**SUMMARY OF THE PRODUCT CHARACTERISTICS**

## 1 NAME OF THE MEDICINAL PRODUCT

TrioBe tablet

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains: folic acid 0.8 mg, cyanocobalamin (vitamin B12) 0.5 mg, pyridoxine hydrochloride (vitamin B6) 3.0 mg. For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Tablet

Pale yellow tablet with small dots, round, convex, marked R109, with a diameter of 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

For oral use. 1 tablet daily with water.

### 4.3 Contraindications

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

Secondary prevention of NTD (neural tube defects).

### 4.4 Special warnings and precautions for use

TrioBe 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. TrioBe should not be used in patients who have been subject to major resection of the small intestine.

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 may increase the metabolism of some antiepileptics, such as phenobarbital and phenytoin. It may also interfere with the action of folic acid antagonists such as methotrexate, trimethoprim and pyrimethamin.
Concurrent use of altretamine and Pyridoxine may result in reduced response to altretamine.

Pyridoxin increases the metabolism of levodopa and can lead to reduced clinical effect when levodopa is used without a dopa decarboxylase inhibitor.
Colchicine, para-aminosalicylic acid (long-term treatment), omeprazole and heavy alcohol intake may produce malabsorption of vitamin B12.

## 4.6 Fertility, pregnancy and lactation

Pregnancy:
There are no known risks of cyanocobalamin/folic acid/pyridoxine hydrochloride supplementation in pregnant women at therapeutic dose levels.
TrioBe can be considered during pregnancy if vitamin B adjustments are clinically needed.

Breast-feeding:
Cyanocobalamin/folic acid/pyridoxine hydrochloride /metabolites are excreted in human milk, but at therapeutic doses of TrioBe no effects on the breastfed newborns/infants are anticipated.

Fertility:
There are no data on the effect of the medicinal product on fertility in human. Non-clinical data does not indicate fertility impairment at therapeutic doses.

## 4.7 Effects on ability to drive and use machines

TrioBe has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Adverse reactions frequencies are defined as:
rare (>1/10,000, <1/1,000)
not known (cannot be estimated from the available data)

*Skin and subcutaneous tissue disorders*
Rare: acne like reactions, allergic reactions (urticaria, pruritus, erythema).

*Immune system disorders*
Not known: 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 [To be completed nationally].

## 4.9 Overdose

*Folic acid* has low toxicity. No side effects have been noted in adults who have either taken 400 mg/day for 5 months or 10 mg/day for 5 years.
At chronic high dose treatment with *pyridoxine,* some individuals have developed peripheral neuropathies. The dose level of vitamin $B_6$ in TrioBe constitute no risk of overdose.
*Cyanocobalamin* has low toxicity. No symptoms are to be expected even after high doses.

Since these are water soluble vitamins, treatment is unlikely to be needed in cases of overdosage.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC-code: A11E Vitamin B-complex
The amounts of folic acid, vitamin $B_6$ and vitamin $B_{12}$ in TrioBe 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.
One intervention trial has shown that treatment with TrioBe 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.
An age-related increase of homocysteine levels has been observed. There is increasing evidence that elevated homocysteine levels are associated with an increased risk for e.g. coronary heart disease.
The recommended intake of vitamin $B_6$ for women is 1.2 mg and for men 1.4 mg per day.
The recommended intake of vitamin $B_{12}$ for women and men is 3 microg per day.
The recommended intake of folic acid is 300 microg per day for both women and men.

### 5.2 Pharmacokinetic properties

Perorally administered *vitamin $B_{12}$* is passively absorbed in the small intestine in the absence of intrinsic factor. The degree of absorption is approx. 1% independent of the dose, and therefore 1 tablet of TrioBe daily well covers the daily need in all kinds of vitamin $B_{12}$ deficiency. The transcobalamines in serum are regarded to be saturated at 750-1500 pmol/l of vitamin $B_{12}$. Not protein bound cyanocobalamin in amounts above this, are very quickly excreted through glomerular filtration.
*Folic acid* is rapidly absorbed mainly from the proximal part of the small intestine. The predominant form of circulatory folic acid is 5-methyltetrahydrofolate. 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 small intestine is able to absorb amounts of vitamin $B_6$ greatly in excess of physiological need. The predominant form of circulatory vitamin $B_6$ is pyridoxal phosphate and pyridoxamine phosphate. 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 $B_6$.

### 5.3 Preclinical safety data

Most effects in non-clinical studies were observed only at dose levels considered sufficiently in excess of the maximum human dose indicating little relevance to clinical use.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate
Colloidal anhydrous silica

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf-life

2 years.

### 6.4 Special precautions for storage

Do not store above 30$^{o}$ C. Store in the original container in order to protect from moisture.

### 6.5 Nature and contents of container

60, 100 and 250 tablets in white plastic bottle of HDPE (polyethylene).
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 locally >>*

## 8 MARKETING AUTHORISATION NUMBER(S)

*<< To be completed locally >>*

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 July 1999
Date of latest renewal: 2 July 2009

## 10 DATE OF REVISION OF THE TEXT

15 September 2023