LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Folsyra BBS
(folic acid)

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This module reflects the scientific discussion for the approval of Folsyra BBS. The procedure was finalised on 2017-08-03. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

BBS Consult ApS has applied for a marketing authorisation for Folsyra BBS, 1 mg and 5 mg, tablet. The active substance is folic acid, a water-soluble B complex vitamin, which is the synthetic form of folate and is converted to folate in the body after administration.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. 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 active substance is not considered a new active substance.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 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 is a B-complex vitamin with pleiotropic functions. Folic acid, after conversion to tetrahydrofolic acid (THF), is necessary for normal erythropoiesis, synthesis of purine and thymidylates, metabolism of amino acids such as glycine and methionine, and the metabolism of histidine. While the pharmacology of folic acid is considered well known, few studies have been presented by the Applicant. No safety pharmacology data has been presented. However, adverse cardiovascular, CNS or respiratory effects are not expected based on the clinical experience of the product.

III.2 Pharmacokinetics

Folic acid will be administered orally. The data provided by the Applicant is from a review paper and is focused on human pharmacokinetics. Folic acid lacks coenzyme activity and must be reduced to the metabolically active tetrahydrofolate form within the cell. L-5-methyl-tetrahydrofolate (L-5-methyl-THF) is the predominant form of dietary folate and the only species normally found in the circulation, and hence it is the folate that is normally transported into peripheral tissues to be used for cellular metabolism. L-5-methyl-THF is also the predominant active metabolite after intake of folic acid.

III.3 Toxicology

The toxicological information for Folsyra BBS submitted by the Applicant is very sparse. Folic acid has been in clinical use for many years and its clinical safety profile is well-known, although recent data have raised concerns about the safe use of folic acid above 400µg (NTP 2015). In accordance with the Guideline on the non-clinical documentation for mixed marketing authorization applications (CPMP/SWP/799/95), focus can be put on genotoxicity, reproductive toxicity and carcinogenicity.

Genotoxicity data is provided from the NTP homepage, where it is stated that an Ames test (Salmonella A32205) was negative. Thus it can be concluded that folic acid is not considered a genotoxicant.

No carcinogenicity studies have been submitted, but the Applicant adds that folic acid is not considered a carcinogen by IARC and that folate deficiency has been implicated in the development of cancer. The IARC statement is without reference why the validity of the statement is unclear. In addition, while folate deficiency has been implicated in the development of colon cancer, this is of no relevance for the carcinogenicity risk of high folate intake.
The safe use of high intakes (above 400ug/day) of folic acid has recently been questioned by the NTP, and the risk of cancer development has been one of the focus issues. Although inadequate dietary folic acid intake increases colon cancer risk in rodent model systems, there also is consistency in showing an acceleration of colon cancer development in the few studies that have tested the effects of folic acid intake above basal requirements for total folate in those systems. It can thus be concluded that there is a dual role of folate with regards to carcinogenicity risk, where both folate deficiency and excess intake may constitute an increased risk.

Two reproductive and developmental toxicity studies with Folsyra BBS of some relevance are referenced by the Applicant. In Wistar rats there were reductions ($P < 0.001$) in body weight

and vertex-coccyx length in foetuses from folate supplemented dams vs. control animals. However, the clinical relevance of these studies is unknown, and the benefit of supplemental folic acid for pregnant women to prevent neural tube defects in their children is well established.

In conclusion, while the non-clinical testing of folic acid is not up to the current standard, the well-established use of the product and the long clinical experience compensates for most of the non-clinical short-comings.

III.4 Ecotoxicity/environmental risk assessment

The Applicant has presented a justification for the absence of an environmental risk assessment of Folsyra BBS, which is considered acceptable. It can be concluded that the use of this product is not considered to increase the risk to the environment beyond that which may be caused by other folic acid products.

IV. CLINICAL ASPECTS

IV.1 Introduction

Folic acid has been used since 1947, and several medicinal products containing folic acid are already approved in Sweden. The main indications are prevention and treatment of folic acid deficiency and prevention of neural tube defects during foetal development.

IV.2 Pharmacokinetics

No bioequivalence or relative bioavailability data was submitted for Folsyra BBS. 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 BBS since the *in vitro* dissolution for Folsyra BBS was similar to another folic acid product on the market.

