

# **Public Assessment Report**

# **Decentralised Procedure**

# **ELEVIT Film-Coated Tablets**

Retinol [Vitamin A], Thiamine nitrate [Vitamin B1], Riboflavin [Vitamin B2], Nicotinamide, Calcium pantothenate [Vitamin B5]/ Pyridoxine hydrochloride [Vitamin B6], Biotin, Folic Acid [Vitamin B9], Cyanocobalamin [Vitamin B12], Ascorbic acid [Vitamin C], Colecalciferol [Vitamin D3], All-rac-α-Tocopheryl acetate [Vitamin E], Calcium, Copper, Iodine, Iron, Magnesium, Manganese, Selenium, Zinc

# UK/H/3933/002/DC

# UK licence no: PL 00010/0632

# **Bayer plc**

Medicines and Healthcare Products Regulatory Agency

#### LAY SUMMARY

On 10<sup>th</sup> April 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) to Bayer plc for the medicinal product ELEVIT Film-coated Tablets (PL 00010/0632, UK/H/3933/002/DC). This is a general sale list medicine (GSL).

ELEVIT is a film-coated tablet containing 12 vitamins and 8 minerals and trace elements. ELEVIT film-coated tablets are indicated for treating or preventing vitamin or mineral deficiencies during pregnancy or breast-feeding.

ELEVIT can also reduce risk of neuronal tube defects (problems in development of nervous system that could occur at very beginning of pregnancy) in your baby if it is started to be used one month before you become pregnant.

ELEVIT can also prevent deficiency of folic acid and iron linked to anaemia (a group of medical conditions characterized by a reduced amount of red blood cells). Vitamins, minerals and trace elements are essential nutrients. They cannot be produced by the body and therefore have to be derived from diet. These substances are vital for human daily living – breathing, digestion, generation of energy, function of brain and nervous system, reproduction, growth – while at the same time they are part of numerous tissues and organs.

Pregnant and breastfeeding women need significantly more vitamins, minerals and trace elements than non-pregnant women since a pregnant women must provide nourishment not only for her own body but also for that of her child.

With a balanced diet and without the consumption of nicotine and alcohol, pregnant and breastfeeding women normally have sufficient levels of vitamins, minerals and trace elements. Nevertheless, deficiencies may occur during pregnancy and lactation. Vomiting frequently during the early stage of pregnancy may, for example, result in a deficiency of essential nutrients.

The consequences of deficiencies can, for example, be anaemia and tiredness for the mother and retarded growth and changes of skin and mucous membranes for the child. ELEVIT film-coated tablets were especially formulated for pregnant and breast-feeding (lactating) women. It contains all essential nutrients required during this phase. Thus the occurrence of deficiency states in mother and child can be prevented. Folic acid helps to prevent malformations of the child.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking ELEVIT Film-coated Tablets outweigh the risks. Hence a Marketing Authorisation has been granted.

# **TABLE OF CONTENTS**

Module 1: Information about initial procedure			
Module 2: Summary of Product Characteristics			
Module 3: Patient Information Leaflet			
Module 4: L	abelling	Page 7	
Module 5: Scientific Discussion		Page 12	
	I. Introduction II. About the Product III. Scientific Overview and Discussion III.1. Quality aspects III.2. Non-clinical aspects III.3. Clinical aspects IV. Overall conclusion and Benefit-Risk Assessm	nent	
Module 6	Steps taken after initial procedure	Page 35	

Module 1						
Information	about initial	procedure				

Product Name	ELEVIT Film-coated Tablets		
Type of Application	Article 10a, Well established use		
Active Substance	Retinol [Vitamin A], Thiamine nitrate [Vitamin B1], Riboflavin [Vitamin B2], Nicotinamide, Calcium pantothenate [Vitamin B5]/ Pyridoxine hydrochloride [Vitamin B6], Biotin, Folic Acid [Vitamin B9], Cyanocobalamin [Vitamin B12], Ascorbic acid [Vitamin C], Colecalciferol [Vitamin D3], All-rac-α-Tocopheryl acetate [Vitamin E], Calcium, Copper, Iodine, Iron, Magnesium, Manganese, Selenium, Zinc		
Form	Film-coated Tablets		
Strength	<ol> <li>Retinol (Vitamin A) 2566 IU</li> <li>Thiamine Nitrate (Vitamin B1) 1.4 mg</li> <li>Riboflavin (Vitamin B2) 1.4 mg</li> <li>Nicotinamide 18 mg</li> <li>Calcium Pantothenate (Vitamin B5) 6 mg</li> <li>Pyridoxine Hydrochloride (Vitamin B6) 1.9 mg</li> <li>Biotin 30 micrograms</li> <li>Folic Acid (in the form of (i.f.o.) Folic Acid and L-methylfolate, Calcium) (Vitamin B9) 800 micrograms</li> <li>Cyanocobalamin (Vitamin B12) 2.6 micrograms</li> <li>Cyanocobalamin (Vitamin D3) 200 IU</li> <li>Ascorbic Acid (Vitamin D3) 200 IU</li> <li>All-rac-α-Tocopheryl acetate (Vitamin E) 15 mg</li> <li>Calcium (derived from: Calcium Pantothenate (above), Calcium Phosphate Dibasic, L-methylfolate, Calcium (above) and Calcium Carbonate) 125 mg</li> <li>Copper (i.f.o. Copper Sulphate Anhydrous) 1 mg</li> <li>Iodine (i.f.o. Potassium Iodide) 220 micrograms</li> <li>Iron (i.f.o. Ferrous Fumarate) 45 mg</li> <li>Magnesium (i.f.o. Magnesium Oxide Heavy and the excipient Magnesium Stearate) 100 mg</li> <li>Manganese (i.f.o. Manganese Sulphate Monohydrate) 2 mg</li> <li>Selenium (i.f.o. Sodium Selenite) 50 micrograms</li> <li>Zinc (i.f.o. Zinc Citrate Trihydrate) 11 mg</li> </ol>		
MA Holder	Bayer plc, Consumer Care Division Newbury, RG14 1JA, UK		
RMS	UK		
CMS	Austria, Bulgaria, Hungary and Romania		
Procedure Numbers	UK/H/3933/002/DC		
Timetable	Day 210 – 14 <sup>th</sup> January 2013		

