Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Mefenamic acid 250 mg Capsules

mefenamic acid

PL 48974/0026

Lyrus Life Sciences Limited

LAY SUMMARY

Mefenamic acid 250 mg Capsules
mefenamic acid

This is a summary of the Public Assessment Report (PAR) for Mefenamic acid 250 mg Capsules. 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 Mefenamic acid capsules in this lay summary for ease of reading.

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

What is Mefenamic acid capsules and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Ponstan 250 mg Capsules.

Mefenamic acid capsules can help to relieve:
- symptoms of inflammation, such as redness and swelling
- pain and discomfort caused by arthritis, muscular or rheumatic disorders
- headache, muscle ache or toothache
- pain after operations, trauma
- childbirth pain
- fever in children
- painful or heavy periods

How does Mefenamic acid capsules work?
Mefenamic acid capsules contain mefenamic acid which is a non-steroidal anti-inflammatory drug (NSAID).

How is Mefenamic acid capsules used?
The pharmaceutical form of this medicine is a capsule and the route of administration is oral (by mouth).

The patients' doctor will decide on the appropriate dose to suit their condition. The patient should check with their doctor or pharmacist if they are not sure.

The capsules should be taken with or immediately after a meal.
Patients should NOT drink alcohol while taking mefenamic acid. Alcohol and smoking can irritate the stomach and make some of the side effects worse.

Dosage
Adults
The recommended dose is 2 capsules three times a day.

Elderly patients (over 65 years)
Elderly patients are at a higher risk of side effects and should take the lowest effective dose for the shortest possible time, with additional monitoring carried out by their doctor.

Use in children
It is recommended that children under 12 years of age should be given Mefenamic Acid Suspension (50mg /5ml).

For further information on how Mefenamic acid capsules 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 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 Mefenamic acid capsules have been shown in studies?
Because Mefenamic acid capsules is a 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 Mefenamic acid capsules?
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.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 Mefenamic acid capsules is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Mefenamic acid capsules approved?
It was concluded that, Mefenamic acid capsules has been shown to 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 Mefenamic acid capsules?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Mefenamic acid capsules. The RMP details the important risks of Mefenamic acid capsules, how these risks can be minimised, any uncertainties about Mefenamic acid capsules (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Mefenamic acid capsules.

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 Mefenamic acid 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 this application and are satisfactory.

Other information about Mefenamic acid capsules
A marketing authorisation for Mefenamic acid capsules was granted in the United Kingdom (UK) on 19 September 2024.

The full PAR for Mefenamic acid capsules follows this summary.

This summary was last updated in October 2024.

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 application for Mefenamic acid 250 mg Capsules (PL 48974/0026) could be approved.

The product is approved for the following indications:

1. As an anti-inflammatory analgesic for the symptomatic relief of rheumatoid arthritis (including Still's Disease), osteoarthritis, and pain including muscular, traumatic and dental pain, headaches of most aetiology, post-operative and post-partum pain; pyrexia in children.
2. Primary dysmenorrhoea.
3. Menorrhagia due to dysfunctional causes and presence of an IUD when other pelvic pathology has been ruled out.

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) with anti- inflammatory, analgesic and antipyretic properties.

Its anti-inflammatory effect was first established in the UV erythema model of inflammation. Further studies included inhibition of granulation tissue growth into subcutaneous cotton pellets in rats and carrageenin induced rat paw oedema tests.

Antipyretic activity was demonstrated in yeast-induced pyresis in rats. In this model its antipyretic activity was roughly equal to that of phenylbutazone and flufenamic acid, but less than that of indomethacin.

Analgesic activity was demonstrated in tests involving pain sensitivity of rats paws inflamed by brewers yeast. Mefenamic acid was less potent than flufenamic acid in this model.

Prostaglandins are implicated in a number of disease processes including inflammation, modulation of the pain response, dysmenorrhoea, menorrhagia and pyrexia.

In common with most NSAIDs mefenamic acid inhibits the action of prostaglandin synthetase (cyclo oxygenase). This results in a reduction in the rate of prostaglandin synthesis and reduced prostaglandin levels.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Ponstan 250 mg Capsules 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 application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. 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 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 for Mefenamic acid capsules was granted in the United Kingdom (UK) on 19 September 2024.

II QUALITY ASPECTS

II.1 Introduction

The active substance is Mefenamic acid. Each capsule contains 250 mg of Mefenamic acid.

The other ingredients are Lactose monohydrate and Sodium lauryl sulfate.

The capsule shells contain gelatin, titanium dioxide (E171), Patent blue V (E131) and quinoline yellow (E104).

Printing ink contains shellac (E904), Dehydrated Alcohol (E1510), Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol (E1520), Strong Ammonia Solution (E527), Black Iron oxide (E172), Potassium hydroxide (E525) and Purified Water.

The finished products are packaged in Clear PVC/Aluminium blister packs of 10, 12, 20, 30, 50, 84, 100 and 168 capsules.

Not all pack sizes may be marketed.

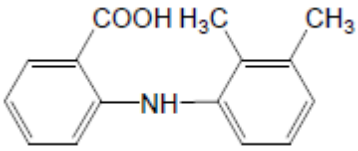
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: mefenamic acid

Chemical Name: N-2,3-Xylylanthranilic acid

Molecular Formula: $C_{15}H_{15}NO_2$



Chemical Structure:

Molecular Weight: 241.29

Appearance: White or almost white, microcrystalline powder.

Solubility: Practically insoluble in water, slightly soluble in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

Mefenamic acid 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.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

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.

With the exception of lactose monohydrate and gelatin, no excipients of animal or human origin are used in the final products. EDQM certificates have been provided for the excipients of animal origin.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

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 3 years, with the storage conditions ‘Do not store above 25°C’ and ‘Store in the original package’, 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 was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of mefenamic acid 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 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
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

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

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of mefenamic acid is well-known. With the exception of data from a single bioequivalence study undertaken (0895-17), 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:

Study 1: 0895-17
This study was an open-label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study comparing Mefenamic acid 250 mg capsules (test product) with Ponstan Capsules 250 mg (reference product) in healthy, adult, human subjects under fed conditions.

In each study period, subjects were administered a single dose of either the test or reference product after an overnight fast of at least 10 hours. Subjects consumed a high fat, high calorie vegetarian breakfast within 30 minutes prior to drug administration. Blood samples were taken pre-dose and up to 16 hours post dose, with a washout period of 4 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	96.0	90.88 - 101.49	8.5
C_{max}	95.8	83.25 - 110.13	21.8

[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 this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application 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 this application.

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 a marketing authorisation was 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 new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with mefenamic acid 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 product.

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

TABLE OF CONTENT 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 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**