Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Mysoline 125mg Tablets
Primidone SERB 125mg Tablets

primidone

PL 26080/0008

SERB

LAY SUMMARY

Mysoline 125mg Tablets
Primidone SERB 125mg Tablets

primidone

This is a summary of the Public Assessment Report (PAR) for Mysoline 125mg Tablets; Primidone SERB 125mg Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Primidone SERB in this lay summary for ease of reading. This Marketing Authorisation has been granted with two product names, Mysoline 125mg Tablets and Primidone SERB 125mg Tablets.

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

What is Primidone SERB and what is it used for?
This application is full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Primidone SERB is used for the treatment of certain types of epilepsy, seizures (fits) or shaking attacks (essential tremor).

How does Primidone SERB work?
Primidone SERB contains primidone as the active ingredient; this belongs to a group of medicines used to treat seizures.

How is Primidone SERB used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

The dosage will be determined by the patient's doctor and adjusted gradually on individual basis.

Primidone SERB is normally taken twice a day. Patients should try to take their tablets at the same time each day. The tablets should be swallowed whole with a drink of water.

The tablet of Primidone SERB 250mg can be divided into equal doses.

<u>Epilepsy</u>
At first, the patient's dose may be as little as 125mg. This will be adjusted by their doctor until their condition is controlled. Typical maintenance doses are as follows:

Age group	Daily dose (milligrams)
Adults and children over 9 years	750 to 1500
Children 6 to 9 years	750 to 1000
Children 2 to 5 years	500 to 750
Children up to 2 years	250 to 500

Shaking attacks (Essential tremor)
The patient's starting dose may be 50 mg. This will be adjusted by their doctor until their condition is controlled. The highest dose tolerated for shaking attacks (essential tremor) is up to a maximum of 750 mg.

Elderly / Patients with renal or liver disease
Lower doses may be prescribed. Patients should check with their doctor.

For further information on how Primidone SERB is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine 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 Primidone SERB have been shown in studies?
No additional studies were needed as Primidone SERB is a line extension of the existing products Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets. The data submitted previously for Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets is sufficient to demonstrate that Primidone SERB shows a benefit in the indications listed.

What are the possible side effects of Primidone SERB?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC 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 the medicine. 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.ukor search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Primidone SERB is a line extension of the existing products Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets, its benefits and possible side effects are taken as being the same as Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets.

Why was Primidone SERB approved?
It was concluded that, as Primidone SERB is a line extension of Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets, the indications and side effects observed with Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets are applicable to Primidone SERB. Therefore, the MHRA decided that, as for Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets, the benefits are greater than the risks and recommended that Primidone SERB can be approved for use.

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

The following safety concerns have been recognised for Primidone SERB:

Summary of safety concerns	
Important identified risks	• Bone disorders • Suicidal ideation • Withdrawal syndrome • Drug reaction with eosinophilia and systemic symptoms (DRESS)
Important potential risks	• Severe skin disorders • Major Congenital Malformations (MCM) • Neurodevelopmental Disorders (NDD)
Missing information	None

The information included in the SmPC 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 Primidone SERB 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 this application and are satisfactory.

Other information about Primidone SERB
A marketing authorisation was granted in the United Kingdom (UK) on 15 November 2023.

The full PAR for Primidone SERB follows this summary.

This summary was last updated in March 2024.

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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 application for Mysoline 125mg Tablets; Primidone SERB 125mg Tablets (PL 26080/0008) could be approved.

As mentioned in the lay summary this Marketing Authorisation has been granted with two product names. However, in the main body of this report we will refer only to Primidone SERB 125mg Tablets for ease of reading.

The product is approved for the following indications:

- The management of grand mal and psychomotor (temporal lobe) epilepsy. It is also of value in the management of focal or Jacksonian seizures, myoclonic jerks and akinetic attacks.
- Management of essential tremor.

The active substance, primidone, is an anticonvulsant largely metabolised into two main metabolites phenobarbital and phenylethylmalonamide (PEMA). The relative contribution of these three moieties to the clinical anticonvulsant effect has not been firmly established.

In addition, primidone has been demonstrated to suppress tremor, with a possible contribution of these metabolites.

Although the precise mode of action of Primidone is unknown, in common with other anticonvulsants, effects on the neuronal membrane particularly with respect to alteration of ionic fluxes are likely to play a fundamental role.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. However, as this application is for a line extension of the existing products Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets (PL 26080/0002-0003), the non-clinical and clinical data are identical to those submitted previously.

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

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

A marketing authorisation was granted in the United Kingdom (UK) on 15 November 2023.

II QUALITY ASPECTS

II.1 Introduction

The active substance is primidone. Each tablet contains 125 mg of primidone. The other ingredients are carmellose calcium, gelatin, magnesium stearate, povidone and stearic acid.

The finished product is packaged in PVC/aluminum blisters, each containing 10 tablets. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

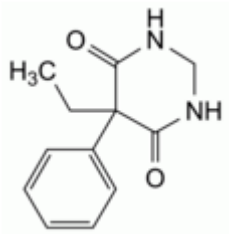
Not all pack sizes may be marketed.

II.2 ACTIVE SUBSTANCE

rINN: primidone

Chemical Name: 5-Ethyl-5-phenyl-1,3-diazinane-4,6-dione

Molecular Formula: $C_{12}H_{14}N_2O_2$



Chemical Structure:

Molecular Weight: 218.3

Appearance:

White or almost white, crystalline powder

Solubility: Very slightly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in alkaline solutions.

Primidone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin, no excipients of animal or human origin are used in the final products.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 5 years, with the storage conditions Store below 25°C, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As this application is for a line extension of the existing products Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets (PL 26080/0002-0003), the non-clinical data are identical to those submitted previously.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a line extension of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

As this application are for a line extension of the existing products Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets (PL 26080/0002-0003), the clinical data are identical to those submitted previously.

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

No new pharmacokinetic data have been submitted for this application and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for this application and none were required.

IV.5 Clinical safety

No new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Primidone SERB 50 and 250 mg Tablets / Mysoline 50 and 250 mg Tablets.

IV.6 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.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no non-clinical or clinical safety concerns have been identified. Clinical experience with primidone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

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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 authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

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