IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ponstan 500 mg capsules
Mefenamic acid
PA22643/001/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Ponstan 500 mg capsules from Chemidex Pharma Limited on 16th August 2024 for:

- Symptomatic relief of mild to moderate pain associated with rheumatic, muscular or arthritic disorders, trauma, headaches, dental pain, post-operative or post-partum states
- Control of pyrexia in children
- Management of dysfunctional menorrhagia
- Primary dysmenorrhoea
- Premenstrual syndrome

This national application for a marketing authorisation was submitted in accordance with Article 10(a) of Directive 2001/83/EC and is referred to as a Well-Established Use application. The legal status is prescription only.

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website.

Name of the product	Ponstan
Name(s) of the active substance(s) (INN)	Mefenamic acid
Pharmacotherapeutic classification (ATC Code)	M01AG01
Pharmaceutical form and strength(s)	Capsule,500 milligrams
Marketing Authorisation Number(s) in Ireland (PA)	PA22643/001/003
Marketing Authorisation Holder	Chemidex Pharma Limited Vision Exchange Building Triq it-Territorjals, Zone 1 Central Business District Birkirkara CBD 1070 Malta

II. QUALITY ASPECTS

II.1. Introduction

This application is for Ponstan 500mg capsules. The drug product is a white powder, in no. 00 hard gelatin capsules, having ivory opaque bodies and powder blue opaque caps, imprinted with the product name "PONSTAN 500", containing 500 mg of the active substance mefenamic acid.

II.2 Drug substance

The active substance mefenamic acid is an established active substance described in the European Pharmacopoeia (Ph. Eur.), which is manufactured in accordance with Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Ponstan 500mg capsules contain the active substance mefenamic acid and the following other ingredients: sodium laurilsulfate, lactose monohydrate, gelatin, purified water, erythrosine, quinoline yellow, titanium dioxide, Patent Blue V and black ink. The black ink contains shellac, black iron oxide, propylene glycol and ammonia.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The applicant demonstrated that the product is a stable product that is essentially similar to Ponstan 250 mg capsules.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the Ph. Eur. monograph for tablets and relevant ICH guidelines. The tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects
The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Ponstan capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction
The active substance, mefenamic acid has demonstrated anti-inflammatory, analgesic, and antipyretic activity and has been available on the European/Irish market for several decades. Preclinical data have been superseded by clinical experience, and no new pre-clinical data has been submitted with this application. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

The nonclinical data have been collected from the published scientific literature, which is based on the results of experiments conducted by numerous independent investigators, there has been no well-structured testing strategy. Therefore, the GLP status of the reported studies is unknown.

III.2 Pharmacology
Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties. In common with most NSAIDs mefenamic acid inhibits the action of prostaglandin synthetase (cyclooxygenase). This results in a reduction in the rate of prostaglandin synthesis and reduced prostaglandin levels.

III.3 Pharmacokinetics
Mefenamic acid is rapidly absorbed after oral administration. The fecal route of elimination accounts for up to 20% of the dose, mainly in the form of unconjugated 3-carboxymefenamic acid. The elimination half-life of mefenamic acid is approximately two hours. Mefenamic acid, its metabolites and conjugates are primarily excreted by the kidneys. Both renal and hepatic excretion are significant pathways of elimination.

Mefenamic acid undergoes metabolism by CYP2C9 to 3-hydroxymethyl mefenamic acid, and further oxidation to a 3-carboxymefenamic acid may occur.

III.4 Toxicology
Safety in pregnancy has not been established and trace amounts of mefenamic acid may be found in breast milk.

III.5 Ecotoxicity/environmental risk assessment
Mefenamic acid is not a new substance and has a widespread use in Europe. A net increase in the amount of mefenamic acid entering the environment as a consequence of Ponstan Capsules 500 mg being put on the market, is not expected, as this is a line extension of an approved product and will merely act as a substitute for the 250 mg strength already on the market. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
As mefenamic acid is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction
This is an Article 10a well-established use application. This is a line extension application for an addition of a new strength Ponstan 500 mg Capsules.

The posology is the same as that for the reference product Ponstan 250 mg Capsules.

No bioequivalence studies have been submitted as the bioequivalence guidelines general requirements for biowaiver were found to have been met. The Ponstan 500 mg Capsulesare manufactured by the same manufacturing process as The Ponstan 250 mg Capsules. The qualitative composition is the same. The composition of the strengths are quantitatively proportional. Finally, the in vitro dissolution data for the Ponstan 500 mg Capsulesis comparable to that of Ponstan 500 mg Capsules.

Mefenamic acid is well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for **Ponstan 250 mg Capsules.**

IV.2 Pharmacokinetics

Absorption and distribution
Mefenamic acid is absorbed from the gastrointestinal tract. Peak levels of 10 mg/l occur two hours after the administration of a 1 g oral dose to adults.

Metabolism
Mefenamic acid is predominantly metabolised by cytochrome P450 enzyme CYP2C9 in the liver, first to a 3-hydroxymethyl derivative (metabolite I) and then a 3-carboxyl derivative (metabolite II). Both metabolites undergo secondary conjugation to form glucuronides. Therefore in patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates, mefenamic acid should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Elimination
52% of a dose is recovered from the urine, 6% as mefenamic acid, 25% as metabolite I and 21% as metabolite II. Assay of stools over a 3 day period accounted for 10-20% of the dose chiefly as unconjugated metabolite II. The plasma levels of unconjugated mefenamic acid decline with a half life of approximately two hours.

IV.3 Pharmacodynamics

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 (cyclooxygenase). This results in a reduction in the rate of prostaglandin synthesis and reduced prostaglandin levels. The anti-inflammatory activity of NSAIDs in the rat paw oedema test has been correlated with their ability to inhibit prostaglandin synthetase.

When mefenamic acid is ranked in both these tests it falls between indomethacin and phenylbutazone and it is probable that inhibition of prostaglandin synthesis contributes to the pharmacological activity and clinical efficacy of mefenamic acid.

There is also considerable evidence that the fenamates inhibit the action of prostaglandins after they have been formed. They therefore both inhibit the synthesis and response to prostaglandins. This double blockade may well be important in their mode of action.

IV.4 Clinical Efficacy

The efficacy of Mefenamic acid is well characterised.

IV.5 Clinical Safety

The safety of Mefenamic acid is well characterised.

Risk Management Plan
A Risk Management Plan, version 0.3, dated 02March 2022 has been submitted, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ponstan 250mg capsules and Ponstan 500mg capsules. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

IV.6 Discussion on the clinical aspects

This is an Article 10a well-established use application. This is a line extension application for an addition of a new strength Ponstan 500 mg Capsules.

The posology is the same as that for the reference product Ponstan 250 mg Capsules.

No bioequivalence studies have been submitted as the bioequivalence guidelines general requirements for biowaiver were found to have been met. The Ponstan 500 mg Capsules are manufactured by the same manufacturing process as The Ponstan 250 mg Capsules. The qualitative composition is the same. The composition of the strengths are quantitatively proportional. Finally, the in vitro dissolution data for the Ponstan 500 mg Capsules is comparable to that of Ponstan 500 mg Capsules.

Mefenamic acid is well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for Ponstan 250 mg Capsules.

V. OVERALL CONCLUSIONS

This is an Article 10a well-established use application. This is a line extension application for an addition of a new strength Ponstan 500 mg Capsules.

No bioequivalence studies have been submitted as the bioequivalence guidelines general requirements for biowaiver were found to have been met.

The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Ponstan 250 mg Capsules demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	CRN009FVF	SmPC, PAR, Product Leaflet	16th August 2024	15th August 2029