LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bevitrio
(cyanocobalamin, folic acid hydrate, pyridoxine hydrochloride)

SE/H/2159/01/DC

This module reflects the scientific discussion for the approval of Bevitrio. The procedure was finalised on 2023-08-23. 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

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bevitrio, 0,5 mg/0,8 mg/3,0 mg, Tablet.

The active substances are cyanocobalamin, folic acid hydrate and pyridoxine hydrochloride. 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 Bevitrio, 0,5 mg/0,8 mg/3,0 mg, tablet, is an application submitted according to Article 10a of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and NO, DK, FI as concerned member states (CMS).

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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
Folic acid is involved in making red blood cells, as well as in the synthesis and repair of DNA and RNA; vitamin B6 is involved in amino acid metabolism, glucose metabolism, one carbon metabolism, fatty acids metabolism, haemoglobin synthesis; Vitamin B12 is involved in nucleic acid metabolism, DNA synthesis, haematopoiesis, myelin synthesis, maintenance of myelin sheets, synthesis of epithelial tissue, synthesis of neurotransmitters, fatty acid metabolism, carbohydrate metabolism.

No secondary pharmacology studies were identified for folic acid. A few publications that the Applicant considers shed light on secondary pharmacological aspects on vitamin B6 and B12 have been submitted but do not add any value to previous knowledge.

No safety pharmacology studies were presented by the applicant.

All these vitamins have been characterised decades ago. Today their pharmacology is part of standard pharmacology knowledge as acknowledged by official bodies and experts in recommendations, reviews, and textbooks. The Applicant has provided publications primarily on primary pharmacology of both folic acid, vitamin B6 and vitamin B12; in general, the existing knowledge suffices and is adequate for the requirements of the marketing application rooted from the Article 10a of Directive 2001/83/EC.

Pharmacokinetics
Folic acid is absorbed within the proximal region of the small intestine by active, carrier-dependent mechanisms, and by passive diffusion; in the rat, it is readily absorbed. The liver contains about one-half of total body folate stores but are distributed into all body tissues, and also into milk and cerebrospinal fluid. Folic acid is largely reduced and methylated in the liver to N-5-methyltetrahydrofolic acid, which is the main transport form of folate in the body. Larger doses of folic acid may escape metabolism by the liver and appear in the blood mainly as folic acid. Folate is excreted in the urine, either as the metabolically active form or as breakdown products, and in the faeces.

The absorption of vitamin B6 mostly takes place in the upper (proximal) jejunum and is stored mainly in the liver with lesser amounts in muscle and brain. In the liver, pyridoxine is phosphorylated to pyridoxine phosphate and transaminated to pyridoxal and pyridoxamine. About 70% of pyridoxalis excreted in the urine as the inactive metabolite 4-pyridoxic acid.

Vitamin B12 binds to the protein in the foods we eat. In the stomach, hydrochloric acid and enzymes unbind vitamin B12 into its free form. From there, vitamin B12 combines with a protein called intrinsic factor so that it can be absorbed further down in the small intestine. The vitamin binds to specific transcobalamins plasma proteins and is stored in the liver. With continued intake of the vitamin, animals show tissue storage of cobalamins principally in the liver (30 to 60% of the total body load) but also at lower levels in the kidney, heart, spleen, and brain. Vitamin B12 diffuses across the placenta and appears in milk.

The Applicant has provided publications on the pharmacokinetics of both folic acid, vitamin B6 and vitamin B12; the existing knowledge suffices and is adequate for the requirements of the marketing application rooted from the Article 10a of Directive 2001/83/EC.

Toxicology

- **General toxicity**

Folic acid
The oral LD50 for folic acid was reported to be very high (10000 mg/kg). LD50 values have low relevance.

Repeat dose toxicity studies with folic acid have been conducted in mouse, rat, and monkey. In mice, repeated administration of folic acid (75 mg/kg/day s.c.) for 3 weeks an immediate weight loss accompanied by severe renal tubular damage. In rats, 250 mg/kg i.v. dose of folic acid caused oliguria followed by polyuria. Microscopy showed distended proximal and distal tubules in the cortex. A study reported that folic acid 25.6 mg/kg/day given to 3 male monkeys for 99 days, did not show any toxic effect. Thus, data indicate low toxicological potential at therapeutic doses.

