Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Primidone Dawa 50 mg tablets
Primidone Dawa 250 mg tablets

primidone

PL 30684/0159-0160

DAWA Limited

LAY SUMMARY

Primidone Dawa 50 mg and 250 mg tablets
primidone

This is a summary of the Public Assessment Report (PAR) for Primidone Dawa 50 mg and 250 mg tablets. 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 Primidone Tablets in this lay summary for ease of reading.

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

What are Primidone Tablets and what are they used for?
These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Mysoline 50 mg and 250 mg tablets, these have been the subject of a number of changes of ownership.

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

How do Primidone Tablets work?
These medicines contain primidone as the active ingredient. Primidone belongs to a group of medicines used to treat seizures.

How are Primidone Tablets used?
The pharmaceutical form of these 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 Tablets are normally taken twice a day.

The patient should try to take their tablets at the same time each day. Swallow the tablets whole with a drink of water.
The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

<u>Epilepsy</u>
At first, the patient's dose may be as little as 125mg (half a 250mg tablet). This will be adjusted by the doctor until the patient's condition is controlled. Typical maintenance doses are as follows:
For adults and children over 9 years, the daily dose is 750 to 1500mg
For children 6 to 9 years, the daily dose is 750 to 1000mg
For children 2 to 5 years, the daily dose is 500 to 750mg
For children up to 2 years, the daily dose is 250 to 500mg

<u>Shaking attacks (Essential tremor)</u>
The patient's starting dose may be 50mg. This will be adjusted by the doctor until the

patient's condition is controlled. The highest dose tolerated for shaking attacks (essential tremor) is up to a maximum of 750mg.

Elderly patient with renal or liver disease
Lower dose may be prescribed. The patient should check with their doctor.

For further information on how Primidone Tablets 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 this 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 Tablets have been shown in studies?
Because Primidone Tablets are generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

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

Because Primidone Tablets are generic medicines and are bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

Why were Primidone Tablets approved?
It was concluded that, Primidone Tablets have been shown be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, 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 Primidone Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Primidone Tablets. The RMP details the important risks of Primidone Tablets, how these risks can be minimised, any uncertainties about Primidone Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Primidone Tablets:

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 Tablets 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 Primidone Tablets
Marketing authorisations for Primidone Tablets were granted in the United Kingdom (UK) on 15 November 2022.

The full PAR for Primidone Tablets follows this summary.

This summary was last updated in March 2025.

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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(s) for Primidone Dawa 50 mg and 250 mg tablets (PL 30684/0159-0160) could be approved.

The products is/are 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.

- the management of essential tremor.

The name of the active substance is primidone which belongs to the pharmacotherapeutic group of antiepileptics (barbiturates and derivatives).

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.

Primidone, as with other anticonvulsants, can induce liver enzymes.

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), as generic medicines of a suitable originator medicinal products, Mysoline 50 mg and 250 mg tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for a generic medicinal products of a suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of a suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

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 for Primidone Tablets were granted in the United Kingdom (UK) on 15 November 2022.

II QUALITY ASPECTS

II.1 Introduction

These products consist of tablets each tablet contains primidone 50 mg, and 250 mg of primidone respectively.

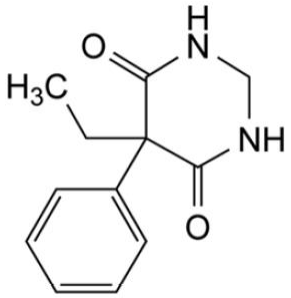
In addition to primidone, these products also contain the excipients calcium carboxymethyl cellulose, povidone K-30, magnesium stearate and stearic acid.

The finished products are packed in a blister made up of PVC-PVDC film & aluminium foil of pack size of 100 tablets, 56 tablets and 30 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.

II.2 ACTIVE SUBSTANCE(S)

rINN: primidone
Chemical Name: 5-ethyl-5-phenyl-2,3-dihyropyrimidine-4,6(1H,5H)-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, practically insoluble in ether.
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(S)

Pharmaceutical development
A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

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

No excipients of animal or human origin are used in the final products.

These products do not contain or consist of genetically modified organisms (GMOs).

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

Satisfactory batch formulation data have been provided for the manufacture of the products, 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 3 years, with the storage conditions “Do not store above 25°C”, is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of primidone are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of an already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

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

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of primidone are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study.

This study was an open-label, balanced, randomized, single dose, two-treatment, two-sequence, two- period, cross over, oral bioequivalence study comparing the test product Primidone 250mg Tablets versus the reference product Mysoline (Primidone) 250mg Tablets in subjects/patients under fasted conditions.

Subjects were administered a single dosing of test/reference products. Blood samples were taken pre-dose and up to 48.00 hours post dose, with a washout period of 23 days for group 1 and 21 days for group 2 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Ratio and 90% Confidence Intervals of Test versus Reference for

Bioequivalence evaluation of Primidone			
Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	90 % Confidence Intervals (%)	CV(%)[1]
Ln (C_{max}) (ng/ml)	101.29	98.22 - 104.45	10.37
Ln (AUC_{0-t}) (hr *ng/ml)	99.78	98.72 - 100.85	3.59

[1]Estimated from the Residual Mean Squares.

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications, and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

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 marketing authorisations was recommended for this/these applications.

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 products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive 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, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these product(s) 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**