Public Assessment Report

Decentralised Procedure

FOLIC ACID 2.5MG/5ML ORAL SOLUTION

UK/H/1930/001/DC
UK Licence No: PL 29831/0358

WOCKHARDT UK LIMITED
LAY SUMMARY

On 9th April 2010, the UK granted Wockhardt UK Limited a Marketing Authorisation (licence) for the medicine Folic Acid 2.5mg/5ml Oral Solution (PL 29831/0358).

Folic acid is a vitamin essential in the production and maintenance of new cells.

Folic Acid 2.5mg/5ml Oral Solution is used in the treatment of:
  • anaemia due to a lack of folic acid in adults and children
  • anaemia in pregnancy
  • anaemia associated with alcoholism
  • anaemia, as a side effect from medicines used to control fitting
  • anaemia due to damaged red blood cells e.g. Sickle Cell anaemia
  • sprue (tropical and non-tropical) - a disorder where essential nutrients are not absorbed from the diet
  • coeliac disease, a disorder caused by gluten in the diet.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Folic Acid 2.5mg/5ml Oral Solution outweigh the risks; hence a Marketing Authorisation has been granted.
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# Module 1

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<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Folic Acid 2.5mg/5ml Oral Solution</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<td><strong>Form</strong></td>
<td>Oral Solution</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>2.5mg/5ml</td>
</tr>
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| **MA Holder** | Wockhardt UK Ltd  
Ash Road North  
Wrexham  
LL13 9UF  
United Kingdom |
| **Reference Member State (RMS)** | UK |
| **CMS** | Cyprus, Ireland, Malta, Poland |
| **Procedure Number** | UK/H/1930/001/DC |
| **End of Procedure** | Day 210 – 25th February 2010 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Folic Acid 2.5mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Folic Acid 2.5mg/5ml
Excipients:
Methyl hydroxybenzoate (E218)
Ethyl hydroxybenzoate (E214)
Propyl hydroxybenzoate (E216)
Phenylalanine
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral Solution.
A clear, yellow, solution with a strawberry flavour and odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
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

4.2 Posology and method of administration
For oral administration only.

Children (persons aged 12 years and younger):
May be given 5 mg to 15 mg daily, in divided doses, according to the severity of the deficiency state.

Adults:
Initial dose of 10 mg to 20 mg daily, in divided doses, for 14 days or until a haemopoietic response has been obtained.
Maintenance dose is 2.5 mg to 10 mg daily.
Prophylactic dose in pregnancy 0.5 mg (1ml) daily.

Elderly:
As for adults.

4.3 Contraindications
Known hypersensitivity to folic acid.
Known hypersensitivity to hydroxybenzoate esters.
Patients with folate dependent tumours.
Patients with malignant disease, unless megaloblastic anaemia due to folic acid deficiency.

4.4 Special warnings and precautions for use
If folic acid is used indiscriminately, there is a danger that patients with pernicious anaemia and other B12 deficiency states, despite a haematological remission, may develop irreparable neurological lesions. Therefore a full clinical diagnosis should be made before initiating treatment.

Folic acid is removed by haemodialysis.
Contains methyl- ethyl- and propyl- p-hydroxybenzoates; may cause allergic reactions (possibly delayed).
Contains 0.75 mmol (or 17.4mg) sodium per 20 ml dose, and is therefore essentially ‘sodium-free’.
Contains phenylalanine. May be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction
Folic acid has been observed to reduce plasma levels of anticonvulsants, particularly phenytoin and primidone and therefore patients should be carefully monitored by the physician and the anticonvulsant drug dose adjusted as necessary.

4.6 Pregnancy and lactation
There are no known hazards to the use of folic acid, indeed folic acid supplements are often necessary in pregnancy.
Folic acid is excreted in breast milk.

4.7 Effects on ability to drive and use machines
There are no known effects of this preparation on the ability to drive or use machines.

4.8 Undesirable effects
Allergic reactions to folic acid have been reported.
Mild gastro-intestinal upsets are rare but may occur.

4.9 Overdose
No cases of acute overdosage appear to have been reported, but even extremely high doses are unlikely to cause harm to patients.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC Code: B03B B
After conversion into co-enzyme forms it is concerned in single carbon unit transfers in the synthesis of purines, pyrimidines and methionine.

5.2 Pharmacokinetic properties
About 70 – 80 % of a 2 mg oral solution of folic acid is absorbed. Larger doses are probably equally well absorbed. It is distributed into plasma and extracellular fluid. In plasma, folate is bound weakly to albumin (70 %). There is a further high affinity binder for folate but this has a very low capacity and is barely detectable in normal sera. About 70 % of small doses of folate (about 1 mg) are retained and the rest excreted into the urine. With larger doses most is excreted into the urine. With a 5 mg dose of folate, urinary excretion will be complete in about five hours. There is an enterohepatic circulation of folate. The retained folate is taken into cells and reduced by dihydrofolate to tetrahydrofolate. Folic acid is a relatively poor substrate for folate reduction, the normal substrate being dihydrofolate.