### Module 2 Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

### Module 3 Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

### Module 4

## Labelling





#### PAR ELEVIT Film-coated Tablets







#### UK/H/3933/002/DC



### Module 5 Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for ELEVIT Film-coated Tablets (PL 00010/0632, UK/H/3933/002/DC), could be approved.

ELEVIT is indicated in women and in female adolescents aged 12 to 18 years who are pregnant or are planning to become pregnant or are breast-feeding, for the:

- Prevention of micronutrient deficiencies during pregnancy and lactation.
- Prevention of iron and/or folate deficiency anemia during pregnancy and lactation.
- Reduction of the risk of the first occurrence of neural tube defects (NTDs).

This application was submitted under Article 10a, well-established use, of Directive 2001/83/EC (as amended). This is justified since the constituents of the applicants' product are generally well established for medicinal use with similar products being marketed in numerous European countries, including the UK.

With the UK as the RMS in this Decentralised Procedure (UK/H/3933/002/DC), Bayer plc applied for a Marketing Authorisation for ELEVIT Film-coated Tablets in Austria, Bulgaria, Hungary and Romania.

Vitamins, minerals and trace elements are essential active agents for maintaining the physiological functions of the organism. Humans cannot synthesise them and are therefore dependent on a continuous exogenous (external) source. Vitamins are essential to all metabolic pathways and are crucial to their well-balanced co-ordination. The oral application of combinations of vitamins and minerals is a natural way of supply, as they would appear in natural foodstuffs.

No new non-clinical or clinical studies were necessary for this application, which is acceptable given that this is a bibliographic application for a product containing active ingredients of well-established use.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for the non-submission of a Risk Management Plan (RMP).

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day  $210 - 14^{th}$  January 2013). After a subsequent national phase, the UK granted a Marketing Authorisation for this product on  $10^{th}$  April 2013 (PL 00010/0632).

#### II. ABOUT THE PRODUCT

Name of the product in the Reference	ELEVIT Film-coated Tablets
Member State	
Name(s) of the active substance(s) (INN)	Retinol [Vitamin A], Thiamine nitrate [Vitamin B1], Riboflavin [Vitamin B2], Nicotinamide, Calcium pantothenate [Vitamin B5],Pyridoxine hydrochloride [Vitamin B6], Biotin, Folic Acid [Vitamin B9], Cyanocobalamin [Vitamin B12], Ascorbic acid [Vitamin C], Colecalciferol [Vitamin D3], All-rac-α-Tocopheryl acetate [Vitamin E], Calcium, Copper, Iodine, Iron, Magnesium, Manganese, Selenium, Zinc
Pharmacotherapeutic classification (ATC code)	A11A A03, Multivitamins and other minerals incl. combinations,
Pharmaceutical form and strength(s)	<ul> <li>Film-coated Tablets,</li> <li>1. Retinol (Vitamin A) 2566 IU</li> <li>2. Thiamine Nitrate (Vitamin B1) 1.4 mg</li> <li>3. Riboflavin (Vitamin B2) 1.4 mg</li> <li>4. Nicotinamide 18 mg</li> <li>5. Calcium Pantothenate (Vitamin B5) 6 mg</li> <li>6. Pyridoxine Hydrochloride (Vitamin B6) 1.9 mg</li> <li>7. Biotin 30 micrograms</li> <li>8. Folic Acid (i.f.o. Folic Acid and L-methylfolate, Calcium) (Vitamin B9) 800 micrograms</li> <li>9. Cyanocobalamin (Vitamin B12) 2.6 micrograms</li> <li>10. Ascorbic Acid (Vitamin C) 85 mg</li> <li>11. Colecalciferol (Vitamin D3) 200 IU</li> <li>12. All-rac-α-Tocopheryl acetate (Vitamin E) 15 mg</li> <li>13. Calcium (derived from: Calcium Pantothenate (above), Calcium Phosphate Dibasic, L-methylfolate, Calcium (above) and Calcium Carbonate) 125 mg</li> <li>14. Copper (i.f.o. Copper Sulphate Anhydrous) 1 mg</li> <li>15. Iodine (i.f.o. Ferrous Fumarate) 45 mg</li> <li>17. Magnesium (i.f.o. Magnesium Oxide Heavy and the excipient Magnesium Stearate) 100 mg</li> <li>18. Manganese (i.f.o. Manganese Sulphate Monohydrate) 2 mg</li> <li>19. Selenium (i.f.o. Zinc Citrate Trihydrate) 11 mg</li> </ul>
Reference numbers for the Decentralised	UK/H/3933/002/DC
Procedures Defense og Mennhan State	United Vineder
Reference Member State	United Kingdom
Marketing Authorization Number(a)	Austria, Bulgaria, Hungary and Komania
Nome and address of the systemication	PL 00010/0052
holder	Bayer pic, Consumer Care Division Newbury, RG14 1JA,
	UK

