Public Assessment Report

Decentralised Procedure

VIAFOL 10 MG/ML ORAL SOLUTION

Procedure No: UK/H/5070/001/DC

UK Licence No: PL 08616/0002

Vianex SA
LAY SUMMARY

On 19 May 2013, the UK and Greece agreed to grant Marketing Authorisations to Vianex SA for the medicinal product Viafol 10 mg/ml Oral Solution (PL 08616/0002; UK/H/5070/001/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a Marketing Authorisation was granted in the UK on 18 June 2013.

This product is a prescription-only medicine (legal status POM) containing the active ingredient folic acid. Folic acid belongs to a group of vitamins called ‘B vitamins’. Viafol is used to prevent babies being born with neural tube defects such as spina bifida. This product is not suitable where there is an increased risk of neural tube defects in the baby, for example in women who have previously had an affected child, or are diabetic, or are receiving medication for epilepsy. In this case, an alternative product and a higher dose of folic acid should be used.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Viafol 10 mg/ml oral solution outweigh the risks and a Marketing Authorisation was granted.
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## Module 1
**Information about initial procedure**

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Viafol 10 mg/ml oral solution</th>
</tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Well established use, Article 10a</td>
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<tr>
<td><strong>Active Substances</strong></td>
<td>Folic acid</td>
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<tr>
<td><strong>Form</strong></td>
<td>Oral solution</td>
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<td><strong>Strength</strong></td>
<td>10 mg/ml</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Vianex SA, Tatoiou Street, 14671 Nea-Erythrea, Greece</td>
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<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Greece</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/5070/001/DC</td>
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<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 19 May 2013</td>
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Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Carton:
Label:

Each 1 ml of solution contains 10 mg of folic acid.

Excipients: propylene glycol, glycerol, sodium hydroxide, purified water.

Store below 25°C. Store in the original package in order to protect from light. This medicine should be disposed of 3 months after first opening. Do not use the product if you notice a change in the appearance or smell of the solution. Read the package leaflet before use. Keep out of the reach and sight of children.

VIANEX S.A., Tatoiou str., 146 71 Nea Erythrea, Greece
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Viafol 10mg/ml oral solution (PL 08616/0002; UK/H/5070/001/DC) could be approved. This application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS) and Greece as a Concerned Member State (CMS).

This was an application submitted according to Article 10a of Directive 2001/83/EC, as amended, as a ‘well-established use’ application.

Viafol 10mg/ml oral solution is a prescription-only medicine (POM), indicated for use in pregnancy to prevent the first occurrence of spina bifida and other neural tube defects in the newborn.

This product contains the active ingredient folic acid, which is a member of the B-complex family of vitamins and works in concert with Vitamin B12. Folic acid functions as a methyl-group donor and has an important role in many body processes, including DNA synthesis. Therapeutically, folic acid has an instrumental role in reducing homocysteine levels and the occurrence of neural tube defects.

No new clinical or non-clinical studies were conducted to support this application, which is acceptable given that the application was a bibliographical application for a product containing an active ingredient of well-established use.

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

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 19 May 2013. After a subsequent national phase, a licence was granted in the UK on 18 June 2013.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Viafol 10 mg/ml oral solution</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Folic acid</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Vitamin supplement (B03BB01)</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>Oral solution, 10mg/ml</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 08616/0002</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Vianex SA, Tatoiou Street, 14671 Nea-Erythrea, Greece.</td>
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</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – Folic acid

rINN: Folic acid

Chemical name: \((2S)-2-[4-[[2-(Amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino]benzoyl]amino]pentanediio acid\)

Structure:

![Structure of Folic Acid](image)

Molecular formula: \(C_{19}H_{19}N_{7}O_{6}\)

Molecular weight: 441.40

Appearance: Crystalline, yellow to yellow-orange, practically odourless powder

Solubility: Very slightly soluble in water, insoluble in alcohol, acetone, ether and chloroform and readily soluble in solutions of alkali hydroxides and carbonates

All aspects of the manufacture and control of the active substance from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely glycerol (E422), propylene glycol (E1520), sodium hydroxide and purified water.

All of the excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

Folic acid products have been commercially available for a long period of time and their clinical use is well-established. However the majority of commercially available products are solid dosage forms. Therefore, the objective of the development programme was to formulate a safe, efficacious, stable oral solution, at a concentration of 10 mg/ml. A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the finished product. The manufacturing process has been validated using three production-scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of analysis have been provided for all working standards used.
Container-Closure System
The finished product is filled into a 15 ml amber (Type III) glass bottle, equipped with a low density polyethylene (LDPE) vertical dropper designed to deliver 20 drops per ml. A tamper-evident high-density polyethylene (HDPE) screw cap closure is also provided.

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.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 21 months when unopened and 3 months once opened, with the storage conditions “Store below 25°C.” and “Store in the original package in order to protect from light.”

Bioequivalence/bioavailability
No bioequivalence studies were conducted and none are required for applications of this type.

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

The results of consultations with target patient groups on the package leaflet (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended, have been provided. The results indicate that the package leaflet 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.

Marketing Authorisation Application (MAA) form
The MAA form is pharmaceutically satisfactory.

Quality Overall Summary (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 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of folic acid are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
No new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required as the product contains an active substance that has been in clinical use for many years and the clinical pharmacology is well-known.

Efficacy
No new data on efficacy have been submitted as this is a well-established use application containing an active substance that has been in clinical use for many years. The clinical expert has presented an acceptable overview of the published literature in support of this application.

Safety
No new safety data were submitted and none are required for this type of application. The applicant has provided an acceptable safety review from the literature. No new safety issues have been raised.

SmPC, PIL and Labels
The SmPC, PIL and labels are medically acceptable.

Pharmacovigilance System and Risk Management Plan
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.

Suitable justification has been provided for not submitting a risk management plan for this product.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Viafol 10 mg/ml 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
No new clinical data were submitted and none are required for applications of this type.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and in line with current guidelines.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical 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 benefit-risk is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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