Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Zonisamide Key 25 mg Hard Capsules
Zonisamide Key 50 mg Hard Capsules
Zonisamide Key 100 mg Hard Capsules
(zonisamide)

PL 34424/0081-0083

Key Pharmaceuticals Ltd

LAY SUMMARY

Zonisamide Key 25 mg Hard Capsules
Zonisamide Key 50 mg Hard Capsules
Zonisamide Key 100 mg Hard Capsules
(zonisamide)

This is a summary of the Public Assessment Report (PAR) for Zonisamide Key 25 mg, 50 mg and 100 mg hard Capsules. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Zonisamide capsules in this lay summary for ease of reading.

For practical information about using Zonisamide capsules, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Zonisamide capsules and what are they used for?
These products have been authorised by MHRA the United Kingdom. This procedure takes into account the outcome of decentralised (DC) and mutual recognition (MR) procedures in European Union Member States (and/or Iceland, Liechtenstein, Norway) on 13 September 2017, 21 February 2019, 19 March 2019, 29 January 2020, 05 June 2020, 13 April 2021 and 05 May 2021 (DE/H/4311/001-003/DC, DE/H/4311/001-003/IB/001, DE/H/4311/001-003/IB/002, DE/H/4311/001-003/R/001, DE/H/4311/003/IA/003 and DE/H/4311/001-003/IA/004). This is known as the MR/DC Decision Reliance Procedure.

These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Zonegran 25 mg, 50 mg and 100 mg hard capsules.

Zonisamide capsules are used to treat seizures that affect one part of the brain (partial seizure), which may or may not be followed by a seizure affecting all of the brain (secondary generalisation).

Zonisamide capsules may be used:
- on their own to treat seizures in adults.
- with other antiepileptic medicines to treat seizures in adults, adolescents, and children aged 6 years and above.

How do Zonisamide capsules work?
The active substance, zonisamide, is an antiepileptic medicine. Zonisamide works by affecting the electrical activity of the brain.

How are Zonisamide capsules used?
The pharmaceutical form of these medicines is a hard capsule and the route of administration is oral (taken by mouth).

The recommended adult dose
When the patient takes Zonisamide capsules on its own:
- The starting dose is 100 mg taken once a day.

- This may be increased by up to 100 mg at intervals of two weeks.
- The recommended dose is 300 mg once a day.

When the patient takes Zonisamide with other antiepileptic medicines:
- The starting dose is 50 mg daily taken in two equal doses of 25 mg.
- This may be increased by up to 100 mg at intervals of one to two weeks.
- The recommended daily dose is between 300 mg and 500 mg.

- Some people respond to lower doses. The dose may be increased more slowly if the patient experiences side effects, are elderly or if the patient suffers from kidney or liver problems.

Use in children (aged 6 to 11 years) and adolescents (aged 12 to 17 years) weighing at least 20 kg:
- The starting dose is 1 mg per kg of body weight taken once a day.
- This may be increased by 1 mg per kg of body weight at intervals of one to two weeks.
- The recommended daily dose is 6 to 8 mg per kg for a child with a body weight of up to 55 kg or 300 to 500 mg for a child with a body weight more than 55 kg (which ever dose is lower) taken once a day.

Example: A child who weighs 25 kg should take 25 mg once a day for the first week, and then increase the daily dose by 25 mg at the start of each week until a daily dose between 150 to 200 mg is reached.

If the patient feels that the effect of Zonisamide capsules is too strong or too weak, they should talk to their doctor or pharmacist.
- Zonisamide capsules must be swallowed whole with water.
- The patient should not chew the capsules.
- Zonisamide capsules can be taken once or twice daily, as instructed by the patient's doctor.
- If the patient takes Zonisamide twice a day, they should take half the daily dose in the morning and half in the evening.

For further information on how Zonisamide capsules are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take these medicines exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Zonisamide capsules have been shown in studies?
As Zonisamide capsules are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Zonisamide capsules?
As Zonisamide capsules are generic medicines and are bioequivalent to the reference medicines, their possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with these medicines. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

Why were Zonisamide capsules approved?
It was concluded that, Zonisamide capsules have been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Zonisamide capsules ?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Zonisamide capsules. The RMP details the important risks of Zonisamide capsules, how these risks can be minimised, any uncertainties about Zonisamide capsules (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Zonisamide capsules:

Summary of safety concerns	
Important Identified Risks	• Hypersensitivity to sulfonamides • Unexplained rash • Hematologic events • Urolithiasis • Disordered body temperature and dehydration • Pancreatitis and elevated amylase and lipase • Muscle disorders/rhabdomyolysis • Weight loss • Metabolic acidosis and its potential for osteopenia • Suicide/suicidal thoughts
Important Potential Risks	• Seizures following sudden withdrawal • Effects on ability to drive and use machines • Use in renal impairment • Hepatic dysfunction in paediatric and adolescent patients • Use in the elderly • Cognitive impairment in children and adolescents • Use in pregnancy and breastfeeding
Important Missing Information	• Use in impaired liver function • Use in children below 6 years

The information included in the SmPCs and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Zonisamide capsules are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Zonisamide capsules
Marketing Authorisations for Zonisamide capsules were granted in the United Kingdom (UK) on 18 November 2022.

