LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bladex
(folic acid, anhydrous)

SE/H/2568/01-02DC

This module reflects the scientific discussion for the approval of Bladex. The procedure was finalised on 2025-04-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bladex, 1 mg, 5 mg, tablet.

The active substance is folic acid, anhydrous. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Bladex, 1 mg, 5 mg, tablet, is a Well-established use Art. 10a application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Norway as concerned member state (CMS).

For an application according to Article 10a, WEU, 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 recognised efficacy and an acceptable level of safety.

Potential similarity with orphan medicinal products
N/A

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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of folic acid is well known. As folic acid is a widely used, well-known active substance, no further studies are required, and Applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Bladex is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

Conclusions on studies:
The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, folic acid is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
Folate is a generic term used for a family of compounds which belong to the group of B-vitamins. Naturally occurring food folates are a mixture of reduced mono- and polyglutamates, and their chemical structure makes them unstable. In contrast, the synthetic folic acid is a fully oxidised monoglutamate and the most chemically stable form.

Bridging the proposed formulation to the provided literature data relies mainly on quality aspects and in vitro dissolution data (see quality section above). The extrapolation of literature data was further considered acceptable based on:
- The broad therapeutic index of folic acid
- The use of well-known excipients that are not expected to influence the bioavailability of folic acid
- The limitation of the therapeutic effect of folic acid by the metabolic capacity of folic acid, which is expected to be saturated even with sub bioequivalent formulations.

Although folic acid is not classified as a BCS class 1 or 3 substance, it is acceptable that no relative bioavailability study has been submitted since 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.

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. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. 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 the enterohepatic circulation and is secreted into bile. However, most biliary folate is reabsorbed, supposedly to moderate between-meal fluctuations in folate supply to cells.

The predominant form of folate in the circulation is 5-methyltetrahydrofolate monoglutamate. It is mainly bound to albumin, which is a low-affinity folate-binding protein (about 50% of all bound folate). However, in folate deficiency, a higher proportion of folate in plasma is bound to albumin.

Plasma also contains a soluble form of the folate receptor, which binds a small proportion of folate; however, in pregnancy, its concentration is increased. One-third of folate in plasma is in a free form. Folate is actively concentrated in the CSF and placental tissue, and is secreted into breast milk. 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 by oxidative cleavage at the C9–N10 bond, generating p-aminobenzoylglutamates, which in turn are acetylated in the liver before excretion.

The 677C variant-polymorphism of the gene encoding the 5-methyltetrahydrofolate reductase enzyme is relevant for the metabolism of folates, in particular the 677TT genotype who need to maintain serum folate levels above 15ng/mL in order to overcome the enzyme defect.

Low systemic folate can arise upon administration of antiepileptics, oral contraceptives, antituberculous drugs, alcohol, glucarpidase, sulfasalazine and folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim, and sulfonamides.
The serum antiepileptic levels may fall in case of coadministration with folates, leading to decreased seizure control in some patients. Toxicity of fluorouracil, fluorouracil prodrugs and capecitabine may be enhanced by coadministration with folic acid.
No solid evidence of interactions between folic acid and chloramphenicol, tetracyclines, biguanides and cholestyramine was found, therefore no such warnings are warranted.

The pharmacokinetic properties for folic acid are adequately described in the dossier.

Pharmacodynamics
Folic acid (folacin or pteroylglutamic acid (PteGlu)) is a water-soluble vitamin necessary for synthesis of DNA, RNA and protein, therefore, the physiological requirement of this nutrient is increased in periods of rapid growth and anabolic activity such as occurs during adolescence, pregnancy, and lactation. Folic acid consists of a pteridine ring, paraaminobenzoic acid and glutamic acid. Folic acid is clinically used to treat megaloblastic anaemia due to folate deficiency which can be caused by poor diet, malabsorption syndromes, and the use of some drugs (e.g. the folate antagonist, methotrexate, or antiepileptics). It can also be used prophylactically in individuals at hazard from developing folate deficiency (e.g. pregnant women, premature infants and patients with severe chronic haemolytic anaemia).

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.
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 proposed indications and posology are mainly supported by submitted documentation.
The indication “Treatment of folate deficiency states confirmed by blood test including B12 status (see section 4.4).” and the proposed posology for adults is considered acceptable. The indication and posology for folate deficient megaloblastic anemia for the pediatric population is supported by one reference, studying children with megaloblastic anaemia, where it states that when folate deficiency is

present, 1 mg of folate is given until dietary management is done. This is accepted as it also states in 4.2 that the dose should be determined individually, and dose adjustment may be needed, and treatment effect monitored.

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.

Risk Management Plan
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 Bladex.

Part II Safety specification

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

The proposed safety specification is accepted.

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.5 signed 17 Feb 2025 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 (PL) has been performed on the basis of a bridging report making reference to Folsyra Vitabalans 1 mg and 5 mg tablets (SE/H/1793/01-02/DC) for content and Dexamcol 1 mg/ml + 5 mg/ml eye drops, solution (DK/H/3155/001/DC) for layout.

The bridging was assessed and accepted at day 120.

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 and quantitative aspects of the use of the substance are considered supported.

The applicant has overall provided adequate information regarding the clinical safety of folic acid for adults and children. 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 ratio is considered positive and Bladex, 1 mg, 5 mg, tablet is recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Bladex, 1 mg, 5 mg, tablet was positively finalised on 2025-04-16.

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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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