LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Folsyra Vitabalans
(folic acid)

SE/H/1793/01-02/DC

This module reflects the scientific discussion for the approval of Folsyra Vitabalans. The procedure was finalised on 2019-01-24. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Vitabalans Oy has applied for a marketing authorisation for Folsyra Vitabalans, 1 mg & 5 mg Tablet. The active substance is folic acid (Folic acid is a part of the coenzymes involved in certain transmethylation processes e.g. synthesis of deoxyribonucleic acid and ribonucleic acid. Folic acid is a component of the B group of vitamins and is necessary for the normal production and maturation of red blood cells. Folic acid deficiency is one of the causes of megaloblastic anaemia).

For approved indications, see the Summary of Product Characteristics.
The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Folic acid is widely used in the EU and has been approved as a medicinal product in Sweden at least since 1950. As WEU application the non-clinical part is evaluated on scientific literature.

III.2 Pharmacology

Folic acid is converted and activated in the body to tetrahydrofolic acid (THF) by dihydrofolate. Folic acid is crucial to ensure various metabolic and biochemical processes. The pharmacology of folic acid is considered well known. Adverse cardiovascular, CNS and respiratory effects are not expected based in the clinical experience of the product.

III.3 Pharmacokinetics

Folic acid will be administered orally and is absorbed completely after administration. The applicant has presented an acceptable literature report based on several original papers.

III.4 Toxicology

Folic acid is a well-established product that has been in use for many years its clinical safety profile is therefore well known. It can, based on bibliographic data be concluded that folic acid is non-mutagenic which indicate that folic acid is not considered genotoxic. The long term clinical experience in FA during pregnancy and the benefits to prevent neural tube defects in children is well established. The Applicant submitted a summary and several scientific studies describing the cancer risk in relation to intake of folic acid. In conclusion these studies roles out an increase in cancer incidence from folic acid supplementation.

III.5 Ecotoxicity/environmental risk assessment

The use of this product is considered not to alter the concentration or distribution of the substance in the environment and therefore not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

For a well-established use (WEU) application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognized efficacy and an acceptable level of safety.
Folic acid is widely used in the EU and has been approved as a medicinal product in Sweden at least since 1950.

IV.2 Pharmacokinetics

Folic acid is absorbed rapidly from the gastrointestinal tract following oral administration. Following oral administration, peak folate activity in blood occurs within 30–60 minutes. Synthetic folic acid is almost 100% bioavailable when administered in fasting individuals. While the bioavailability of naturally occurring folate in food is about 50%, bioavailability of synthetic folic acid consumed with a meal ranges from 85–100%. Also, the bioavailability of folic acid is dependent on the nutrient status of the patient as the absorption is regulated by the folic acid homeostasis. Folic acid is largely reduced and methylated in the liver to N 5-methyltetrahydrofolic acid.

IV.3 Pharmacodynamics

The applicant has provided an adequate description of the pharmacodynamic aspects of folate. The most important aspect is that a deficiency of folate reduces the ability of the organism to restore damaged tissues and enable the growth of new cells. The hematopoietic system is a tissue with a high level of multiplication and restoration and it reacts to the folate deficiency with anaemia.

IV.4 Clinical efficacy

Overall, the fairly large number of articles presented by the applicant confirms the scientific interest for studies of the clinical efficacy of folic acid. Most of the studies seem to report a positive clinical response to folic acid.

Folate is a vitamin which is essential to healthy humans and normally consumed through food. In certain instances however higher doses are required and folic acid can be used for medicinal purposes e.g deficiency states.
Folate deficiency can be confirmed using blood test. Deficiency is an elusive term with surprisingly limited conceptual and pragmatic consensus on its definitions. The textbook uses the term clinical deficiency of folate to denote the presence of vitamin-specific clinical signs and symptom that require medical intervention. However, folate deficiencies can be subclinical and expressed only by (often minimal) biochemical manifestations. Cobalamin and folate deficiencies can cause similar clinical manifestations. The most frequent manifestation, megaloblastic anemia, is identical in both deficiencies.Treatment of folate-deficient megaloblastic anemia with folic acid is considered well-established and accepted. The posology 5 mg/day presented by the applicant is considered supported by data.

