IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Stirlescent 250mg Effervescent Tablets
Naproxen
PA23138/002/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5782/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 01/05/2020 under procedure number IE/H/1131/001/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA23138/002/001
Marketing Authorisation Holder: Stirling Anglian Pharmaceuticals Ireland Limited

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Stirlescent 250 mg Effervescent Tablets (PL 42582/0009; UK/H/5782/001/DC) indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute musculoskeletal disorders, dysmenorrhoea and acute gout in adults, is approvable.

The application was submitted using the Decentralised Procedure (DCP) with the UK as the RMS and Malta and Republic of Ireland as CMSs. The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended. The originator product is Naprometin® 250 mg tablets by Roche Oy, registered in Finland since 27 July 1977. The applicant has cross-referred to Naprosyn 250 mg Tablets, which was originally licensed to Syntex Pharmaceuticals Limited on 16 March 1988. This reference licence underwent a change of ownership procedure to the current Marketing Authorisation Holder, (Roche Products Limited; PL 00031/0471), on 31 May 1996. The product used for the purpose of bioequivalence study was Naprometin® 250 mg Tablets (Roche Oy, Finland). The reference products belong to the same global Marketing Authorisation holder and have the same composition.

Naproxen is a non-steroidal anti-inflammatory analgesic compound with antipyretic properties as has been demonstrated in classical animal test systems. Naproxen exhibits its anti-inflammatory effect even in adrenalectomised animals, indicating that its action is not mediated through the pituitary-adrenal axis.

Naproxen inhibits prostaglandin synthetase (as do other non-steroidal anti-inflammatory drugs (NSAIDs)). As with other NSAIDs, however, the exact mechanism of its anti-inflammatory action is not known.

One bioequivalence study was submitted to support this application comparing the test product Naproxen 250 mg effervescent tablet (Hermes Arzneimittel GmbH, Germany) with the reference product Naprometin® 250 mg tablets (Roche Oy, Finland) in healthy adult subjects, under fasting conditions. The applicant has stated that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

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

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 19 November 2015). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 42582/0009) for this product on 03 December 2015.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

This product is an effervescent tablet and contains 250 mg naproxen, as active ingredient. The excipients present are citric acid, sodium hydrogen carbonate, sodium carbonate, sodium cyclamate, saccharin sodium, sodium citrate, povidone, macrogol 6000, mannitol (E421), simeticone, docusate sodium and blackcurrant flavour. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of blackcurrant flavour which complies with an in-house specification.

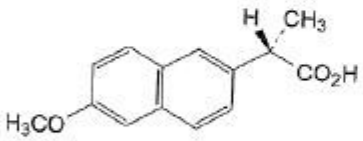
The finished product is packaged in polypropylene tube with polyethylene desiccant stopper or laminated aluminium paper foil containing 10, 12, 15, 20, 24 and 30 effervescent tablets. Not all pack sizes may be marketed.

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 Drug Substance

INN: Naproxen
Chemical name(s): (+)-6-methoxy-∞-methyl-2-naphthalineacetic acid
(S)-2-(6-methoxy-2-naphthyl)propionic acid

Structure:



Molecular formula: $C_{14}H_{14}O_3$
Molecular weight: 230.3 g/mol
Appearance: White or almost white crystalline powder.
Solubility: Naproxen is practically insoluble in water, soluble in ethanol (96 per cent) and in methanol.

Naproxen is the subject of a European Pharmacopoeia monograph.

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

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, tablets containing 250 mg naproxen that is bioequivalent to the reference product Naprometin® 250 mg Tablets (Roche Oy, Finland).

Comparative dissolution and impurity profiles have been presented for the proposed and reference products.

Manufacture of the product
A satisfactory batch formula has 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. No process validation data has been presented as the manufacturing process is considered standard. Satisfactory in-process controls are in place for this product.

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 specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf-life of 36 months with no special storage conditions is set. This is satisfactory.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

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

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS
III.1 Introduction
This generic application has been submitted in accordance with Article 10.1 of Directive 2001/83/EC, a amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of naproxen are well known. As naproxen is a widely used, well-known active substance, no new non-clinical data have been supplied and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the proposed product is intended for a generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under the Decentralised Procedures according to Article 10.1 of Directive 2001/83/EC, as amended, for Stirlescent 250 mg Effervescent Tablets.

