug product was dissolved within 15 minutes under all conditions studied, the applicant concluded that the profiles were similar without any further mathematical evaluation.

The CHMP considered that the tests were generally conducted in line with the bioequivalence guideline recommendations except for the paddle speed which was selected at 75 rpm rather than 50 rpm as recommended by the guideline. The applicant justified the choice of the paddle speed as the experimental conditions were selected in line with the compendial standard conditions set in the European Pharmacopoeia

and since a paddle speed of 50 rpm would not allow an even distribution of particles throughout the vessel, thus producing a high variability in the results.

Upon request by the CHMP, the applicant provided additional dissolution profiles generated with a paddle speed of 50 rpm. Similarity of dissolution profiles for results obtained at 50 rpm was determined by calculating the similarity factor (f2). For all conditions studied, the similarity factor lay either between 50 to 100, or, the dissolved quantities of active substance at 15 minutes were above 85% for both doses. Thus, similarity of the dissolution profiles between the different applied strengths was shown.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study, study 1631.

2.4.2. Pharmacokinetics

Study 1631: A Single-Dose, Randomized, Open-Label, Crossover, Pivotal, Comparative Bioavailability Study of Zonisamide 100 mg Hard Capsules and Zonegran 100 mg Hard Capsules in Healthy Male and Female Volunteers under Fasting Conditions.

Methods

Study design

This was a pivotal, single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-centre, crossover study designed to evaluate the comparative bioavailability of zonisamide from Zonisamide 100 mg capsules (J. Uriach y Compañía S.A.) and Zonegran 100 mg capsules (Eisai Manufacturing Ltd.) administered to healthy male and female subjects under fasting conditions.

Subjects were randomly assigned to one of the two dosing sequences.

Prior to study commencement, subjects were randomly assigned to one of two treatment sequences. Subjects were confined to the clinical facility from at least 10 hours prior to drug administration until after the 24.0-hour post-dose blood draw, in each period. Subjects took their assigned formulation after at least a 10-hour fast, with 240 mL of ambient temperature water at their scheduled time point.

Blood samples were taken at the following time points: Pre-dose (2 samples) and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 48 and 72 hours in each study period. After centrifugation, the serum was aspirated and aliquoted. The samples were stored at -20°C (±5°C) in a freezer.

The 2 treatment phases were separated by a washout period of 28 days.

Test and reference products

Table 2 – Overview of Test and Reference product used in study 1631

Product Characteristics	Test Product	Reference Product
Name	Zonisamide	Zonegran

Product Characteristics	Test Product	Reference Product
Strength	100 mg	100mg
Dosage form	Hard capsules	Hard capsules
Manufacturer	J. Uriach y Compaña S.A., Spain	Eisai Manufacturing Ltd., U.K.
Batch number	H003	106008
Batch size (Biobatch)	100,000 capsules	
Potency	99.19%	99.24%

Population(s) studied

Healthy, non-smoking (for at least 6 months prior to first drug administration), male and female volunteers, 18 years of age or older, with a body mass index (BMI) within 18.5-30.0 kg/m², inclusive and a minimum body weight of greater than 40 kg were recruited.

Thirty-two (32) subjects aged between 26 and 77 years BMI in the range 19.5 – 29.6 kg/m² were included in the study.

A sample size of 32 subjects (which included a moderate buffer of 4 subjects for withdrawals and/or dismissals) was estimated to attain at least 80% statistical power to demonstrate bioequivalence between the Test and Reference products, assuming the mean Test to Reference difference was within 5%, based on an estimated intrasubject variability of approximately 25%. Subjects who were dosed (and were withdrawn or dismissed) were not to be replaced.