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

Folic acid is the precursor of tetrahydrofolic acid which is involved as a cofactor for 1-carbon transfer reactions in the biosynthesis of purines and thymidylates of nucleic acids. Impairment of thymidylate synthesis in patients with folic acid deficiency is thought to account for the defective DNA synthesis that leads to megaloblast formation and megaloblastic and macrocytic anaemias. Folate is involved in amino acid interconversions (e.g., catabolism of

histidine to glutamic acid, interconversion of serine and glycine, conversion of homocysteine to methionine), and generation of formate.
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.
No relevant information on pharmacodynamic interactions has been provided.

IV.4 Clinical efficacy

The Applicant's Clinical Overview was based entirely on published scientific literature. Primarily English language literature was selected initially on the basis of search results including abstracts, and subsequently on the basis of original publications acquired. Where necessary, reference lists of original publications were searched manually for complementary publications.
Scientific support has been provided that treatment with folic acid reversed folate-deficient megaloblastic anaemia in a small number of patients with hypothyroidism. Given the difficulty to find scientific proof of efficacy in such an old substance, this is considered sufficient support for the sought indications "Makrocytär, megaloblastisk anemi med folsyrabrist" and "Folatbrist".

The proposed posology is based on clinical praxis presented in clinical guidelines. This is considered adequate given that folic acid has been used for more than fifty years.

The Applicant has provided support for that patients with reduced intestinal uptake due to e.g. celiac disease and inflammatory bowel diseases may develop anaemia, and that folate deficiency may contribute to this. Anaemia in IBD is multifactorial, with iron deficiency being most prevalent. The prevalence of folate deficiency in Crohn's disease (CD) patients was reported as being 0% to 81%. In CD patients, folate deficiency seems to be more common than vitamin B_{12} deficiency. According to common recommendations, patients at risk for vitamin B12 or folic acid deficiency (e.g., small bowel disease or resection) need proper surveillance.
No dose recommendation for folic acid has been given.
Given the difficulty to find scientific proof of efficacy in such an old substance, this is considered sufficient support for the sought indication "Försämrat upptag av folat från tarmen vid malabsorption".

Methotrexate (MTX) is a folate antagonist that is being used frequently in the treatment of rheumatoid arthritis (RA), psoriasis, asthma, inflammatory bowel disease (IBS), and cancer. Many RA patients treated with MTX experience mucosal, gastrointestinal, hepatic or haematological side effects. A meta-analysis aimed to identify trials of supplementation with folic acid or folinic acid during MTX therapy for RA and to assess the benefits and harms of folic acid and folinic acid. The results support a positive effect on GI side effects, serum transaminase elevation and of supplementation with either folic or folinic acid for patients with rheumatoid arthritis during treatment with MTX. The proposed indication "Long term treatment with medicinal products inhibiting the uptake of folate or the metabolism of folate" is thus endorsed for Methotrexate. In the literature, mean folate absorption was measured in six patients with newly diagnosed ulcerative colitis. It was concluded that sulphasalazine impairs folate absorption but this only becomes significant if other reasons for folate deficiency are also present. There are no clinical data regarding folate supplementation for IBD patients while on sulfasalazine therapy, except during pregnancy.
Trimethoprim antagonize the actions of folate by inhibition of dihydrofolate reductase. This could diminish serum folate levels in humans and causes folate deficiency in some patients.

However, considering the short course of sulphonamide/trimethoprim combination therapy, folate supplementation is not recommended. In malaria, involving long-term treatment with antibiotics, the administration of folic acid to folate antagonist therapy is controversial. In a study on Zambian children with malaria anaemia treated with sulfadoxine/pyrimethamine, co-treatment with folic acid (1 mg/day) had a modest effect on hematological recovery and that it had some antagonistic effect on treatment efficacy of sulfadoxine/pyrimethamine.
Treatment with certain anticonvulsant drugs, such as phenytoin, carbamazepine produce folate deficiency in a high proportion of patients. A double-blind trial using folic acid 15 mg daily and identical placebo was carried out in 51 epileptic patients having a serum folate level below 3.6 ng/ml. Treatment was for a minimum of six months and in 41 patients more than one year. There were no significant changes in the frequency of seizures, behaviour, and personality, or in a number of cognitive functions. No data on the haematologic effects of folic acid supplementation were presented. The ILAE Treatment Guidelines do not recommend routine folic acid supplementation for epileptic patients in carbamazepine or similar antiepileptic drug (AED) therapy. There seems to be a dual interaction between folate and the AED phenytoin. Falling serum folate levels on long term administration of phenytoin were observed, but on the other hand, folic acid administered at pharmacological doses has been blamed for a decrease in the serum concentration of phenytoin.