# IIISCIENTIFIC OVERVIEW AND DISCUSSIONIII.1QUALITY ASPECTSDRUG SUBSTANCE

#### 1. Vitamin A (in the form of retinol palmitate)

rINN: Retinol palmitate

Chemical Name: all-(E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraen-1-yl palmitate

Structure:



Molecular Formula: C<sub>36</sub>H<sub>60</sub>O<sub>2</sub>

Molecular Weight: 542.9

Appearance: It is a light yellow, fine granular powder, nearly odourless Solubility: Retinol esters are practically insoluble in water, soluble or partly soluble in anhydrous ethanol and miscible with organic solvents

Retinol palmitate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance retinol palmitate are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### 2. Vitamin B1 (in the form of thiamine nitrate)

rINN: Thiamine nitrate

Chemical name: 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium nitrate

Structure



Molecular Formula: C<sub>12</sub>H<sub>17</sub>O<sub>4</sub>N<sub>5</sub>S.

Molecular Weight: 327.4

Appearance: White or almost white, crystalline powder or small, colourless crystals. Solubility: Sparingly soluble in water, freely soluble in boiling water, slightly soluble in alcohol and in methanol.

Thiamine nitrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance thiamine nitrate are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### 3. Vitamin B2 (Riboflavin)

rINN: Riboflavin

Chemical Name: 7,8-Dimethyl-10-[(2S,3S,4R)-2,3,4,5-tetrahydroxypenthyl]benzo[g] pteridine-2,4(3H,10H)-dione

Structure:



Molecular Formula: C17H20N4O6

Molecular Weight: 376.4

Appearance: yellow or orange-yellow, crystalline powder. Solubility: very slightly soluble in water, practically insoluble in ethanol (96 per cent). Solutions deteriorate on exposure to light, especially in the presence of alkali.

Riboflavin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance riboflavin are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### **4. Nicotinamide** rINN: Nicotinamide

Chemical name: Pyridine-3-carboxamide

Structure:

Molecular Formula: C<sub>6</sub>H<sub>6</sub>N<sub>2</sub>O.

Molecular Weight: 122.1

Appearance: White, crystalline powder or colourless crystals. Solubility: freely soluble in water and in ethanol

Nicotinamide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance nicotinamide are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### 5. Vitamin B5 (Calcium pantothenate)

rINN: Calcium pantothenate

Chemical names: Calcium bis[3-[[(2R)-2,4-dihydroxy-3,3-dimethylbutanoyl]amino] propanoate]  $\beta$ -Alanine N-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-,calcium salt (2:1),(R)-(R)-3-(2,4-dihydroxy-3,3-dimethylbutyramido)propionic acid, calcium salt

Structure



Molecular Formula: C<sub>18</sub>H<sub>32</sub>CaN<sub>2</sub>O<sub>10</sub>

Molecular Weight: 476.5

Appearance: white powder, (slightly hygroscopic) Solubility: freely soluble in water, slightly soluble in alcohol

Calcium pantothenate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance calcium pantothenate are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### 6. Vitamin B6 (pyridoxine hydrochloride)

rINN: Pyridoxine hydrochloride

Chemical name: (5-hydroxy-6-methylpyridine-3,4-diyl)dimethanol hydrochloride

Structure:



Molecular Formula: C<sub>8</sub>H<sub>11</sub>NO<sub>3</sub> HCl

Molecular Weight: 205.6

Appearance: White or almost white, crystalline powder Solubility: Freely soluble in water, slightly soluble in ethanol (96 per cent).