Folic acid itself does not occur in natural materials, it is entirely a pharmacological form of the compound. Once reduced, folate has additional glutamic acid residues added, a folate pentaglutamate being the dominant intracellular analogue. These polyglutamates are the active co-enzymes.

5.3 Preclinical safety data
Folic Acid is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol (E421)
Glycerol (E422)
Methyl hydroxybenzoate (E218)
Ethyl hydroxybenzoate (E214)
Propyl hydroxybenzoate (E216)
Sodium dihydrogen phosphate dihydrate
Disodium hydrogen phosphate dodecahydrate
Disodium edetate
Strawberry flavour (contains phenylalanine, cherry juice concentrate and maltol)
Purified water

6.2 Incompatibilities
None stated.

6.3 Shelf life
Unopened: 18 months
After first opening: Three months.

6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C)
Store in the original bottle and outer cardboard carton in order to protect from light.

6.5 Nature and contents of container
150 ml amber soda glass (type III) bottle fitted with a 28 mm white child resistant tamper evident screw cap, with expanded polyethylene (EPE) liner, and outer cardboard carton.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORITY HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
U.K.

8 MARKETING AUTHORITY NUMBER(S)
PL 29831/0358

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
09/04/2010

10 DATE OF REVISION OF THE TEXT
09/04/2010
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
Folic Acid 2.5mg/5ml Oral Solution

In this leaflet:
1. What Folic Acid Oral Solution is and what it is used for
2. Before you take Folic Acid Oral Solution
3. How to take Folic Acid Oral Solution
4. Possible side effects
5. How to store Folic Acid Oral Solution
6. Further information

1. What Folic Acid Oral Solution is and what it is used for

The name of your medicine is Folic Acid Oral Solution, which contains folic acid, a vitamin essential in the production and maintenance of new cells.

Folic Acid Oral Solution is used in the treatment of:
- anaemia due to a lack of folic acid in adults and children
- anaemia in pregnancy
- anaemia associated with alcoholism
- anaemia, as a side effect from medicines used to control fitting
- anaemia due to damaged red blood cells e.g. Sickle Cell anaemia
- sprue (tropical and non-tropical) - a disorder where essential nutrients are not absorbed from the diet
- coeliac disease, a disorder caused by gluten in the diet.

2. Before you take Folic Acid Oral Solution

You should not take Folic Acid Oral Solution if you:
- are allergic (hypersensitive) to folic acid, hydroxybenzoate esters or to any of the other ingredients in Folic Acid Oral Solution (see section 6, Further information)
- have a tumour
- have cancer (unless you have anaemia due to a deficiency of folic acid).

Talk to your doctor before taking Folic Acid Oral Solution if you:
- suffer from pernicious anaemia (a disorder preventing the absorption of vitamin B12) or could be suffering from a lack of vitamin B12
- are under going haemodialysis due to kidney failure.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The following medicines can affect or be affected by treatment with Folic Acid Oral Solution:
- phenytoin and primidone (used to control epileptic fits).

Pregnancy and breast-feeding
This medicine can be taken in pregnancy to treat anaemia.

If you are breast-feeding please speak with your doctor before taking this medicine.

Driving and using machinery
This medicine does not affect your ability to drive a car or operate machinery.

Important information about some of the ingredients in Folic Acid Oral Solution
This medicine contains hydroxybenzoates which are used as preservatives. These ingredients may cause allergic reactions and could happen some time after starting the medicine.

This medicine contains phenylalanine. May be harmful for people with phenylketonuria.

3. How to take Folic Acid Oral Solution

Always take Folic Acid Oral Solution as your doctor has told you. Your doctor will decide the right dose for you, this will be on the pharmacist's label. Check this carefully, it will tell you how much of this medicine to take and how often to take it. This medicine should be swallowed. The usual doses are as follows:

Adults and the elderly
- 10 to 20ml, twice a day, for up to 14 days or until an appropriate blood response is achieved
- this may be reduced to 2.5 to 10ml, twice a day, for ongoing treatment.

Pregnant women
- 1ml per day.

Children (persons aged 12 years and younger)
- 5 to 15ml, twice a day.

If you take more Folic Acid Oral Solution than you should
If you (or anybody else, including a child), takes more Folic Acid Oral Solution than you should, it is unlikely that this medicine will cause any harm. If you are at all concerned contact your doctor. Always take the bottle and this leaflet with you.
If you forget to take Folic Acid Oral Solution
If you forget a dose, take another as soon as you remember. If it is almost time for your next dose, then do not take the missed dose at all. NEVER take a double dose to make up for the one missed.

4. Possible side effects
Like all medicines, Folic Acid Oral Solution can cause side effects, although not everybody gets them. Mild stomach upsets have been reported but are rare.

As can happen with any medicine, a few people may develop an allergic reaction. If you experience any of the following, seek medical help immediately:
• rash, itching, difficulty breathing.

If you experience any side effects or feel that the medicine is affecting you badly, tell your doctor or pharmacist immediately.