The relative risks of cardiovascular defects and oral clefts in infants whose mothers were exposed to dihydrofolate reductase inhibitors during the second or third month after the last menstrual period, as compared with infants whose mothers had no such exposure. It was shown that folic acid antagonists, which include such common drugs as trimethoprim, triamterene, carbamazepine, phenytoin, phenobarbital, and primidone, may increase the risk not only of neural-tube defects, but also of cardiovascular defects, oral clefts, and urinary tract defects. Treatment with folic acid may reduce the risks of such defects.

Neural tube defects arise during the development of the brain and spinal cord. The aetiology of neural tube defects is thought to be multifactorial, but genetics plays a large role. The effects of increased consumption of folate or multivitamins on the prevalence of neural tube defects periconceptionally (before pregnancy and in the first two months of pregnancy) were investigated. In one article, the Cochrane Pregnancy and Childbirth Group trials register was searched for randomised and quasi-randomised trials comparing periconceptional supplementation by multivitamins with placebo, folate with placebo, or multivitamins with folate in different dosages of multivitamins or folate; pre-pregnancy dietary advice and counselling in primary care settings to increase the consumption of folate-rich foods, or folate-fortified foods, with standard care. Periconceptional folate supplementation reduced the incidence of neural tube defects but did not significantly increase miscarriage, ectopic pregnancy or stillbirth, although there was a possible increase in multiple gestations. In conclusion, periconceptional folate supplementation has a protective effect against neural tube defects.

Thus the indication “Prophylactic treatment before and during pregnancy” is endorsed.
The posology during pregnancy is considered supported. The Applicant has supplied a review, covering for example guidelines from American Congress of Obstetrics and Gynecology, Royal College of Obstetrics and Gynecologists and Society of Obstetricians and Gynecologists of Canada. The recommendations from these guidelines are reflected in the proposed posology.

The Applicant has provided support for that folate deficiency is common in chronic alcoholic patients. In addition to low dietary intake in such individuals, studies have shown that folate deconjugation and absorption are impaired by chronic alcohol use. Alcohol ingestion also

appears to block the secretion of folate into the bile, interfering with enterohepatic recirculation and re-absorption. However, no evidence has been presented that subjects, with chronic alcohol consumption and folate deficiency have a beneficial effect (e.g. reversal of macrocytosis, improvement of anaemia etc) of folate supplementation, not only during pregnancy. The Applicant therefore proposes to delete alcoholism from the indication. This is considered adequate.
Using homocysteine as a functional marker, etermined optimal folic acid, vitamin B12, and vitamin B6 dosages in 21 paediatric sickle cell disease (SCD) patients, a disorder characterized by haemolytic anaemia. Given the difficulties in finding scientific support for the sought indication and posology in the published literature, this is accepted, since it is in line with clinical praxis.
The Applicant has provided data from the three studies on treatment with folic acid in subjects (Mexican women, Mexican American men and Chinese women, respectively, in the three articles) with different MTHFR genotypes. No measurements of haemoglobin or haematocrit were performed in any of the studies, only folate and homocysteine. A beneficial role for folic acid in this condition cannot be established. However, there seem to be a clinical praxis for folic acid treatment in subjects with MTHFR gene polymorphism with folate deficiency. The wording is accepted.

There are several examples where folic acid has been safely administered to a paediatric population in the literature referred to in the Applicant's clinical overview. For the paediatric population, support from a database has been provided for the sought posology 1 mg/day in children 10-18 years. This is accepted in this context, given the difficulty in finding scientific support for the posology.

IV.5 Clinical safety

Folic acid is used since 1947. It is usually well tolerated and adverse reactions are rare.
There is concern that folic acid may obscure the diagnosis of pernicious anaemia by alleviating hematologic manifestations of the disease while allowing neurologic complications due to deficiency of vitamin B12 to progress. This may result in severe nervous system damage before the correct diagnosis is made. Decreased serum vitamin B12 concentrations may occur in patients receiving prolonged folic acid therapy. This is covered by a proposed warning in section 4.4, which is considered adequate.