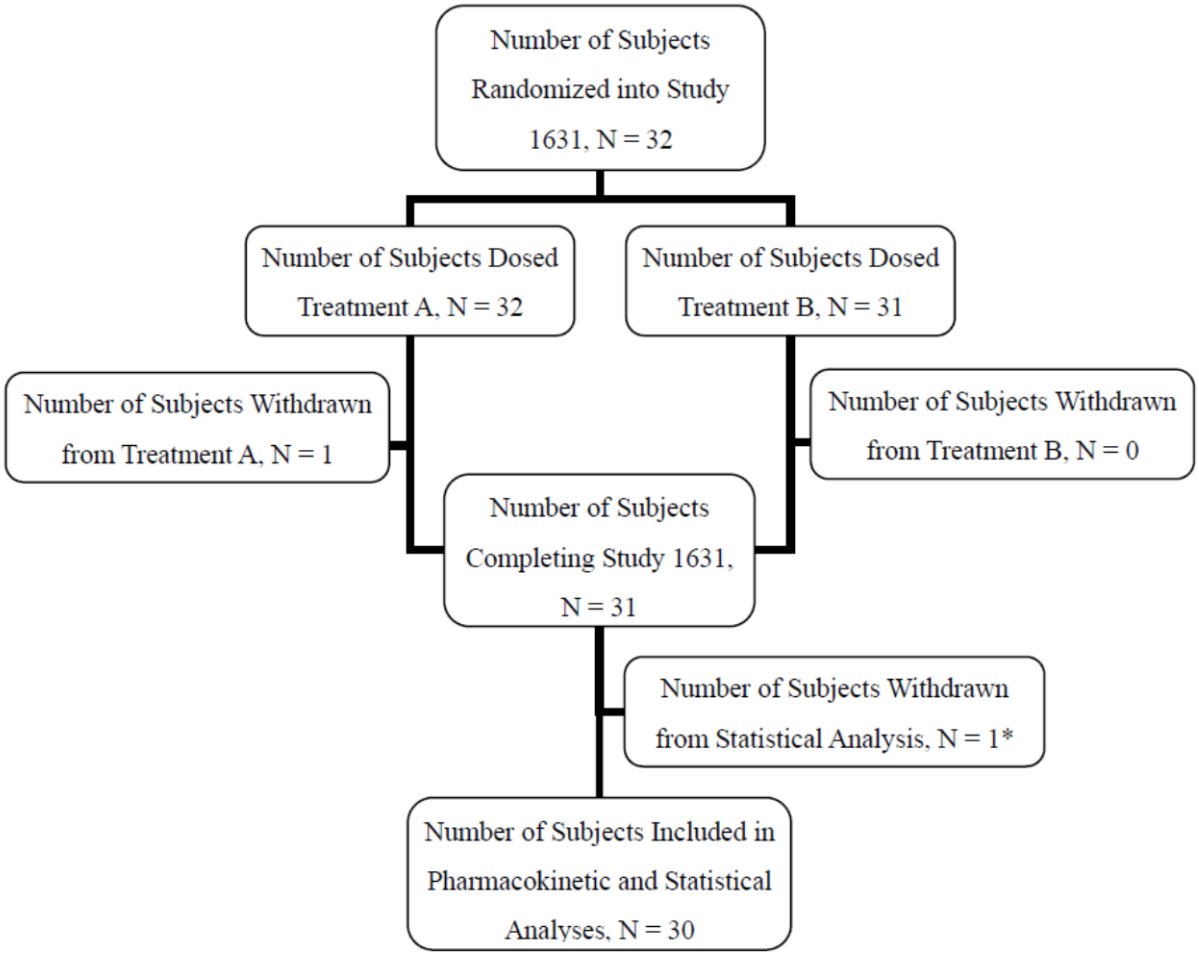

Figure 2 - Subjects disposition

* Due to the adverse events reported, one subject was not considered healthy. Samples from this subject were analysed by the bioanalytical laboratory but were not included in pharmacokinetic and statistical analyses.

One subject withdrew from the study due to personal reasons prior to the second period of the study. Due to the adverse events (AEs) reported for another subject, , the fact that he had fever 38.1, feeling cold, shaking, headache, increased heart rate and feeling nauseous, this subject was not considered healthy. Samples from this subject were analysed by the bioanalytical laboratory but were not included in pharmacokinetic and statistical analyses.

Analytical methods

Plasma samples of subjects were analysed using a validated LC/MS/MS method for zonisamide using zonisamide-d4 as internal standard. The bioanalytical report showed that the lower limit of quantification (LLOQ) of zonisamide was 9.98 ng/mL (accuracy of 95.22% and precision of 2.54%).

Duration of storage of plasma samples at -20°C from first blood draw until the final quantification amounts to 47 days. Long-term stability was demonstrated until 68 days.