Pyridoxine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance pyridoxine hydrochloride are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### 7. Biotin

rINN: Biotin

Chemical name: 5-[(3aS,4S,6aR)-2-oxohexahydrothieno[3,4-d]imidazol-4-yl] pentanoic acid

Structure:

Molecular Formula: C10H16N2O3S

Molecular Weight: 244.3

Appearance: White crystalline powder

Solubility: Very slightly soluble in water and in alcohol, practically insoluble in acetone. It dissolves in dilute solutions of alkali hydroxides

Biotin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance biotin are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### 8. Vitamin B9 (Folic acid)

rINN: Folic acid

Chemical name: (2S)-2-[[4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino] benzoyl]amino]pentanedioic acid

Structure:



Molecular Formula: C<sub>19</sub>H<sub>19</sub>N<sub>7</sub>O<sub>6</sub>

Molecular Weight: 441.4

Appearance: Yellow to orange crystalline powder. Solubility: Practically insoluble in water and in most organic solvents. It dissolves in dilute acids and alkaline solutions.

Folic acid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance folic acid are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

No details about the second form of folic acid (L-methyl folate calcium, details to be found in the relevant 3.2.S) are included (please note that a LoA to the manufacturer's Active Substance Master File (ASMF) was submitted and approved in this case).

#### L-methylfolate calcium (second form of Folic acid)

Chemical name: (2S)-2-[[4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino] benzoyl]amino]pentanedioic acid

Structure:



Molecular Formula: C20H23CaN7O6

Molecular Weight: 497.52

Appearance: White to yellow beige powder. Solubility: Practically insoluble in water and in most organic solvents. It dissolves in dilute acids and alkaline solutions.

The drug substance is the subject of an Active Substance Master File (ASMF).

Synthesis of the drug substance from the designated starting material(s) has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided, which comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated to support a suitable retest period when the drug substance is stored in the proposed packaging.

#### 9. Cyanocobalamin (Vitamin B12)

rINN: Cyanocobalamin

Chemical name: α-(5,6-dimethylbenzimidazol-1-yl) cobamide cyanide

Structure:



Molecular Formula: C63H88CoN14O14 P

Molecular Weight: 1355

Appearance: Dark red crystalline powder or dark red crystals.

Solubility: Sparingly soluble in water and in ethanol (96 per cent), practically insoluble in acetone. The anhydrous substance is very hygroscopic.

Cyanocobalamin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance cyanocobalamin are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### **10.** Ascorbic acid (Vitamin C)

rINN: Ascorbic acid

Chemical name: (5R)-5-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5H)-one

Structure:



Molecular Formula: C<sub>6</sub>H<sub>8</sub>O<sub>6</sub>

Molecular Weight: 176.1

Appearance: A white or almost white, crystalline powder or colourless crystals, becoming discoloured on exposure to air and moisture. Solubility: Freely soluble in water, sparingly soluble in ethanol (96 per cent).

Ascorbic acid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance ascorbic acid are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

#### 11. Cholecalciferol (Vitamin D3)

rINN: Cholecalciferol

Chemical name: (5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-3β-ol

Structure:



Molecular Formula: C<sub>27</sub>H<sub>44</sub>O

Molecular Weight: 384.65

Appearance: White or almost white crystals. Solubility: Practically insoluble in water, freely soluble in ethanol (96 per cent), soluble in trimethylpentane and in fatty oils.

Cholecalciferol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance cholecalciferol are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### 12. All-rac-α-tocopheryl acetate (Vitamin E)

rINN: All-rac-α-tocopheryl acetate

Chemical name: (2RS)-2,5,7,8-tetramethyl-2-[(4RS,8RS)-4,8,12-trimethyltridecyl]-3,4-dihydro-2H-1-benzopyran-6-ol acetate

Structure:



Molecular Formula: C<sub>31</sub>H<sub>52</sub>O<sub>3</sub>

Molecular Weight: 472.7

Appearance: clear, colourless or slightly greenish-yellow, viscous, oily liquid. Solubility: practically insoluble in water, freely soluble in acetone, in anhydrous ethanol and in fatty oils.

All-rac-α-tocopheryl acetate is the subject of a European Pharmacopoeia monograph.

#### PAR ELEVIT Film-coated Tablets

All aspects of the manufacture and control of the active substance all-rac- $\alpha$ -tocopheryl acetate are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### 13. Calcium hydrogen phosphate, anhydrous

rINN: Calcium hydrogen phosphate

Chemical name: Calcium hydrogen orthophosphate anhydrous.

Structure:

HO-P-O-

Molecular Formula: CaHPO<sub>4</sub>

Molecular Weight: 136.1

Appearance: A white or almost white crystalline powder or colourless crystals. Solubility: Practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute hydrochloric acid and in dilute nitric acid.

Calcium hydrogen phosphate is the subject of a European Pharmacopoeia monograph.

