LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Folsyra Pilum
(folic acid)

Asp no: 2013-0667

This module reflects the scientific discussion for the approval of Folsyra Pilum. The procedure was finalised at 2014-10-03. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Pilum Pharma AB has applied for a marketing authorisation for Folsyra Pilum, 5 mg, tablet. The application is submitted in accordance with Directive 2001/83/EC Article 10a, so called well-established use (WEU) application. For a WEU application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use.

In a WEU application, results of pre-clinical and clinical trials are replaced by detailed references to published scientific literature.

The active substance is folic acid. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Folsyra Pilum is presented in the form of tablets containing 5 mg of folic acid. The excipients are lactose monohydrate, crospovidone, povidone, magnesium stearate, and microcrystalline cellulose. The tablets are packed in PVC/aluminium blister.

II.2 Drug Substance

Folic acid has a monograph in the Ph Eur.

Folic acid is a yellowish or orange, crystalline powder. It is practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions. The structure of folic acid has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Folsyra Pilum, 5 mg, tablet is formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin/has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

No new animal or in vitro studies have been performed with Folsyra Pilum. This is acceptable since the use of folic acid is well established in the clinic. Some deficiencies have been identified in the submitted non-clinical data but these are considered to be superseded by the long clinical experience with the use of folic acid. No further non-clinical data are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To describe the pharmacokinetics of folic acid the applicant has summarised bibliographic data in a clinical overview.
Orally administered folicic acid is rapidly absorbed from the gastrointestinal tract, mainly from the proximal portion of the small intestine and peak folate activity in blood occurs within 30–60 minutes.
Vitamin and mineral bioavailability is affected not only by product but also by host factors including homeostatic mechanisms that regulate absorption or excretion depending on the nutrient status of the patient. The size of the ingested load may affect bioavailability, and single high doses of folic acid exceed the metabolic capacity for reduction and methylation. Folic acid is largely reduced and methylated in the liver to N 5-methyltetrahydrofolic acid. Larger doses (>1 mg) of folic acid may escape metabolism by the liver and appear in the blood mainly as folic acid. Only a trace amount of the drug appears in urine. However, following administration of large doses, the renal tubular re-absorption maximum is exceeded, and excess folate is excreted unchanged in urine.
No bioequivalence or relative bioavailability data was submitted for Folsyra Pilum. For an application in accordance with Directive 2001/83/EC Article 10a, so called well- established use, the applicant has to motivate that the clinical data (efficacy and safety) referred to is relevant for the applied product i.e. that comparable exposure is achieved. However, it is acceptable that no data on relative bioavailability has been submitted for Folsyra Pilum since the *in vitro* dissolution for Folsyra Pilum was similar to another folic acid product on the market. 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.

IV.2 Pharmacodynamics

Folates play a key role in the synthesis of nucleic acids. Folate deficiency or disorder in the metabolism of folates causes the development of megaloblastic macrocytic anaemia, caused by the disorder of the normal cell proliferation of bone marrow. Folate deficiency affects all cell functions but it is most important that it reduces the ability of the organism to restore damaged tissues and enable the growth of new cells. Hematopoietic system is a tissue with the highest level of multiplication and restoration and thus it reacts first to the folate deficiency with anaemia.

IV.3 Clinical efficacy

To support the application for marketing authorisation, the applicant refers to a large number of publications where the efficacy and safety of folic acid have been studied. These bibliographic data include a number of double-blind, randomized and placebo-controlled clinical trials and also open label trials. Although the overview is comprehensive and includes recent data there was apparently no link between the literature data and the SmPC for the product under application and a number of issues was therefore raised in the first round. In response to this first list of questions the applicant revised the list of indications and provided rationales for their inclusions in the SmPC. With these justifications the new list of indications is found acceptable.

The doses proposed were justified based on formularies. This approach is acceptable.

IV.4 Clinical safety

Folic acid is historically well tolerated and adverse reactions are rare. Gastrointestinal disturbances and hypersensitivity reactions have been reported rarely. The safety profile of folic acid has been well established during decades of use worldwide having been used for several years. No new safety data has been reported or submitted with this application, but the Company has made a review of safety data from literature and from post marketing. This review appears to adequately cover known safety concerns. In response to the LoQ the applicant updated the SmPC section 4.8 to more adequately reflect the adverse reactions as discussed in literature.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 Swedish.

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.

The risk/benefit ratio is considered positive and Folsyra Pilum, 5 mg, tablet is recommended for approval.

VI. APPROVAL

Folsyra Pilum, 5 mg, tablet was approved in the national procedure on 2014-10-03.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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