5. How to store Folic Acid Oral Solution
Keep out the reach and sight of children.

• Folic Acid Oral Solution should be stored in a refrigerator (2°C - 8°C). Store in the original container to protect from light; do not transfer to another container.
• Folic Acid Oral Solution should not be taken after the expiry date on the bottle label and carton; the expiry date refers to the last day of the month.
• Throw away any unused Folic Acid Oral Solution three months after first opening the bottle.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Further information
What Folic Acid Oral Solution contains
The active ingredient is: folic acid (2.5mg per 5ml of Folic Acid Oral Solution).
The other ingredients are: mannitol (E421), glycerol (E422), methyl hydroxybenzoate (E218), ethyl hydroxybenzoate (E214), propyl hydroxybenzoate (E216), disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, disodium edetate, strawberry flavour (contains phenylalanine, cherry juice concentrate and maltol) and purified water.

What Folic Acid Oral Solution looks like and the contents of the pack
Folic Acid Oral Solution is a clear yellow solution, which tastes and smells of strawberry. The medicine is supplied in a 150ml amber glass bottle, with a child resistant screw cap, in a cardboard outer container.

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

Other formats:
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:
0800 198 5000 (UK Only).

Please be ready to give the following information:

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Reference number</th>
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<tbody>
<tr>
<td>Folic Acid 2.5mg/5ml Oral Solution</td>
<td>29831/0358</td>
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</table>

This is a service provided by the Royal National Institute of Blind People.

For the Republic of Ireland please call + 353 52 36253.

This medicinal product is authorised in the following Member States in the EEA, under the following names:

Cyprus - Folic Acid Wockhardt 2.5mg/5ml Oral Solution
Malta - Folic Acid 2.5mg/5ml Oral Solution
Poland - Wockhardt Folic Acid 2.5mg/5ml Oral Solution
Republic of Ireland – Folic Acid 2.5mg/5ml Oral Solution
United Kingdom - Folic Acid 2.5mg/5ml Oral Solution


104572/1
Module 4
Labelling

5 ml of solution contains 2.5 mg of folic acid

Dose: As directed by your doctor
Read the package leaflet before use

Contains methyl hydroxybenzoate (E218), ethyl hydroxybenzoate (E214), propyl hydroxybenzoate (E216) and phenylalanine. Read the package leaflet for further information

Store in a refrigerator (2°C - 8°C)
Store in the original bottle and outer cardboard carton in order to protect from light
Discard three months after first opening
Keep out of the reach and sight of children

PL 29831/0358  PA 1393/22/1  MA154/01302

Marketing Authorisation Holder:
Wockhardt UK Ltd,
Ash Road North,
Wrexham, LL13 9UF, UK
23L03786PW

For oral use
Folic Acid 2.5mg/5ml Oral Solution

For oral use

5 ml of solution contains 2.5 mg of folic acid

Dose: As directed by your doctor

Read the package leaflet before use

Contains methyl hydroxybenzoate (E218), ethyl hydroxybenzoate (E214), propyl hydroxybenzoate (E216) and phenylalanine. Read the package leaflet for further information

Store in a refrigerator (2°C - 8°C)

Store in the original bottle and outer cardboard carton in order to protect from light

Discard three months after first opening

Keep out of the reach and sight of children

Marketing Authorisation Holder:

Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

PL 29831/0358 PA 1339/22/1
MA154/01302
23PCG1209PW
Folic Acid 2.5mg/5ml Oral Solution

For oral use

5 ml of solution contains 2.5 mg of folic acid

Dose: As directed by your doctor

Read the package leaflet before use

Contains methyl hydroxybenzoate (E218), ethyl hydroxybenzoate (E214), propyl hydroxybenzoate (E216) and phenylalanine. Read the package leaflet for further information

Store in a refrigerator (2°C - 8°C)

Store in the original bottle and outer cardboard carton in order to protect from light

Discard three months after first opening

Keep out of the reach and sight of children

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wreatham, LL13 9UF, UK

PL 2983120558  PA 1333/231 MA154/01302 23PCO1209PW
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION
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 ratio as 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 oral 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).
## II. ABOUT THE PRODUCT

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<tr>
<th>Name of the product in the Reference Member State</th>
<th>Folic Acid 2.5mg/5ml Oral Solution</th>
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<tr>
<td>Name(s) of the active substance(s) (INN)</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Folic acid and derivatives (B03B B)</td>
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<tr>
<td>Member States concerned</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0358</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Wockhardt UK Ltd</td>
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<tr>
<td></td>
<td>Ash Road North</td>
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<tr>
<td></td>
<td>United Kingdom</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

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

Structural formula:

\[
\begin{align*}
\text{Molecular formula: } & C_{19}H_{19}N_{7}O_{6} \\
\text{Appearance: } & \text{a yellowish or orange, crystalline powder.} \\
\text{Solubility: } & \text{practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions.} \\
\text{Molecular weight: } & 441.4
\end{align*}
\]

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.2 PRE-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.
III.3 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 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.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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.
## Module 5

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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