#### 14. Copper sulfate, anhydrous

rINN: Copper sulfate, anhydrous

Chemical name: Copper (II) sulfate anhydrous.

Molecular Formula: CuSO<sub>4</sub>

Molecular Weight: 159.6

Appearance: Greenish-grey powder, very hygroscopic Solubility: Freely soluble in water, slightly soluble in methanol, practically insoluble in ethanol (96 per cent).

Copper sulfate, anhydrous is the subject of a European Pharmacopoeia monograph.

#### 15. Potassium iodide

rINN: Potassium iodide

Chemical name: Potassium iodide.

Molecular Formula: KI

Molecular Weight: 166

Appearance: White or almost white powder or colourless crystals. Solubility: Very soluble in water, freely soluble in glycerol, soluble in ethanol (96 per cent)

Potassium iodide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance potassium iodide are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

#### 16. Ferrous fumarate

rINN: Ferrous fumarate

Chemical names: Iron (II) (E)-butenedioate, 2-butenetioic acid, (E)-, iron (2+) salt, 2-butenedioic acid ferrous salt

Structure:



Molecular Formula: C<sub>4</sub>H<sub>2</sub>FeO<sub>4</sub>

Molecular Weight: 169.9

Appearance: fine, reddish-orange or reddish-brown powder Solubility: slightly soluble in water, very slightly soluble in ethanol (96 per cent)

Ferrous fumarate is the subject of a European Pharmacopoeia monograph.

#### 17. Magnesium oxide, heavy

rINN: Magnesium oxide, heavy

Chemical name: Magnesium oxide

Molecular Formula: MgO

Molecular Weight: 40.30

Appearance: Fine ,white or almost white powder (Ph. Eur.) Solubility: Practically insoluble in water. It dissolves in dilute acids with at most slight effervescence

Magnesium oxide, heavy is the subject of a European Pharmacopoeia monograph.

#### **18.** Manganese sulfate monohydrate

rINN: Manganese sulphate monohydrate

Chemical name: Manganese (II) sulphate monohydrate.

Molecular Formula: MnSO<sub>4</sub>,H<sub>2</sub>O

Molecular Weight: 169

Appearance: Pale pink crystalline powder, slightly hygroscopic (Ph. Eur.). Solubility: Freely soluble in water, practically insoluble in ethanol (96 per cent)

Manganese sulphate monohydrate is the subject of a European Pharmacopoeia monograph.

#### **19. Sodium selenite (pure)**

rINN: Sodium selenite anhydrous

Chemical name: Sodium selenite

Structure:

Na+ 
$$\begin{bmatrix} 0 \\ II \\ 0 - Se - 0 \end{bmatrix}$$
 Na+

Molecular Formula: Na<sub>2</sub>SeO<sub>3</sub>

Molecular Weight: 172.94

Appearance: White powder Solubility: soluble in water.

The drug substance is the subject of an Active Substance Master File (ASMF).

Synthesis of the drug substance from the designated starting material(s) has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided, which comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated to support a suitable retest period when the drug substance is stored in the proposed packaging.

#### 20. Zinc citrate trihydrate

rINN: Zinc citrate trihydrate.

Chemical name: 2-Hydroxy-1,2,3-propanetricarboxylic acid zinc salt, trihydrate.

Structure



Molecular Formula: C12H10O14Zn3.3H20

Molecular Weight: 628.4

Appearance: White powder, odourless or almost odourless Solubility: Very slightly soluble in water, soluble in dilute mineral acids, practically insoluble in alcohol.

Synthesis of the drug substance from the designated starting material(s) has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided, which comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated to support a suitable retest period when the drug substance is stored in the proposed packaging.

#### DRUG PRODUCT Other Ingredients

Other ingredients consist of the pharmaceutical excipients calcium carbonate (E 170), citric acid anhydrous (E 330), corn starch, gelatin, magnesium stearate, maltodextrin, microcrystalline cellulose, modified food starch, mono and di-glyceride fatty acids (E 471),

povidone, silica (colloidal anhydrous), sodium ascorbate (E 301), sodium croscarmellose, sucrose, talc (E 553b), triglycerides medium chain, trisodium citrate (E 331) making up the tablet core. The tablet coat consists of hypromellose, microcrystalline cellulose, stearic acid and titanium dioxide (E171).

All excipients comply with their respective European Pharmacopoeia monographs except the film-coat which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

Confirmation has been given that the magnesium stearate used in the tablet is of vegetable origin.

No novel excipients are used in the drug product.

No genetically modified organisms (GMO) have been used in the preparation of this product.

#### **Pharmaceutical Development**

The objective of the development programme was to formulate robust, stable film-coated tablets that could deliver the desired drug substances in a single unit.

A satisfactory account of the pharmaceutical development has been provided.

#### Manufacture

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on pilot-scale batches have been provided. The applicant has committed to perform process validation on three consecutive commercial-scale batches prior to marketing the drug product.