The full PAR for Zonisamide capsules follows this summary.

This summary was last updated in February 2023.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Zonisamide Key 25 mg, 50 mg and 100 mg Hard Capsules (PL 34424/0081-0083) could be approved.

The products are approved for the following indications:

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

The active substance, zonisamide, is a 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.

These products have been authorised by MHRA the United Kingdom. This procedure takes into account the outcome of decentralised (DC) procedure and mutual recognition (MR) procedures in European Union Member States (and/or Iceland, Liechtenstein, Norway) on 13 September 2017, 21 February 2019, 19 March 2019, 29 January 2020, 05 June 2020, 13 April 2021 and 05 May 2021 (DE/H/4311/001-003/DC, DE/H/4311/001-003/IB/001, DE/H/4311/001-003/IB/002, DE/H/4311/001-003/R/001, DE/H/4311/003/IA/003 and DE/H/4311/001-003/IA/004).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted during the DC procedure (DE/H/4311/001-003/DC), please refer to the Reference Member State (RMS) Public Assessment Report, available on the RMS regulatory agency website or on the Heads of Medicines Agencies website.

These applications were approved under Regulation 51B of the Human Medicines Regulation 2012, as amended (previously Article 10 (1) of Directive 2001/83/EC, as amended).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations were granted in the United Kingdom (UK) on 18 November 2022.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL
The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS
The MHRA considered that the quality data submitted for these applications is satisfactory.

The grant of marketing authorisations is recommended.

IV. NON-CLINICAL ASPECTS
The MHRA considered that the non-clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations is recommended.

V. CLINICAL ASPECTS
The MHRA considered that the clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations is recommended.

VI. RISK MANAGEMENT PLAN (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

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VII. USER CONSULTATION
A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the applications, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

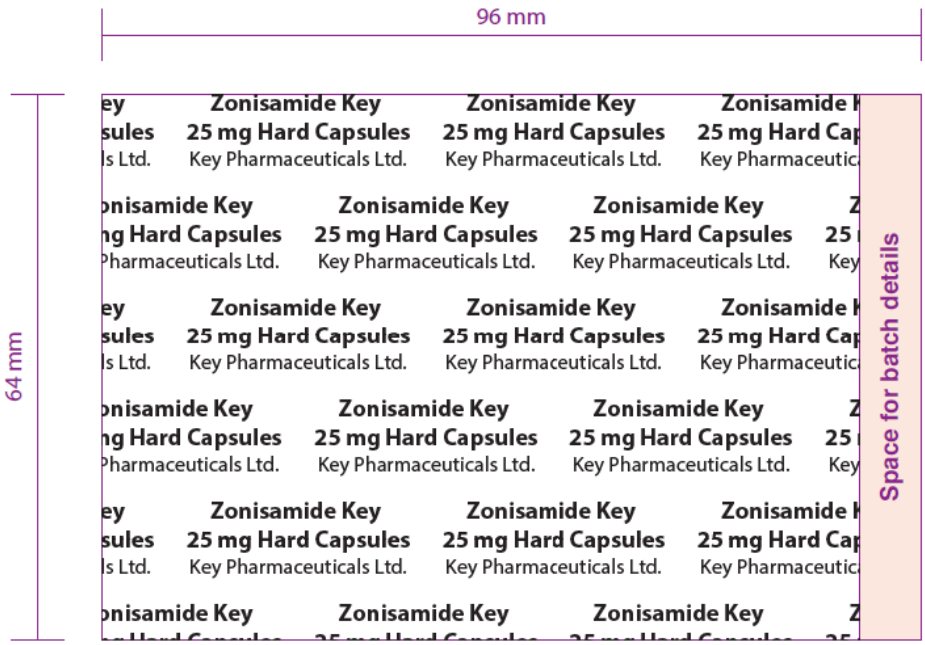
VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

The SmPCs, PIL and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.