Vitamin B6
The acute toxicity of vitamin B6 is 5500 mg/kg (oral) and 545 mg/kg (i.v.) in the mouse and 4000-6000 mg/kg (oral) and 675 mg/kg (i.v.) in the rat. In repeat dose studies, symptoms of neuropathy have occurred at variable time intervals in different species following doses of pyridoxine ranging from 50 to 7000 mg/kg b.w./day. Thus, data indicate very low toxicity vitamin B6 at therapeutic doses.

Vitamin B12
Doses of 1.5 to 3.0 mg/kg bw by i.p. and s.c. administration was found to be acutely toxic in mice (CNS effects; convulsions, cardiac and respiratory failure and ultimately death). However, much higher doses (≥5 g/kg b.w.) cyanocobalamin appeared to be tolerated by mice following oral administration. The Council for Responsible Nutrition in the USA concludes that vitamin B12 has no observable adverse effects at any level of oral intake, even when consumed parenterally at 1 mg twice weekly for up to 3 years or i.v. 1 mg per day for 1 year. Thus, at therapeutic doses, the toxicity of vitamin B12 is low.

- **Genotoxicity/carcinogenicity**

Folic acid
Two references are provided indicating low risk of genotoxic potential of folic acid.

Folate deficiency is associated with the development of colorectal carcinogenesis in rodent models. Folate-deficient diet was also associated with the development if macroscopic colorectal tumours. Furthermore, dietary folate supplementation up to 4 times (8 mg of folic acid/kg diet) the basal dietary requirement (BDR) (2 mg of folic acid/kg diet) was further shown to retard the progression from microscopic colorectal neoplastic foci to macroscopic tumours in a dose-dependent manner. However, a trend toward increased colorectal tumorigenesis in rats fed a supraphysiological dose of folate (20 × BDR; 40 mg of folic acid/kg diet) was noted. In support of this latter finding, dietary folate supplementation exceeding 1000 times × BDR (2.0-5.0 g of folic acid/kg diet) increased the development of aberrant crypt foci in other rat models, the probable earliest precursor of colorectal cancer.

In yet another rat model, folic acid supplementation was shown to promote the progression of established mammary tumours. Thus, there is a preclinical indication of a potential tumour-promoting effect of folic acid supplementation in breast cancer patients and survivors. In this study, folic acid supplementation between 2.5x and 5x the basal dietary requirement significantly promotes the progression of established mammary tumours.

It is concluded that these are academic studies and that the observations available do not indicate any risks at therapeutic levels. Folic acid has been used for decades and the existing knowledge suffices and is adequate for the requirements of the marketing application rooted from the Article 10a of Directive 2001/83/EC.

Vitamin B6
Two academic references are provided, with unclear value to the overall assessment on the genotoxic potential. In one of these, in lymphocyte cultures, after adding 4 drops of blood from normal subjects, a dose dependent increase in sister chromatid exchange (SCE) was noted, which is an indication of mutagenic potential. This increase was noted already following 2 ug/ml. Furthermore, it was also

shown that pyridoxine concentrations above 60 µg/ml delay proliferation. The relevancy of these findings is however unclear. Overall, data indicate low risk of genotoxic potential of vitamin B6.

Data presented show that high levels of vitamin B6 can retard the growth of rat hepatoma cells and inhibit growth of a human malignant melanoma cell line. Furthermore, vitamin B6 supplemented diets suppress azoxymethane-induced colon tumorigenesis in mice compared with a low vitamin B6 diet by reducing cell proliferation. Another study showed a delayed growth of H238 cell -induced tumours was shown following high intake of vitamin B6. This was shown in mice, and the seemed to have this suppressive effect on tumour growth through enhancement of immune status.

Vitamin B12
Three references are provided indicating low risk of genotoxic potential of vitamin B12; rather, data indicate a protective effect.