The applicant has proposed therapeutic use with folic acid during treatment with drugs that inhibit folate absorption or folate metabolism. Bibliographic evidence supporting concomitant use with methotrexate is considered firm and in line with clinical practice for other folic acid products. The applicant quotes the British National Formulary recommending 5 mg weekly. This is also in line with other folic acid containing medicinal products on the EU-market. Concomitant use with anticonvulsants appears less well-established. As pointed out by the applicant, anticonvulsants or anti-epileptics are a wide group of drugs which may alter the absorption and/or metabolism of folic acid in different ways, which could make posology recommendations difficult.

A protective effect of folate against the development of NTD in pregnancy is well accepted. Prophylactic use of Folsyra Vitabalans 4 weeks before conception and continued through the first trimester (12 weeks) agrees with other folic acid containing medicinal products on the EU market.

The applicant has provided several up-to-date bibliographic references in support of paediatric use. In these references it is pointed out that folic acid deficiency should be confirmed using blood test, that clinical judgement is important when deciding the treatment course and that an objective response to folic acid provides the diagnostic confirmation. Altogether, these references are considered to support the proposed wording of both the indication and the posology.

IV.5 Clinical safety

The applicant has overall provided adequate information regarding the clinical safety of folic acid. Supportive to the safe use is that folic acid has a documented long-standing use in the EU (in Sweden since the 1950´s). No new alarming safety findings regarding folic acid have been presented by the applicant. Folic acid is generally well tolerated with few adverse effects, even

in long-term use. Listed adverse events relates mainly to allergic reactions and mild gastro-intestinal symptoms such as nausea, abdominal distension and flatulence. The acute toxicity is very low and normally no symptoms are expected in case of an overdose.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan, 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 Folsyra Vitabalans.

Safety specification

Important identified risks	None
Important potential risks	None
Missing information	None

The applicant proposes not to have any listed safety concerns in the updated RMP, version 0.2. Considering the well-known safety profile and long-standing use of folic acid containing medicinal products, this is deemed acceptable.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 0.2 signed September 5, 2018 is considered acceptable.

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. The language used for the purpose of user testing the PIL was Czech.
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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The applicant has demonstrated that folic acid has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, e.g folic acid has been approved as a medicinal product in Sweden at least since 1950.

The fairly large number of articles presented by the applicant confirms the scientific interest for studies of the clinical efficacy of folic acid. Most of the studies seem to report a positive clinical response to folic acid. Overall, included studies are considered to support the WEU-criteria regarding the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments.

Folate is a vitamin which is essential to healthy humans and normally consumed through food. In certain instances however higher doses are required and folic acid can be used for medicinal purposes e.g deficiency states. Folate deficiency can be confirmed using blood test. Treatment of folate-deficient megaloblastic anemia with folic acid is considered well-established and accepted.

Therapeutic use with folic acid during treatment with drugs that inhibit folate absorption or folate metabolism e.g methotrexate is also considered well-established and in line with clinical practice for other folic acid products. Lastly, a protective effect of folate against the development of NTD in pregnancy is also well accepted.

Regarding the risks related to folic acid, the applicant has overall provided adequate information on the clinical safety of folic acid and the safety profile is benign; folic acid is a vitamin and has a documented long-standing medicinal use in the EU (in Sweden since the 1950´s). No new alarming safety findings regarding folic acid have been presented by the applicant. Folic acid is generally well tolerated with few adverse effects, even in long-term use. Listed adverse events relates mainly to allergic reactions and mild gastro-intestinal symptoms such as nausea, abdominal distension and flatulence. The acute toxicity is very low and normally no symptoms are expected in case of an overdose.

The benefit-risk balance is considered to be positive.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Folsyra Vitabalans, 1 mg & 5 mg
Tablet was positively finalised on 2019-01-24.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se