IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Folic Acid 2.5mg/5ml Oral Solution
Folic acid
PA0281/232/001

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/1930/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 22nd November 2018 under procedure number IE/H/0851/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/232/001
Marketing Authorisation Holder: Pinewood Laboratories Ltd.

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.

Based on the review of the data on quality, safety and efficacy, Cyprus, Ireland, Malta, Poland and the UK considered that the application for Folic Acid 2.5mg/5ml Oral Solution could be approved. The product is a prescription only medicine (POM) and indicated for the following:

1. Folate deficient megaloblastic anaemia

2. Folate deficient megaloblastic anaemia in infants

3. Treatment of folate deficiency in malabsorption syndromes (parenteral administration of folic acid may need to be considered if oral treatment is not effective)
3.1 Tropical sprue. Tropical sprue responds to folate supplements in the early stages of the disease but cobalamin status must also be checked, particularly later.
3.2 Coeliac disease. The necessity of supplementation with folate ceases once a gluten free diet is introduced.
3.3 Non-tropical sprue. In congenital folate malabsorption, oral treatment may not be effective and parental folate may therefore be required.

4. Megaloblastic anaemia in pregnancy

5. Megaloblastic anaemia associated with alcoholism

6. Megaloblastic anaemia associated with anti-convulsant therapy

7. Folic acid deficiency/megaloblastic anaemia associated with haemolytic anaemia e.g. Sickle Cell Anaemia

This application for Folic Acid 2.5mg/5ml Oral Solution is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Lexpec Folic Acid 2.5mg/5ml Oral Solution, first authorised in the UK to Rosemont Pharmaceuticals Limited in October 1974.

Folic acid deficiency causes megaloblastic haemopoiesis in which there is disordered erythroblast differentiation and defective erythropoiesis in the bone marrow. Large abnormal erythrocyte precursors appear in the bone marrow each with a high DNA to RNA ratioas a result of decreased DNA synthesis.

Dihydrofolate FH2 and tetrahydrate FH4 act as carriers and donors of methyl groups particularly in DNA synthesis as a result of its cofactor action in synthesis of purines and pyrimidines. Clinically folic acid is used in treatment of megaloblastic anaemia, treatment or prevention of toxicity from methotrexate and prophylactically in individuals at risk of folate deficiency.

No new preclinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies have been performed and none are required for this application as the pharmacology of folic acid is well-established. No clinical pharmacology data is required for this generic infusion solution.

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.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP).

ABOUT THE PRODUCT

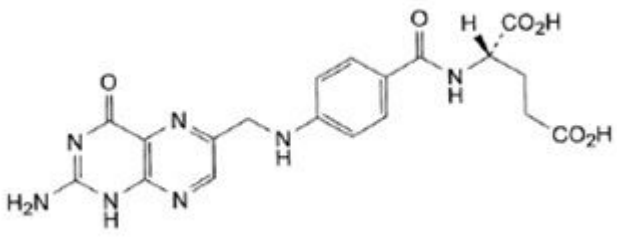
Name of the product in the Reference Member State	Folic Acid 2.5mg/5ml Oral Solution
Name(s) of the active substance(s) (INN)	Folic Acid
Pharmacotherapeutic classification (ATC code)	Folic acid and derivatives (B03B B)
Pharmaceutical form and strength(s)	2.5mg/5ml Oral Solution
Reference numbers for the Decentralised Procedure	UK/H/1930/001/DC
Reference Member State	United Kingdom
Member States concerned	Cyprus, Ireland, Malta, Poland
Marketing Authorisation Number(s)	PL 29831/0358
Name and address of the authorisation holder	Wockhardt UK Ltd Ash Road North Wrexham LL13 9UF United Kingdom

II. QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Folic acid
Chemical name: (2*S*)-2-[[4-[[2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino]benzoyl]amino]pentanedioic acid.

Structural formula:



Molecular formula: $C_{19}H_{19}N_7O_6$

Appearance: a yellowish or orange, crystalline powder.
Solubility: practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions.

Molecular weight: 441.4

Folic acid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance folic acid from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance folic acid.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

The other ingredients are the pharmaceutical excipients mannitol (E421), glycerol (E422), methyl hydroxybenzoate (E218), ethyl hydroxybenzoate (E214), propyl hydroxybenzoate (E216), sodium dihydrogen phosphate dehydrate, disodium hydrogen phosphate dodecahydrate, disodium edetate, strawberry flavour (contains phenylalanine, cherry juice concentrate and maltol) and purified water.

All excipients with the exception of methyl hydroxybenzoate (E218) and strawberry flavour (contains phenylalanine, cherry juice concentrate and maltol) comply with their relevant European Pharmacopoeia monographs.

Methyl hydroxybenzoate (E218) and strawberry flavour (contains phenylalanine, cherry juice concentrate and maltol) comply with in-house specifications.
None of the excipients contain materials of animal or human origin.
No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Lexpec Folic Acid 2.5mg/5ml Oral Solution (Rosemont Pharmaceuticals Limited, October 1974).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Lexpec Folic Acid 2.5mg/5ml Oral Solution (Rosemont Pharmaceuticals Limited).

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The applicant has committed to perform process validation on future commercial-scale batches of the product.

Finished Product Specification

The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System

The product is packaged in 150ml amber EP Type III glass bottles, fitted with a 28 mm white child resistant tamper evident screw cap, with expanded polyethylene (EPE) liner, and outer cardboard carton.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

Stability of the product

Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 18 months for an unopened product with storage

conditions "Store in a refrigerator (2°C-8 °C)" and "Store in the original bottle and outer cardboard carton in order to protect from light".

The shelf-life of the product after first opening is three months.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for a PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III. NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of folic acid are well-known. As folic acid is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report is based on literature sources and has been written by an appropriately qualified person.

IV. CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

No bioequivalence studies have been performed and none are required for this application, as As per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived, if the excipients contained in it do not affect gastrointestinal transit, absorption, solubility or in-vivo stability of the active substance.

3. Post marketing experience

Folic acid has a well-recognised efficacy and an acceptable level of safety in the indications approved for Lexpec Folic Acid 2.5mg/5ml Oral Solution, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

4. Benefit-Risk assessment

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with folic acid is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. Conclusions
The grant of a Marketing Authorisation for Folic Acid 2.5mg/5ml Oral Solution is recommended from a clinical viewpoint.

V. OVERALL CONCLUSIONS

Quality
The important quality characteristics of Folic Acid 2.5mg/5ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

CLINICAL
No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with folic acid is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

VI. REVISION DATE

August 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/1930/001/DC to IE/H/0851/001/DC	N/A	N/A	N/A	Approved 22/11/2018
MA Transfer	CRN009YVT	SmPC, Leaflet Old MA holder: Wockhardt UK Limited New MA Holder: Pinewood Laboratories Ltd	31/12/2020	31/12/2020	Approved

		OLD PA number: PA1339/022/001 New PA number: PA0281/232/001			