#### **Finished Product Specification**

The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided, which comply with the release specification. Certificates of Analysis have been provided for any working standards used.

#### **Container-Closure System**

The finished product is packed in polyvinylchloride (PVC)/polyurethane (PU)/polyvinylidene chloride (PVDC)-aluminium foiled blisters with pack sizes of 30 or 100 film-coated tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with relevant EU legislation regarding contact with food.

#### Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with storage conditions "Do not store above 25°C" and "Store in the original package to protect from light and moisture" are set. These are satisfactory.

# Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SmPC, PIL and label are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

The Marketing Authorisation Holder has committed to submit mock-ups for any nonmarketed pack size to the relevant regulatory authorities for approval before those packs are marketed.

#### Marketing Authorisation Application (MAA) Forms

The MAA form is satisfactory from a pharmaceutical perspective.

#### **Expert** report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

#### Conclusion

There are no objections to the approval of this product from a pharmaceutical point of view.

#### **III.2 NON-CLINICAL ASPECTS**

The pharmacodynamic, pharmacokinetic and toxicological properties of the 20 active substances (combination of 12 vitamins, 2 minerals and 6 trace elements) are well known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Suitable justification has been provided for not submitting an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

#### **III.3 CLINICAL ASPECTS**

The marketed product ELEVIT PRONATAL is the precursor of ELEVIT which is the object of the applicant's clinical overview; it was developed in the early 1980s and was the first multivitamin/mineral preparation with folic acid successfully tested with a controlled clinical trial for the prevention of first occurrence neural tube defects.

In order to meet the latest standards in vitamin supplementation and new medical knowledge on fetus development, it was decided to update ELEVIT PRONATAL composition. In this respect the newly proposed formula is ELEVIT which was supplemented as follows from the original ELEVIT PRONATAL product:

 The amounts of several active ingredients, i.e. vitamins A, B1, B2, B5, B6, B12, C, D, nicodinamide, biotin, and the trace elements manganese and zinc, have been adapted to the latest Recommended Dietary Allowances (RDAs) for pregnancy as set by the US Institute of Medicine;

- 2. The original amount of 800 micrograms folic acid has been divided into two forms of folate: *a*) 400 micrograms as folic acid, and *b*) an equimolar amount (451 micrograms) of L-5-methyltetrahydrofolate-calcium salt (L-5-MTHF, Ca). The total amount of folate remains 800 micrograms.
- 3. The amount of iron has been reduced from 60 mg to 45 mg, in accordance with the Upper Safety Intake Levels for chronic intake in pregnancy as set by the US Institute of Medicine.
- 4. Due to their importance during early embryo development, iodine and selenium have been included in the formula.
- 5. Because its frequency and high abundance in most standard foods and beverages, phosphorus has been omitted from the new formula.

No new clinical data have been supplied with this application and none are required.

A literature review and previous clinical trial data have been submitted. This is satisfactory. In the sections that follow, the key information has been summarised.

#### PHARMACOKINETICS

The active ingredients of ELEVIT, vitamins, minerals, and trace elements, are essential micronutrients, which are widely distributed in the human body. The discrimination between the physiological nutrient concentration in the plasma and its changes after additional intake of corresponding pharmaceutical preparations is, on the one hand, difficult to assess, and conveys, on the other hand, little or no information on the biological activity of the individual nutrient in the target tissue (mainly due to the complex interdependence of the biological properties of various micronutrients). The plasma and tissue levels of micronutrients are homeostatically regulated and affected by various factors such as diurnal fluctuations, nutritional status, growth, and pregnancy and lactation.

#### PHARMACODYNAMICS

The applicant has provided a comprehensive review from bibliographic sources for each of the 20 active substances in ELEVIT.

#### **CLINICAL EFFICACY**

The nutritional status of the mother-to-be plays a primary role in conception, the course of pregnancy and postpartum, as mother and child face special nutritional requirements and problems during pregnancy and lactation.

The most critical phase of organogenesis takes place during the first few weeks of embryonic life. The key phases in neural tube closure occur between the second and fourth weeks of pregnancy, i.e. most often before the mother-to-be knows that she is pregnant. For other malformations however, such as those of the genito-urinary tract or of cleft palate for instance, the critical phases take place later on. This implies that the nutritional status of both mother and unborn child should be optimal throughout the whole pregnancy. Several European and US surveys have shown subclinical deficiencies of micronutrients during pregnancy.

During pregnancy, nutritional requirements are increased for at least two well-recognised physiological reasons:

- the maternal organism needs energy and nutrients for the expansion in blood volume and increase in organ size,

- fetal growth requires nutrients and energy as well.

ELEVIT is intended to be used for supplementation and prevention of various vitamin, mineral and trace element deficiencies during the whole pregnancy and lactation period. The RDAs for various countries show that there is increased demand for vitamins and trace elements during the whole period of pregnancy and lactation.

A great number of enzymes regulating key metabolic pathways depend on the presence of vitamins and trace elements, thus maternal nutritional deficiency could affect the functioning of enzymes in fetal tissue.