A total of 1258 study samples were analysed. Three study samples were re-assayed due to pre-dose concentration (1) and processing errors (2). A total of 114 samples were used for “Incurred sample analysis”.

In 100% of the samples the difference between the two values measured was less than 20% of the mean of chromatographic assay.

Pharmacokinetic (PK) variables

The following PK parameters for the parent compound were calculated by standard non-compartmental methods:

1) Cmax: maximum observed serum concentration

2) Tmax: time of observed Cmax

3) AUC0-72: area under the concentration-time curve from time zero to the time of the last measureable concentration

Statistical methods

Descriptive statistics of all PK parameters (min, max, median, mean, standard deviation and coefficient of variability) were provided for zonisamide for the Test and Reference products.

Analysis of variance (ANOVA) including sequence, subjects nested within sequence, period and treatment were to be performed on the logarithmic ln-transformed data for AUC72 and Cmax and on the untransformed data for Tmax. Tmax was to be analyzed using an additional non-parametric test (Wilcoxon test).

The 90% confidence intervals (CI) of the Test/Reference ratios of geometric means for AUC72 and Cmax were to be calculated based on the least square means and estimate of the ANOVA.

Results

One subject presented a measurable pre-dose zonisamide concentration in the 2nd period. This value was, however, <5% of Cmax and was included in the statistical analysis.

Table 3 PK parameters for zonisamide (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product[1]	Reference Product[2]
$AUC_{(72)}$ (ng.h/mL)	44557.74 (9543.09)	43910.10 (9842.19)
$AUC_{(0-\infty)}$(ng.h/mL)	Not applicable	Not applicable
Cmax (ng /mL)	1014.60 (259.99)	1005.61 (262.35)
Tmax[3] (h)	2.50 (1.00-6.00)	3.50 (0.55-8.00)

[1] Test Product (Treatment A): Zonisamide 100 mg Capsules; Lot No: H003; (J. Uriach y Compañía S.A.)
[2] Reference Product (Treatment B): Zonegran® 100 mg Capsules; Lot No: 106008; (Eisai Manufacturing Ltd.)
[3] Median (Min, Max)

Table 4 Statistical analysis for zonisamide (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean RatioTest Product[1] / Reference Product[2]	Confidence Intervals	CV%
$AUC_{(72)}$ (ng.h/mL)	101.49	99.70 - 103.31	4.05
Cmax (ng /mL)	100.78	98.93 - 102.66	4.21

[1] Test Product (Treatment A): Zonisamide 100 mg Capsules; Lot No: H003; (J. Uriach y Compañía S.A.)

[2] Reference Product (Treatment B): Zonegran® 100 mg Capsules; Lot No: 106008; (Eisai Manufacturing Ltd.)

The intra-subject coefficient of variations (CV) for AUC0-72 and Cmax can be regarded as low (4.05% and 4.21% for zonisamide).

Safety data

There were 25 adverse events (AEs) involving 11 subjects in this study.

No serious AEs were reported during the conduct of this study.

There were 10 AEs associated with 5 subjects who received the Test Product. These included 4 cases of pain in the extremity, and 1 case each of headache, somnolence, catheter site swelling, nausea, vessel puncture site pain, and back pain.

There were 15 AEs associated with 8 subjects who received the Reference Product, including 3 cases of headache, 2 cases of somnolence, 2 cases of contusion, and 1 case each of catheter site haematoma, catheter site swelling, heart rate increased, nausea, tremor, feeling cold, body temperature increased and decreased appetite.

No AEs associated with clinical laboratory tests were experienced by the subjects post-study.

Conclusions

Based on the presented bioequivalence study, Zonisamide Mylan 100 mg hard capsules are considered bioequivalent with Zonegran 100 mg hard capsules.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

This is an application pursuant to Article 10.1 of Directive 2001/83/EC, as amended. As such, no new efficacy or safety studies have been performed with Zonisamide Mylan. However, the results from a bioequivalence

study (study 1631) comparing the bioavailability of Zonisamide Mylan 100 mg capsules and Zonegran 100 mg capsules were provided.