The scientific evidence mainly speaks against that B12 could be carcinogenic / genotoxic. The applicant reports a few findings; however, these findings not been verified and are considered to have low relevance for intended use.

- **Reproductive and developmental toxicity**

Folic acid
A lower than recommended dose of folic acid (14.3% of RDI) affected sperm quality in mice through altered methylation of histone H3 and DNA. In rats, foetal growth, together with maternal liver and placentas, were increased with maternal folic acid supplementation before/during conception. In another study, pregnant female rats were supplemented with folic acid, from days 7 – 17 of gestation, by gavage. Folic acid treatment (50 mg/kg bw/day) showed no significant maternal or embryotoxicity, as compared with vehicle-only treatment. Altogether, the impact of supplementary folic acid intake on fertility and early embryonic development seems low.

It is concluded that oral folic acid supplementation alone has generally not shown reproductive or embryotoxic effects in animal models. However, high folate intake during 6 weeks in mice (40 mg/kg folic acid; 20-fold higher than the RDA) seem to affect foetal development manifested as embryonic delay, growth retardation and thinner ventricular wall thickness. Although authors state that the high folate diet was 20 times the RDA, plasma measurements indicated a 10-fold increase of folate compared to mice on a control diet. In a similar study in mice, the authors used half of the previously stated dose, i.e., 20 mg/kg folic acid. Therein, high folate intake was associated with embryonic loss and growth retardation, together with thinner ventricular wall thickness of the embryonic hearts. In this study, plasma levels are not presented. The relevance from these academic studies is however unclear.

In line with the fact that folic acid plays an important role during pregnancy by preventing folic acid deficiency-related neural tube defects, a study showed in mice that supplementation with high-dose folic acid during pregnancy protects against LPS-induced neural tube defects through its anti-inflammatory and anti-oxidative effects. However, the relevance to therapeutic doses are unclear.

In another study, rats were fed with either folic acid supplemented diet, 40 mg/kg, or control diet, 2 mg folic acid/kg, for 3 wk. Even though gestational development (number of live foetuses) was adequate in both diet groups regardless of folate supplementation body weight and vertex-coccyx length in foetuses from supplemented dams were less than in foetuses of control dams.

Based on another study, it is concluded that a dose of 50 mg/kg/d in rat dams does not have any adverse effects on embryonic development. Keeping in mind when comparing this study with the others presented earlier is that this dosing takes place only between days 7-17 and not several weeks in advance, as was done in the other studies. Therefore, it will be difficult to know exactly what this study provides from a safety point of view.

It is concluded that some findings come from academic studies and that the observations available do not indicate any risks at therapeutic levels. Folic acid has been used for decades and the existing knowledge suffices and is adequate for the requirements of the marketing application rooted from the Article 10a of Directive 2001/83/EC. The information provided is thus considered sufficient.

Vitamin B6
No effects on foetal development have been observed in animal studies. Doses of 250 and 500 mg/kg bw/day vitamin B6 i.p. produced histological changes in the testes of rats and doses of 50 mg/kg/day administered i.p. to female rats prevented prolactin release. It should be noted that high doses of vitamin B6 during early chicken embryogenesis produces teratogenic effect, manifested as large fibre sensory neuropathy; however, it is agreed that the relevancy of these high doses for mammals are highly uncertain.

No effects of pyridoxine on foetal development have been observed in animal studies.

No PPND or juvenile studies have been presented.

Vitamin B12
In a quite recent review the overall conclusion highlights the positive effects of vitamin B12 on semen quality: first, by increasing sperm count, and by enhancing sperm motility and reducing sperm DNA damage. The authors of this review state that there are “a few in vivo system studies that have indicated some adverse effects”. However, these “negative effects” seem to be defined as absence of positive effect. Thus, there is no evidence relating vitamin B12 to teratogenicity or adverse effects on fertility.

Overall, EFD-studies indicate that high vitamin B12 supplementation increases birth weights.
There is no evidence relating to vitamin B12 and adverse effects on postnatal development.