Infant health is highly dependent on maternal nutritional status, both in utero and after delivery in the case of breast feeding: milk quality is closely correlated to maternal nutritional status (Sneed 1981, Emmett 1997, Picciano 1998, Urgell 1998, Kontovic-Vucinic 2006).

After pregnancy, the restoration of maternal nutritional balance and reconstitution of nutrient stores are determined by nutritional status at delivery or end of lactation and by the quality of postpartum nutrition.

During lactation, it is equally difficult to meet the increased requirements in micronutrients with a normal diet. This was again emphasised by recent investigations (Mackey 1998, Picciano 1998). Milk content of most micronutrients can be positively influenced by maternal intake of these nutrients (Hamosh 1996).

# The applicant has provided adequate bibliographic data to support the indication for 'Prevention and correction of micronutrient deficiencies during pregnancy as well as in the lactating period'

#### Indication: Reduction of the risk of the first occurrence of neural tube defects

The efficacy of the precursor preparation, ELEVIT PRONATAL, in the prevention of neural tube defects (NTDs), has been investigated in two large studies and in a third small study to evaluate IU 1610100 using a well established surrogate marker associated with the risk of NTD:

# 1. A randomised placebo-type controlled clinical trial including 2819 pregnant women treated with ELEVIT PRONATAL (1984 – 1992).

<u>Objective</u>: To examine the effect of periconceptional supplementation with ELEVIT PRONATAL on the prevention of the first occurrence of NTD and orofacial clefts, and to evaluate the occurrence of other congenital malformations in comparison to a placebo treatment. A second objective was to check the safety of the medication. This was done in a very detailed way in the first 1,000 pregnancies showing a very low incidence of adverse reactions. Moreover this evaluation showed that the use of ELEVIT PRONATAL can help reduce minor ailments such as nausea and vomiting in early pregnancy.

In April 1992, the international scientific committee advised to stop the placebo controlled study, as sufficiently conclusive results had emerged and the interim analysis showed a significant preventive effect of NTDs with ELEVIT PRONATAL. Due to these positive results it was no longer ethical to continue with a placebo dose for pregnant women.

It is important to note that this was the first and only placebo-controlled randomised study on peri-conceptional use of multivitamins to prevent the first occurrence of NTDs and other

malformations. Such a study can now no longer be repeated because inclusion of a placebo group would no longer be ethical.

<u>Results</u>: In summary, ELEVIT PRONATAL showed a significant reduction in the first occurrence of NTDs resulting in no NTDs in the ELEVIT PRONATAL group and 6 NTD-cases in the placebo-group. The evaluation of the other congenital malformations also demonstrated a protective effect of peri-conceptional ELEVIT PRONATAL intake, as there were only 51 major congenital abnormalities (without NTD) found in the ELEVIT PRONATAL group versus 91 in the placebo group. In the particular sub-groups, the reduction was significant concerning urinary tract defects (2 versus 9) and cardiovascular defects (10 versus 20), but also a decrease in the rate of limb deficiencies and congenital hypertrophic pyloric stenosis. However, no reduction of the occurrence of orofacial clefts was found in the group treated with ELEVIT PRONATAL.

# 2. A pharmacoepidemiological cohort study evaluating 3069 pregnant women treated with ELEVIT PRONATAL.

<u>Objective</u>: To study the efficacy of peri-conceptional multivitamin supplementation with ELEVIT PRONATAL daily in the reduction of certain congenital abnormalities compared to a group of women who were not supplemented with vitamins or folic acid alone.

There were some methodological flaws in the study design. In particular, the comparison of maternal comorbidity and previous pregnancy outcomes between the two cohorts showed a difference. Pregnant women in the ELEVIT PRONATAL group recruited from the Hungarian Peri-conceptional Service had a higher rate of comorbidity and considerably more previously unsuccessful pregnancy outcomes (fetal death and congenital abnormalities) compared to the unsupplemented pregnant women recruited at the Antenatal Care Clinics. So there is no doubt that women with a high risk for adverse pregnancy outcomes were somewhat concentrated in the intervention group supplemented with ELEVIT PRONATAL.

<u>Results</u>: 3056 informative offspring were evaluable between both cohorts. The protective effect of ELEVIT PRONATAL for the reduction of neural tube defects (1 versus 9), was confirmed. The occurrence of congenital cardiovascular malformations (31 versus 50) was significantly reduced. This was explained mainly by a lower occurrence of ventricular septal defect (5 versus 19). There was also a reduction (14 versus 19) of informative offspring with abnormalities of the urinary tract, although only the reduction of obstructive defects (10 versus 19) due to the stenosis of the pelvicureteric junction (2 versus 13) showed a statistically significant difference. The occurrence of orofacial clefts (4 versus 3) showed no difference between the two cohorts.