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of naproxen are well known. As naproxen is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is considered appropriate.

With the exception of the bioavailability study, no new clinical data have been submitted and none are required for applications of this type. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study under fasting conditions.

This is a single centre, open-label, randomised, single dose 2x2 crossover bioequivalence study comparing the pharmacokinetics of the test product Naproxen 250 mg effervescent tablets (Hermes Arzneimittel GmbH, Germany) with the reference product Naprometin® 250 mg tablets (Roche Oy, Finland) in healthy adult subjects, under fasting conditions.

Blood samples were collected for plasma levels before dosing and up to and including 60 hours after each administration. The washout period was 6 days.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	657641.9 ± 117966.34	734086.8 ± 177070.66	45037.5 ± 5583.33	1.75 (0.75-3.50)
Reference	665447.3 ± 125012.60	744914.3 ± 182711.38	46210.8 ± 7589.17	2.00 (0.50-3.50)
*Ratio (90% CI)	99.00% (97.01 - 101.04%)	98.73% (96.42 - 101.09%)	98.00% (92.98 – 103.28%)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of $AUC_{0-\infty}$ in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable.
Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Conclusion

The 90% confidence intervals for C_{max} and AUC were within the pre-defined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Naproxen 250 mg effervescent tablet) and the reference formulation (Naprometin® 250 mg tablets) under fasting conditions.

IV.3 Pharmacodynamics

No new data have been submitted and none are required for applications of this type.

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical safety

No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), 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 Stirlescent 250 mg Effervescent Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern (Identified risks)	Routine risk minimisation measures	Additional risk minimisation measures
Gastrointestinal bleeding, ulceration and perforation	Proposed text in SmPC	Not applicable
Bleeding / inhibition of platelet function	Proposed text in SmPC	Not applicable

Safety concern (Identified risks)	Routine risk minimisation measures	Additional risk minimisation measures
Arterial thrombotic events (myocardial infarction, stroke).	Proposed text in SmPC	Not applicable
Sodium / fluid retention, oedema	Proposed text in SmPC	Not applicable
Hypersensitivity reactions including anaphylactic/anaphylactoid reactions and bronchospasm in people with asthma	Proposed text in SmPC	Not applicable
Nephrotoxicity	Proposed text in SmPC	Not applicable
Severe hepatic reactions such as jaundice and hepatitis.	Proposed text in SmPC	Not applicable
Serious skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis	Proposed text in SmPC	Not applicable
Interactions with methotrexate, lithium, tacrolimus, cardiac glycosides	Proposed text in SmPC	Not applicable
Use during pregnancy	Proposed text in SmPC	Not applicable
Presence of sodium	Proposed text in SmPC	Not applicable

Safety concern (potential risk)	Routine risk minimisation measures	Additional risk minimisation measures
Impaired female fertility	Proposed text in SmPC	Not applicable
Ocular effects	Proposed text in SmPC	Not applicable
Aseptic meningitis in people with SLE and mixed connective tissue disease	Proposed text in SmPC	Not applicable
Agranulocytosis, aplastic anaemia and haemolytic anaemia	Proposed text in SmPC	Not applicable
Use during breast-feeding	Proposed text in SmPC	Not applicable
Safety and effectiveness in children below the age of 18 years	Proposed text in SmPC and other routine risk minimisation measures	Not applicable

Safety concern (Missing information)	Routine risk minimisation measures	Additional risk minimisation measures
Safety and effectiveness in children below the age of 18 years	Proposed text in SmPC	Not applicable

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V User consultation

The package leaflet 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, as amended. The language used for the purpose of user testing the package information leaflet (PIL) was English.

The results show that the package leaflet 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.*

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The data provided by the applicant showed that the test product is comparable to the reference product. Extensive clinical experience with naproxen is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

VI. REVISION DATE

28/02/2022

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
RMS transfer	From UK/H/5782/001/DC to IE/H/1131/001/DC			
MAH transfer				18/12/2020