Folic acid plays a role in the synthesis of nucleic acid, thus providing a putative role for folic acid in carcinogenesis.
Based on animal experiments, a 'dual-modulator' role for folate in colorectal carcinogenesis has been proposed in which moderate dietary increases initiated before the establishment of neoplastic foci have a protective influence, whereas excessive intake or increased intake once early lesions are established may increase tumorigenesis. Folate deficiency has been implicated in the development of cancer, especially colorectal cancer. In humans, the 'dual modulator' role of folic acid is less established. An analysis of 6837 patients - from WENBIT and NORVIT studies - suggested a higher cancer incidence and mortality after treatment with folic acid and vitamin B12, prompting alerts.

In a meta-analysis, it was explored if there is an increased cancer risk associated with folic acid supplements given orally. From 4104 potential references, 19 studies contributed data to the meta-analyses, including 12 randomised controlled trials (RCTs). Meta-analysis of the 10 RCTs reporting overall cancer incidence (N=38,233) gave an RR of developing cancer in patients randomised to folic acid supplements of 1.07 (95% CI 1.00 to 1.14) compared to controls. Overall cancer incidence was not reported in the seven observational studies. Meta-

analyses of six RCTs reporting prostate cancer incidence showed an RR of prostate cancer of 1.24 (95% CI 1.03 to 1.49) for the men receiving folic acid compared to controls. No significant difference in cancer incidence was shown between groups receiving folic acid and placebo/control group, for any other cancer type. Total cancer mortality was reported in six RCTs, and a meta-analysis of these did not show any significant difference in cancer mortality in folic acid supplemented groups compared to controls (RR 1.09, 95% CI 0.90 to 1.30). None of the observational studies addressed mortality. This meta-analysis of 10 RCTs showed a borderline significant increase in frequency of overall cancer in the folic acid group compared to controls. Overall cancer incidence was not reported in the seven observational studies. Prostate cancer was the only cancer type found to be increased after folic acid supplementation (meta-analyses of six RCTs). Prospective studies of cancer development in populations where food is fortified with folic acid could indicate whether fortification similar to supplementation moderately increases prostate cancer risk. This meta-analysis fails to give an answer on the dilemma on the cancer risk in patients with high folate intake and/or levels.

A subsequent meta-analysis included 10 prospective studies reporting data on 202,517 individuals. High dietary folate intake had little or no effect on prostate cancer risk (risk ratio [RR] = 1.02; 95% CI = 0.95-1.09; P = 0.598). The dose-response meta-analysis suggested that a 100 μg per day increase in dietary folate intake has no significant effect on the risk of prostate cancer (RR = 1.01; 95% CI = 0.99-1.02; P = 0.433). However, high serum folate levels were associated with an increased risk of prostate cancer (RR = 1.21; 95% CI = 1.05-1.39; P = 0.008). The dose-response meta-analysis indicated that a 5 nmol/L increment of serum folate levels was also associated with an increased risk of prostate cancer (RR = 1.04; 95% CI = 1.00-1.07; P = 0.042). In conclusion, increased serum folate levels have potentially harmful effects on the risk of prostate cancer.

Another meta-analysis demonstrated that folic acid supplementation had no effect on colorectal cancer risk. However, this finding must be validated by further large studies.
A most recent dose-response meta-analysis indicated that a 100 μg/day increment in dietary folate intake reduced the estimate risk of oesophageal cancer by 12%. These findings suggest that dietary and serum folate exert a protective effect against oesophageal carcinogenesis.

In the National Toxicology Program (NTP) and the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) (NTP, 2015) convened an expert panel to identify research needs related to high intakes of folic acid. In conclusion, the Cancer Subpanel states that:

- Although inadequate dietary folate intake increases colorectal cancer risk in humans, there is no benefit for cancer reduction from supplements among people whose baseline folate status is adequate.
- There is a consistent enough suggestion in human studies of an adverse effect on cancer growth from supplemental folic acid to justify further research.

The role of folate in the development of malignancy is thus inconsistent. The Applicant suggests a text stating that folate treatment can enhance progression of pre-existing malignancies should be included in section 4.4, which is endorsed. Even though there are indications that folic acid in some situations can act as a protector against tumorigenesis, there are also data indicating an increased risk for tumour development with folic acid treatment. This is also supported by animal studies. For the time being, this issue is not further reflected in the SmPC or RMP.
Even though a beneficial role for folic acid in preventing neural tube defects has been shown, there are also data suggesting that there might be an increased risk of multiple gestation and/or an increased risk for early pregnancy loss. The balance between homocysteine and folate is vital for normal pregnancy. Hyperhomocysteinaemia has been reported to be an independent

risk factor for many pregnancy-related disorders such as neural tube defects, placental abruption or infarction, preeclampsia and unexplained recurrent miscarriage. In general, usual folic acid supplementation can be a protective factor.