Study 1631 was conducted according to the standard randomised, two-period, two-sequence single dose crossover design as recommended in the bioequivalence guideline. The SmPC of Zonegran states that zonisamide capsules may be taken with or without food. Therefore, the bioequivalence study was correctly conducted under fasted condition. The wash-out period of 28 days was regarded sufficient in view of mean elimination half-life of 60 hours. The sampling scheme was adequate to estimate pharmacokinetic parameters (main distribution of zonisamide is between 2 and 5 hours). Termination of the sampling scheme at 72h is also acceptable for a long half-life drug in an immediate release formulation. Furthermore, the choice of the study population was considered adequate. The exclusion of one subject who was not considered healthy did not affect the study outcome.

The within study validation was considered adequate. The long-term stability period of 68 days at - 20°C covered the sample storage period of 47 days. Re-assay of samples was minimal and well justified. The incurred samples reanalysis met the required criteria of 20% of the original concentration.

Standard pharmacokinetic variables have been used in study 1631. Since zonisamide is a long half-life drug and the formulation is an immediate release one, use of truncated AUC at 72h is acceptable. Statistic is described adequately. Standard methods for the statistical analysis were utilized, which was acceptable.

The results of the study showed that the Test/Reference ratio of geometric means and the corresponding 90% confidence intervals for the ln-transformed AUC0-72 and Cmax parameters were entirely contained within the acceptance interval of 80.00% to 125.00%. Therefore, it could be concluded that BE was demonstrated between Zonisamide Mylan 100 mg capsules and Zonegran 100 mg capsules. Furthermore, as all criteria for a biowaiver for the remaining strengths (25 and 50 mg) were met, the CHMP considered that *in vivo* BE studies for the other strengths could be waived.

The safety data from study 1631 did not raise new safety concerns. No serious AEs were reported.

2.4.6. Conclusions on clinical aspects

Based on the available data, the CHMP concluded that Zonisamide Mylan 100 mg capsules are bioequivalent to Zonegran 100 mg capsules. As all criteria for a biowaiver were met, the CHMP agreed that no additional *in vivo* bioequivalence study with the remaining capsule strengths (25 and 50 mg) was needed. Zonisamide Mylan 25 mg, 50 mg and 100 mg hard capsules were thus considered essentially similar to the reference product Zonegran.

Taken together, the CHMP concluded that the available clinical data were adequate to support the application for Zonisamide Mylan 25 mg, 50 mg and 100 mg hard capsules as a generic medicinal product to Zonegran.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity

Summary of safety concerns	
	• Skin eruptions • Hematologic events • Kidney stones • Disordered body temperature (oligohidrosis and hyperthermia) and dehydration • Pancreatitis and elevated amylase and lipase • Muscle disorders • Metabolic acidosis and its potential osteopenia • Suicide/suicidal thoughts • Weight loss
Important potential risks	• Seizures following sudden withdrawal • Effects on ability to drive and use machines • Use in renal impairment • Use in pregnancy • Use in elderly • Developmental and maturational impairment in children and adolescents
Missing information	• Use in impaired liver function • Use in children below 6 years

Pharmacovigilance plan

The applicant is proposing routine pharmacovigilance for all safety concerns which is considered sufficient.

Risk minimisation measures

No additional risk minimisation measures are necessary.

Conclusion

The CHMP and PRAC considered that the risk management plan version 2 is acceptable.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Zonegran for content and to Duloxetine Mylan 30 mg hard gastro-resistant capsules for design and layout. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of zonisamide hard capsules (25 mg, 50 mg and 100 mg). The reference product Zonegran is indicated as monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy as well as adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A bioequivalence study with the 100 mg capsule strength forms the pivotal basis with a randomised, two-period, two-sequence single dose crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Zonisamide Mylan 100 mg hard capsules met the protocol-defined criteria for bioequivalence when compared with the reference product Zonegran 100 mg hard capsules. The point estimates and their 90% confidence intervals for the parameters AUC0-72 and Cmax were all contained

within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated. Furthermore, a biowaiver was granted for the remaining capsule strengths, 25 and 50 mg, thus waiving the requirement for additional *in vivo* bioequivalence studies with these strengths.

A benefit/risk ratio for Zonisamide Mylan 25 mg, 50 mg and 100 mg hard capsules comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zonisamide Mylan as monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy as well as adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.