#### 3. A Single-centre, double-blinded, randomized parallel trial evaluating 46 nonpregnant women treated with supplementation of multivitamin containing 800 micrograms of folic acid.

<u>Objective</u>: To assess the efficacy of daily supplementation with IU 1610100 containing 800 micrograms folic acid to increase erythrocyte folate concentrations in women of child-bearing age to levels exceeding 906 nmol/L and to establish the timeframe required.

<u>Results</u>: After an average of 4.2 weeks, daily supplementation of IU 1610100 containing 800 micrograms folic acid increases mean erythrocyte folate levels above 906 nmol/L. In contrast, results from another study have shown that after daily intake of 400 mg/d folic acid

mean erythrocyte folate concentrations reached the recommended value only after 8 weeks of intervention

In the applicant's view, results of the clinical trials with ELEVIT PRONATAL, the pharmacokinetic data provided for IU 1610100 (both precursors of ELEVIT) together with several reports published in recent years on folic acid and multivitamins with folic acid, as well as the literature data on the natural folate form L-5-MTHF strongly support the efficacy of these preparations in the indication "*Reduction of the risk of the first occurrence of neural tube defects*".

In addition, comparison of the pooled data of the two studies conducted with ELEVIT PRONATAL has shown that multivitamins with 0.4-0.8 mg of folic acid were more effective for the reduction of NTDs than high dose, 5 mg, of folic acid (Czeizel 2004a). Also, multivitamins and folic acid can prevent some congenital cardiovascular malformations such as ventricular septal defects. Finally, only multivitamins were able to reduce the prevalence at birth of obstructive defects of the urinary tract, limb deficiencies and congenital pyloric stenosis. These conclusions are further supported by a review of the data of the Atlanta population-based case-control study (Botto 2004) and from a recent meta-analysis by Goh et al 2006.

#### Indication: Prevention of iron and folic acid deficiency anaemia.

Supplementary data have been provided by the applicant to demonstrate the efficacy of levels of iron and folate in Elevit to support this indication. The 800 micrograms dose level of folic acid has been shown to cause significant increases in plasma and erythrocyte folate concentrations (Brämswig 2009). A Cochrane Review by Peña-Rosas in 2009 presents a body of published evidence for supporting the use of iron with folic acid for the prevention and treatment of anaemia during pregnancy.

#### **CLINICAL SAFETY**

No clinical trials have been performed with ELEVIT.

Approximately 6000 pregnant women were exposed to ELEVIT PRONATAL in two trials. In the controlled clinical trial, excess incidence of gastrointestinal adverse events (constipation, diarrhoea in 0.6 - 2% of cases) was seen compared to placebo (0.2 - 1.2%). In both the controlled and the epidemiological study, isolated cases of non-serious allergic skin reactions were reported.

No post-marketing data is available for ELEVIT as the medicinal product has not been marketed in any country.

However, an extensive safety information body has been gathered on ELEVIT PRONATAL; based on the number of sold packs it was calculated that approximately 9.2 million women have been exposed to the product according to latest available consumption data.

During this 13-year period, 9 medically-confirmed case reports were received by the Marketing Authorisation Holder; none of the reports led to an amendment of the safety information in the Summary of Product Characteristics.

#### **Expert Report (Clinical Overall Summary)**

A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

#### Marketing Authorisation Application forms (MAA)

The MAA form is satisfactory from a clinical perspective.

#### Summary of Product Characteristics (SmPC)

The SmPC is satisfactory from a clinical perspective and consistent with that for the reference product.

#### **Patient Information Leaflet (PIL)**

The PIL is satisfactory from a clinical perspective and consistent with the SmPC.

#### Labelling

The Labelling is satisfactory from a clinical perspective.

#### Conclusion

There are no objections to the approval of this product from a clinical point of view.

# IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of ELEVIT Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

#### NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

#### EFFICACY

ELEVIT is a multivitamin/multimineral preparation specifically developed to meet the increased requirements of pregnant and lactating women. The composition of the product matches latest U.S. and European dietary recommendations and can be considered as adequate to cover the increased needs of mother and child during pregnancy and lactation with the aim of preventing transient deficiency and correcting existing deficiency during this eminently sensitive period.

Additionally, the results of the clinical trials with ELEVIT PRONATAL, the pharmacokinetic data provided for IU 1610100 are considered adequate to support the claim that the product is efficacious in the prevention of the first occurrence of NTDs and other congenital malformations.

#### SAFETY

All the active ingredients in ELEVIT are well-known, essential nutrients that are usually present in a balanced diet; the amounts of each of the vitamins, minerals and trace elements are well within generally accepted safety levels.

No new or unexpected safety concerns arose from this application.

The SmPC and PIL are satisfactory and consistent with those for the reference product. Satisfactory labelling has been submitted.

#### **RISK-BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with the 20 active substances is considered to have demonstrated the therapeutic value of the product. The risk-benefit balance is considered to be positive.

## Module 6

#### **STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

Date submitted	Application type	Scope	Outcome