Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Mefenamic Acid 500 mg film-coated Tablets

(mefenamic acid)

PL 11311/0668

Tillomed Laboratories Ltd.

LAY SUMMARY

Mefenamic Acid 500 mg film-coated Tablets (mefenamic acid)

This is a summary of the Public Assessment Report (PAR) for Mefenamic Acid 500 mg film-coated 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 Mefenamic Acid Tablets in this lay summary for ease of reading.

For practical information about using Mefenamic Acid Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Mefenamic Acid Tablets and what are they used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Ponstan Forte Tablets 500mg.

Mefenamic Acid Tablets are used to treat the following:

- Symptoms of pain or swelling associated with arthritis, rheumatoid or muscular disorders.
- Pain associated with trauma or surgery.
- Muscle or dental pain, headaches.
- Pain after childbirth.
- Period pain or abnormally heavy periods.

How do Mefenamic Acid Tablets work?
Mefenamic Acid Tablets contain the active substance mefenamic acid which belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). Mefenamic acid works by blocking the effect of natural chemicals called cyclo-oxygenase (COX) enzymes. These enzymes help to make other chemicals in the body, called prostaglandins. Some prostaglandins are produced at sites of injury or damage, and cause pain and inflammation.

How are Mefenamic Acid Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (via the mouth). Mefenamic Acid Tablets should preferably be taken with or after food.

Do not drink alcohol whilst taking Mefenamic Acid Tablets. Alcohol and smoking may irritate the stomach and make some side effects worse.

Adults and the elderly
The usual dose is one tablet, three times a day.
Elderly patients are at a higher risk of side effects and should take the lowest effective dose, for the shortest possible time. The patient's doctor may perform additional monitoring.

Use in children
Mefenamic Acid Tablets are not suitable for children under the age of 12 years.

For further information on how Mefenamic Acid Tablets are used, refer to the package leaflet and Summary of Product Characteristics 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 Tablets have been shown in studies?
Because Mefenamic Acid Tablets 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 Tablets?
Because Mefenamic Acid Tablets 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.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why were Mefenamic Acid Tablets approved?
It was concluded that, in accordance with EU requirements, Mefenamic Acid Tablets has been shown to be comparable to and 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 Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Mefenamic Acid Tablets is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Mefenamic Acid Tablets
A Marketing Authorisation was granted in the UK on 13 January 2021.

The full PAR for Mefenamic Acid Tablets follows this summary.

This summary was last updated in February 2021.

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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 Mefenamic Acid 500 mg film-coated Tablets (PL 11311/0668) 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.
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 member of the anthracitic acid derivatives class of non-steroidal anti-inflammatory drug (NSAID). It binds to the prostaglandin synthetase receptors COX-1 and COX-2, inhibiting the action of prostaglandin synthetase. Decreased levels of prostaglandin result in anti-inflammatory, analgesic and antipyretic effects.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine of a suitable originator medicinal product, Ponstan Forte Tablets 500mg (PL 17736/0007) that has been licensed within the EU 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 based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP). The reference product used for the demonstration of bioequivalence is Mefenamic acid 250 mg Capsule (PL 17736/0004) authorised to Chemidex Pharma Limited on 16/08/2002. This is acceptable, considering that Ponstan Forte 500 mg Capsules (PL 17736/0007) and Mefenamic acid 250 mg Capsule (PL 17736/0004) are both authorised to Chemidex Pharma (i.e. belong to same global marketing authorisation).

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.

Advice was sought from the Commission of Human Medicines (CHM) on 23 April 2020 and as a result of its consideration was of the opinion that on the grounds relating to quality and quality in relation to efficacy and safety it may be unable to advise the licensing authority to grant the authorisation. In response, the Applicant submitted further quality data for the medicinal product addressing these concerns which were deemed acceptable and a Marketing Authorisation was granted on 13 January 2021.

II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 500 mg of mefenamic acid.

In addition to mefenamic acid, this product also contain the excipients lactose monohydrate, pregelatinised starch, croscarmellose sodium, povidone, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate and Opadry II Yellow [consisting of hypromellose, lactose monohydrate, titanium dioxide (E 171), macrogol, iron oxide yellow (E 172), talc, iron oxide red (E 172)].

The finished product is packaged in PVC/PVDC blisters, sealed with aluminium lidding foil in pack sizes of 28, 84 and 100 tablets. 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 European regulations concerning materials in contact with food.

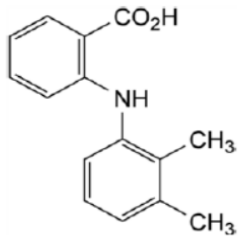
II.2 ACTIVE SUBSTANCE

rINN: Mefenamic acid

Chemical Name: 2-[(2, 3-Dimethylphenyl) amino]-benzoic acid
Or
N-(2,3-Xylyl) anthranilic acid

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

Chemical Structure:



Molecular Weight: 241.3 g/mol

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.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been 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 have been provided for all excipients.

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

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

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.

A satisfactory batch formula has 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 Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. 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 24 months, with the storage conditions ‘Do not store above 25°C. 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 is 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
Suitable justification has been 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 is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of mefenamic acid 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:

STUDY
This study was a randomised, open label, balanced, single dose, two-treatment, two-sequence, two-period crossover oral bioequivalence study comparing the test product Mefenamic Acid 500 mg film-coated Tablets (1 x tablet) versus the reference product Ponstan 250 mg Capsules (Mefenamic Acid 250 mg × 2 capsules) in subjects under fasted conditions.

Subjects were administered an oral dose of mefenamic acid 500 mg of the test or reference after an overnight fast of at least 10 hours. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Table: Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals

	Geometric mean ratio Test/Reference (%)	90% Confidence Intervals (%)	CV%
AUC_{0-t} (ng.h/mL)	97.25	88.55 - 106.81	23.47
C_{max} (ng/mL)	99.32	87.70 - 112.48	31.47

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), 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 have been 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 Directive 2001/83/EC, 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

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. 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.

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 Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product is available on the MHRA website.

The following text is the currently approved label text. No label mock-ups have been provided for this product. In accordance with medicines legislation, this product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mefenamic Acid 500 mg film-coated Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg of mefenamic acid

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
28 film-coated tablets
84 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Tillomed laboratories Limited
220 Butterfield, Great Marlings,
Luton,
LU2 8DL
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 11311/0668

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mefenamic Acid 500 mg film-coated Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PVDC-Aluminium BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Mefenamic Acid 500 mg film-coated Tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Tillomed laboratories Limited
220 Butterfield, Great Marlings,
Luton,
LU2 8DL
United Kingdom

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

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**