No juvenile animal toxicity study was identified in public domain.

- **Overall conclusion on toxicology**

In conclusion, folic acid, vitamin B6 and B12 have been used for decades and the existing knowledge on toxicology suffices and is adequate for the requirements of the marketing application rooted from the Article 10a of Directive 2001/83/EC.

The information provided is thus considered sufficient.

Environmental Risk Assessment (ERA)
Vitamins are natural components of foods in which they are usually present in varying amounts. For the most part since they are essential compounds that cannot be synthesised by humans, vitamins must be obtained through the diet. All three vitamins in this application can be found in vide range of foods:

- Pyridoxine hydrochloride (B6) is found in a wide variety of foods. The richest sources of vitamin B6 include fish, beef liver and other organ meats, potatoes and other starchy vegetables, and fruit (other than citrus).

- Folic acid (B9) can be found in many food sources such as dark green leafy vegetables (turnip greens, spinach, romaine lettuce, asparagus, brussels sprouts, broccoli), beans, peanuts, sunflower seeds, fresh fruits, fruit juices, whole grains, liver, seafood and eggs.

- Cyanocobalamin (B12) is found only in animal products. Good sources include meat, liver, kidney, poultry, fish, eggs, and dairy products. From the list above it is evident that both folic acid, pyridoxine hydrochloride and cyanocobalamin are commonly present in the environment.

Based on the common presence of vitamin B in the environment, the test product is unlikely to alter the concentration or distribution of the substance in the environment. Additionally, they are essential vitamins and hence unlikely to result in a significant risk to the environment. Consequently, it can be assumed that the medicinal product Folic acid 0.8mg, Cyanocobalamin 0.5mg, Pyridoxine hydrochloride 3.0mg Tablets is unlikely to represent a risk to the environment following its prescribed usage in patients and no further PBT or risk assessment is required, the presented ERA is sufficient, and no further data are necessary.

The justification for not submitting ERA studies is acceptable.

IV. CLINICAL ASPECTS

Pharmacokinetics
The Applicant has discussed the bridging of their product to the formulations used in literature to support efficacy and safety. The Vitamins (Pyridoxin hydrochloride (B6), folic acid (B9) and cyanocobalamin (B12)) included in this formulation are intended as adjuvants to dietary sources, with the aim to increase the body deposit of these substances on a long-term basis. A potential minor difference in in vivo release properties from different dosage forms would not be expected to lead to a different therapeutic profile. Moreover, as the absorption and elimination of the active substances in the body are controlled by a number of physiological processes and factors, the true absorption of these partly endogenous substances may be difficult to determine in a bioavailability study. Further, at least for folic acid and vitamin B12, the plasma concentrations might not be directly related to its therapeutic effects. The absence of a BE-study is acceptable. The properties and composition of the formulation with further aspects of the bridging is discussed in the quality AR.

Generally, the basic ADME-properties of the active substances have been adequately described. The Applicant has discussed an issue of finding adequate references (as defined in the Notice to Applicants), many reviews have been included in this application not with all cited references provided. Still, it is considered that the discussion in the clinical overview benefits from including information based on reviews and e.g., publications from EFSA. Few pharmacokinetic claims are made in the SmPC, and it is considered that these are sufficiently supported.

Pharmacodynamics
Folic Acid:
Folic acid is a water-soluble B vitamin that is naturally present in some foods, added to others, and available as a dietary supplement. Folic acid functions as a coenzyme or co-substrate in single carbon transfers in the synthesis of nucleic acids (DNA and RNA) and metabolism of amino acids. One of the most important folate-dependent reactions is the conversion of Hcy (Homocysteine), an amino acid in the blood, to methionine in the synthesis of S-adenosyl-methionine, an important methyl donor.

Vitamin B12:
Vitamin B12 is a water-soluble vitamin that is naturally present in some foods, added to others, and available as a dietary supplement and a prescription medication. Vitamin B12 functions as a co-factor for methionine synthase, which catalyses the conversion of Hcy to methionine. Methionine is required for the formation of S-adenosylmethionine, a universal methyl donor for almost 100 different substrates, including DNA, RNA, hormones, proteins, and lipids.

