SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bevitrio 0.5 mg/0.8 mg/3 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 0.5 mg cyanocobalamin (vitamin B_{12}), 0.8 mg folic acid and 3 mg pyridoxine hydrochloride (vitamin B_6).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Red/yellow, mottled with small red spots, round and biconvex tablet. Diameter 10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of symptomatic vitamin B_6, vitamin B_{12} and folic acid deficiency due to insufficient food intake or malabsorption, primarily in the elderly.

4.2 Posology and method of administration

Posology
1 tablet daily with water.

Method of administration
For oral use.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

[Invented name] is not intended for the treatment of symptomatic deficiencies of the vitamins included. Especially, it should be noted that the effective treatment of manifest megaloblastic anaemia and pernicious anaemia may need parenteral administration of vitamin B_{12} at the start of therapy.
[Invented name] should not be used in patients who have been subject to major resection of the small intestine.

[Invented name] is not intended for secondary prevention of NTD (neural tube defects), which requires a higher intake of folic acid.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Folic acid

Antiepileptics
Most antiepileptic drugs can cause a decrease in the plasma concentration of folic acid by inhibition of folic acid absorption and/or metabolism.
Folic acid may increase the metabolism of some antiepileptics, such as phenobarbital and phenytoin.

Antibiotics
Some antibiotics can interfere with microbiological tests, which can lead to falsely low results of folic acid concentrationå measurement in serum and erythrocytes.

Folic acid antagonists
Folic acid antagonists such as methotrexate, pyrimethamine, trimethoprim, sulfonamides and sulfasalazine can inhibit the conversion of folic acid to tetrahydrofolic acid and thus increase the risk of folic acid deficiency.

Pyridoxine
Levodopa
Pyridoxine has been shown to decrease the effects of levodopa. However, this effect is not seen when levodopa is prescribed in combination with carbidopa, which prevents the interaction from occurring. In the rare instance that patients are taking levodopa in absence of carbidopa, physicians should advise their patients to avoid any products containing pyridoxine.

Cyanocobalamin
The absorption of vitamin B_{12} from the gastrointestinal tract can be reduced by aminoglycosides, aminosalicylic acid, antiepileptics, biguanides (metformin), chloramphenicol, cholestyramine, potassium salts and gastric acid inhibiting substances (for example omeprazole and cimetidine). The clinical relevance of several of these interactions is probably small.

4.6 Fertility, pregnancy and lactation

No known risks.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The undesirable effects are presented according to system organ class and frequency.

Skin and subcutaneous tissue disorders Not known (cannot be estimated from the available data)	Acne like reactions, allergic reactions (urticaria, pruritus, erythema)
Immune system disorders Not known (cannot be estimated from the available data)	Anaphylactic reaction

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Folic acid has low toxicity. No symptoms are to be expected even after high doses.

At chronic high dose treatment with *pyridoxine*, some individuals have developed peripheral neuropathies. The dose level of vitamin B_6 in [invented name] constitute no risk of overdose.

Cyanocobalamin has low toxicity. No symptoms are to be expected even after high doses.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin B-complex, plain, ATC code: A11EA.

The amounts of folic acid, vitamin B_6 and vitamin B_{12} in [invented name] have been chosen to provide protection against symptomatic deficiencies especially in elderly people who frequently have malabsorption of folic acid and vitamin B_{12}.
Folic acid and vitamin B_{12} are necessary for certain transmethylation processes, e.g. in the synthesis of DNA and RNA. Folic acid deficiency leads to megaloblastic anaemia of the same type as in vitamin B_{12} deficiency.
It has been shown that treatment with a combination of folic acid/vitamin B_6/vitamin B_{12} reduces elevated plasma levels of homocysteine. Homocysteine is a metabolite formed during the metabolism of the essential amino acid methionine. The turnover of homocysteine is influenced by folic acid, vitamin B_6 and vitamin B_{12} and the plasma level of homocysteine rises markedly in folic acid and vitamin B_{12} deficiency.
Increased levels of homocysteine have been observed among elderly people.

5.2 Pharmacokinetic properties

Perorally administered *vitamin B_{12}* is absorbed via active and passive mechanisms. Absorption via the active transport mechanism includes intrinsic factor, while vitamin B_{12} is passively absorbed in the small intestine in the absence of intrinsic factor. The degree of passive absorption is approx. 1% of the administered dose. An important component of normal vitamin B_{12} absorption and body conservation of vitamin B_{12} is enterohepatic circulation. Vitamin B_{12} is bound to transcobalamines in serum. The transcobalamines in serum are regarded to be saturated at 750-1500 pmol/l of vitamin B_{12}. Not protein bound cyanocobalamin are excreted through glomerular filtration.

Folic acid is rapidly absorbed mainly from the proximal part of the small intestine. Synthetic folic acid is highly bioavailable (approximately 85-100%). Folic acid undergoes enterohepatic circulation. Following absorption, folic acid is largely reduced and methylated in the liver to 5-methyltetrahydrofolic acid, which is the predominant form of circulatory folic acid. The principal storage site is the liver, it is also actively concentrated in the cerebrospinal fluid. Administration of larger doses of folic acid leads to proportionately more of the vitamin being excreted in the urine.

All forms of *vitamin B_6* are freely absorbed by passive diffusion in the jejunum and ileum. The predominant form of circulatory vitamin B_6 is pyridoxal phosphate and pyridoxamine phosphate. Especially pyridoxal phosphate circulates tightly bound to albumin while other vitamin B_6 forms are bound to a lesser extent. The storage and metabolism of vitamin B_6 is mainly in the liver where it is oxidized to form pyridoxic acid, the major excretory product of vitamin B_6. The products of vitamin B_6 metabolism are excreted in the urine.

5.3 Preclinical safety data

There are no preclinical data of relevance to the safety evaluation beside those already referred to in the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline (E 460)
Calcium hydrogen phosphate dihydrate
Sodium starch glycolate (type A)
Silica, colloidal anhydrous (E 551)
Magnesium stearate (E 470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original container in order to protect from light.

6.5 Nature and contents of container

White HDPE container with HDPE/LDPE closure.
Pack sizes: 100 and 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2023-08-24