LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Folsyra EQL Pharma
folic acid hydrate

Asp no:2019-1082
Applicant: EQL Pharma AB

This module reflects the scientific discussion for the approval of Folsyra EQL Pharma. The procedure was finalised on 2020-10-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

EQL Pharma AB has applied for a marketing authorisation for Folsyra EQL Pharma,1 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).

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 Pharmacology

Folic acid participates in 1-carbon unit transfer reactions, forming substrates necessary in the synthesis of proteins, RNA and DNA and therefore, the physiological requirement of this nutrient is increased in periods of rapid growth and anabolic activity which occurs during adolescence, pregnancy and lactation.

III.2 Toxicology

Folic acid is a water soluble vitamin and excess amounts are secreted via urine. A risk for accumulation and toxicity is thus not likely given that Folic Acid supplementation will be used within the proposed indications.

III.3 Ecotoxicity/environmental risk assessment

Since the product is a natural occurring substance intended to substitute other products containing folic acid, an increased environmental exposure is not to be expected.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Oral folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Active and saturable, as well as passive and unsaturable mechanisms are involved in folate absorption. Bioavailability of food folate is around 50 %, i.e. half that of folic acid taken on an empty stomach, whereas the bioavailability of folic acid from fortified foods or from a supplement ingested with food is about 85 %.

Absorbed folate is transported to the liver, which contains about half the body pool of folate and retains 10 to 20% of absorbed folate due to the first-pass effect, while the rest is transported via the systemic circulation to body tissues. Some liver folate participates in enterohepatic circulation.

Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Unbound folates are subjected to catabolism.

No bioequivalence or relative bioavailability data was submitted for Folsyra EQL Pharma. For an application in accordance with Directive 2001/83/EC Article 10a, so called well- established use, the applicant has to justify that the clinical literature data referred to for efficacy and safety is relevant for the applied product i.e. that comparable exposure is achieved. This has not been addressed in any depths by the Applicant. Although folic acid is not classified as a BCS class 1 or 3 substance, it is acceptable that no data on relative bioavailability has been submitted for Folsyra EQL Pharma since the *in vitro* dissolution for Folsyra EQL Pharma was similar to another folic acid product on the market. Further, the absorption and elimination of folic acid in the body is controlled by different physiological processes, including folic acid homeostasis, and the plasma concentrations might not be directly related to its therapeutic effects. The therapeutic effect of folic acid is limited by the metabolic capacity of folic acid, which is expected to be saturated even with sub bioequivalent formulations.

The pharmacokinetic information provided by the Applicant was initially scarce and briefly discussed, further evidence has been provided during the procedure. The clinical overview has been updated and adequate references in support of the pharmacokinetic claims have been provided. Considering that folic acid is a well-known substance the provided data and proposed SmPC are considered acceptable.

Pharmacodynamics

Folic acid is vital for DNA synthesis as well as for various metabolic and nervous system biochemical processes through its activity as methyl donor in the form of a co-enzyme. Serine reacts with tetrahydrofolate, forming 5,10- methylenetetrahydrofolate, the folate derivative involved in DNA synthesis. A methyl group is donated to cobalamin (B12) by 5-methyltetrahydrofolate, forming methylcobalamin. With the help of the enzyme methionine synthase, methylcobalamin donates a methyl group to the amino acid metabolite homocysteine, converting it to the amino acid methionine. Methionine subsequently is converted to S-adenosylmethionine (SAMe), a methyl donor involved in numerous biochemical processes.

The pharmacodynamic particulars for folic acid are well known and adequately described in the dossier.

Clinical efficacy

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.
The bibliographic application is based on published literature, 38 articles from 1945 to 2019, including 14 review articles and one monograph. Most of the studies 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. Also the WEU criteria regarding the time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods are considered supported.

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). The WEU criteria regarding the time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods are considered supported. No new alarming safety findings regarding folic acid have been presented by the applicant.
It is agreed that folic acid is generally well tolerated.

IV.2 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 Folic acid EQL Pharma.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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 submitted Risk Management Plan, version 0.3 signed 19 August 2020 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Folvidon 1 mg. The user test of the Folvidon 1 mg leaflet was assessed and accepted in Dnr 5.4.4-2016-67916. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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. Also the WEU criteria regarding the time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods are considered supported.

The applicant has overall provided adequate information regarding the clinical safety of folic acid. 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.

The benefit-risk balance is considered 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

Folsyra EQL Pharma,1 mg, tablet was approved in the national procedure on 2020-10-12.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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