Vitamin B6:
Vitamin B6 is also a water-soluble vitamin that is naturally present in many foods, added to others, and available as a dietary supplement. Vitamin B6 in its coenzyme form performs a wide variety of functions in the body and is very versatile, with involvement in more than 100 enzyme reactions, mostly concerned with protein metabolism. Vitamin B6 plays a role in maintaining normal levels of Hcy and in cognitive development through the biosynthesis of neurotransmitters. Vitamin B6 is involved in gluconeogenesis and glycogenolysis, immune function (for example, it promotes

lymphocyte and IL-2 production), and Hb formation.

Clinical efficacy
This bibliographic application submitted according to Article 10a of Directive 2001/83/EC, Well-established use, for the combination of folic acid, vitamin B6 and vitamin B12 and the applied for indication is: prevention of symptomatic vitamin B_6, vitamin B_{12} and folic acid deficiency due to insufficient food intake or malabsorption, primarily in the elderly.

The submitted Clinical Overview is based on an updated literature search, as expected for a WEU application. The active ingredients of the medicinal product, i.e. vitamin B6, vitamin B12 and folic acid, are generally well established for medicinal use and are acknowledged as being both efficient and possessing an acceptable level of safety, and comprehensive information exists on their biochemistry, pharmacology and clinical use. Overall, the submitted literature is considered to support the WEU-criteria regarding the degree of scientific interest in the use of the substances, 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. A variety of comparable products containing vitamin B12, folic acid and/or vitamin B6 are marketed in numerous countries both in and outside Europe for many decades. It is acknowledged that folic acid, vitamin B6 and vitamin B12 is a well-established therapy since more than 10 years. It is thus acceptable to regard this as well-established use according to Art. 10a.

Prevention of malnutrition, which is common in the older age group, is a challenge for the health care system. Many studies have found a direct relation between the degree of malnutrition and increased length of stay, treatment costs, return to usual life, and readmission to hospital rates. Ageing is frequently associated with decreases in taste acuity and smell, deteriorating dental health, and decreases in physical activity, which may all affect nutrient intake. Also, absorption of B-vitamins might be decreased in elderly due to decreased active intestinal transport, an increased propensity for atrophic gastritis and intake of multiple drugs. Thus, treatment in the elderly to prevent deficiencies of the three included B-vitamins is deemed adequately supported by data and endorsed.

Dietary reference values from the EU shows that the risk of intoxication is considered low for the proposed strength of the fixed dose combination of folic acid, vitamin B12 and vitamin B6 in the applied for tablet. The posology is reasonable in relation to EFSA recommendations, and it is concurred that the elderly may need supplements of these three vitamins.

Clinical safety
The Applicant has provided acceptable information regarding the clinical safety of folic acid, vitamin B12 and B6. Several studies in humans have been performed with folic acid, vitamin B12 and B6 combinations. Overall, no AEs were reported that were considered related to oral B vitamins in these studies. Therefore, the fixed combination of folic acid, vitamin B12 and B6 is considered well-tolerated. Taking into account the current state of knowledge from published literature, there are no specific safety concerns for the fixed dose combination of folic acid, vitamin B12 and vitamin B6 going beyond those identified for each single ingredient, all three vitamins are generally considered non-toxic when given as a food supplement. The safety of the product containing folic acid, vitamin B12 and vitamin B6 is expected to be similar to individual constituents.

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 Bevitrio.

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 1.0 signed 2022-03-24 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 Bexon (DE/H/5008/001/DC) concerning content and Prednisolon Alternova 2,5 mg; 5 mg; 10 mg tablet (Dnr: 2121:2012/37638) for layout.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of Bevitrio is found adequate. There are no objections to approval of Bevitrio from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application submitted according to Article 10a of Directive 2001/83/EC is therefore 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 Bevitrio, 0,5 mg/0,8 mg/3,0 mg, tablet was positively finalised on 2023-08-23.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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)

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