A cohort study investigated the association between periconceptional vitamin intake and foetal death. Multivitamin use was associated with a modest increased risk of early foetal death. For late foetal death, regular supplement use after conception may decrease risk, but numbers were small. However, further studies on preconceptional multivitamin use are needed to guide public health recommendations.

A population-based cohort study assessed the association between multiple births and use of vitamin supplements. In the study, 1496 multiple births occurred, representing 0.62% of the women. The rate of multiple births in women who did and did not take folic acid before or during early pregnancy was 0·59% and 0·65%, respectively (rate ratio 0·91; 95% CI 0·82–1·00). Their findings suggest that consumption of folic acid supplements during pregnancy is not associated with an increased occurrence of multiple births.
In another study, the association between folic acid supplementation and twinning in an extended Swedish material was explored. The effect of a number of possible confounders was particularly analysed. This study found an increase in twinning rate after folic acid supplementation in a Western population. The odds ratio (OR) for dizygotic twinning after folic acid supplementation was then 1.71 (95%CI=1.21–2.42) and for the years 2000–2001 2.09 (95%CI=1.39–3.12). Thus, the results in this area are still conflicting. It is not considered necessary to include this issue as a safety concern at this time point.

In section 4.8 of the SmPC, pruritus, erythema and urticaria are proposed as adverse events. The frequency cannot be determined from published clinical data, thus the frequency for pruritus, erythema and urticaria is labelled as not known. The Applicant also provides a reference to a case report regarding an anaphylactic reaction with the use of folic acid containing products. The Applicant suggests including anaphylactic reactions in section 4.8 of the SmPC, which is endorsed.

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 BBS.

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity • Vitamin B12 deficiency • Use in patients with malignant disease
Important potential risks	None
Missing information	None

The summary of safety concerns is endorsed.

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 Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypersensitivity	Proposed text in SmPC (and reflected in the PIL): **4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. **4.8 Undesirable effects** Not known - Anaphylactic reaction	None
Vitamin B12 deficiency	Proposed text in SmPC (and reflected in the PIL): **4.4 Special warnings and precautions for use** Folic acid treatment can mask a concurrent vitamin B12 deficiency, or the development of such, at risk of serious neurological damage. This can be detected by analysis of methylmalonic acid in plasma.	None
Use in patients with malignant disease	Proposed text in SmPC (and reflected in the PIL): **4.4 Special warnings and precautions for use** Since folate may stimulate cell partition, caution should be shown when treating patients with folate dependant tumour disease. Folic acid supplements may increase growth of already existing malignity.	None

The Summary of Safety Concerns and Planned Risk Minimisation Activities is endorsed.

Summary of the RMP
No additional risk minimisation measures or pharmacovigilance activities are suggested, which is endorsed.

The MAH has satisfactory responded to the questions raised and updated the RMP accordingly.
The submitted Risk Management Plan is considered acceptable.

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 Folsyra Pilum, in the national procedure 5.4.1-2013-61047. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Folic acid has been used for many years and several medicinal products containing folic acid are already approved in Sweden. The Applicant is now applying according to Directive 2001/83/ EC art 10a for approval of Folsyra BBS 1 mg and 5 mg. The claimed indication and posology are largely similar to the approved folic acid containing products in Sweden.
As a stand-alone application according article 10a all claimed indications should be supported by adequate bibliographic data. It is acknowledged that it is difficult to retrieve scientific proof of efficacy in such an old substance and in some cases referral to clinical praxis in a reliable clinical guideline is considered sufficient support for an indication. The Applicant has provided acceptable support for indications and posology provided in the SmPC.

From a safety perspective, folic acid has been used for a very long time and is in principle considered as a safe treatment. Known and potential safety issues are reflected in the SmPC. However, there are some conflicting results regarding the putative role of folic acid in oncogenesis and in the development of multiple births. The Applicant has discussed both topics with support from the published literature, but the results are conflicting in both areas. As folic acid has been widely used for a long time, it is not deemed necessary with any further actions.

The benefit/risk ratio for Folsyra BBS 1 mg and 5 mg is positive. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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 BBS, 1 mg and 5 mg, tablet was approved in the national procedure on 2017-08-03.

LÄKEMEDELSVERKET
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)

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