Zonisamide Key 25 mg Hard Capsules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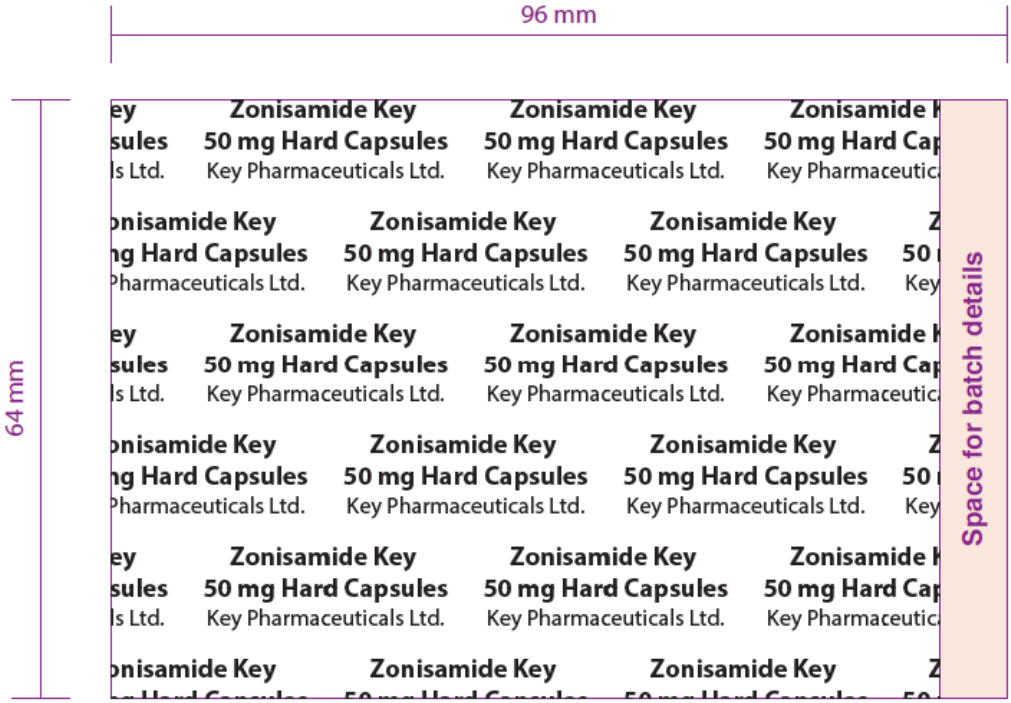
64 mm
Zonisamide Key
25 mg Hard Capsules
Key Pharmaceuticals Ltd.
Space for batch details

Zonisamide Key 50 mg Hard Capsules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Zonisamide Key
50 mg Hard Capsules
Key Pharmaceuticals Ltd.
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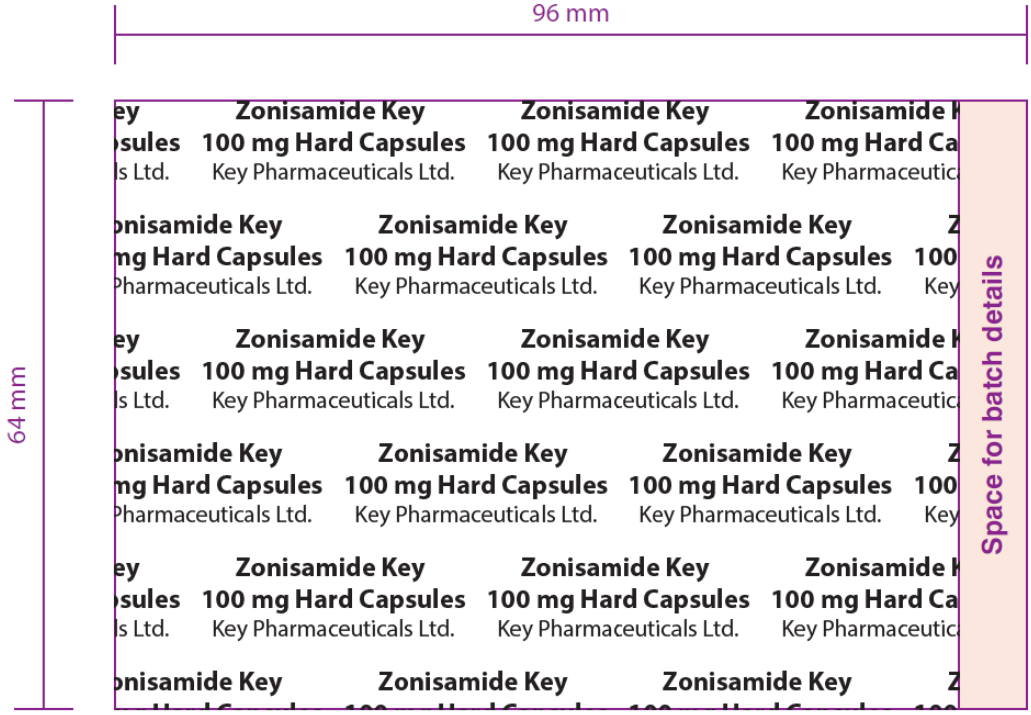
Zonisamide Key 100 mg Hard Capsules


96 mm
64 mm
Zonisamide Key
100 mg Hard Capsules
Key Pharmaceuticals Ltd.
Space for batch details

IX. Table of contents of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisations are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

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