Public Assessment Report

Decentralised Procedure

VITAMIN B COMPOUND STRONG TABLETS
(nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine mononitrate)

UK Licence No: PL 33831/0025

Blue Bio Pharmaceuticals Limited
LAY SUMMARY
Vitamin B Compound Strong Tablets
(nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine mononitrate)

This is a summary of the Public Assessment Report (PAR) for Vitamin B Compound Strong Tablets (PL 33831/0025). It explains how Vitamin B Compound Strong Tablets were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Vitamin B Compound Strong Tablets.

For practical information about using Vitamin B Compound Strong Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Vitamin B Compound Strong Tablets and what are they used for?
Vitamin B Compound Strong Tablets are a medicine with a ‘well-established use’. This means that the medicinal use of the active substances of Vitamin B Compound Strong Tablets have been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Vitamin B Compound Strong Tablets are used to treat vitamin B deficiency. The effects of vitamin B deficiency can include swelling of the tongue, mouth or lips; swelling of nerves which can cause pain, tenderness or loss of function; and the growth of new blood vessels in the eye which can affect vision. This medicine is also used to treat the effects on the heart which occur in beriberi (a condition caused by vitamin B1 (thiamine) deficiency) and the effects on the skin which occur in pellagra (a condition caused by niacin deficiency).

How do Vitamin B Compound Strong Tablets work?
This medicine contains the active substances nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine mononitrate, which are vitamins. Vitamins are a group of compounds that are necessary for the development, normal growth and functioning of the human body. Most people should get all the vitamins they need by eating a varied and balanced diet; however, sometimes the body requires a supplement.

How are Vitamin B Compound Strong Tablets used?
This medicine can be obtained from pharmacies, supermarkets and other retail outlets without the supervision of a pharmacist.

The usual dose of Vitamin B Compound Strong Tablets in adults, the elderly and children over 3 years is one to two tablets, three times a day.

These medicines are not recommended for children under 3 years of age.

What benefits of Vitamin B Compound Strong Tablets have been shown in studies?
As nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine mononitrate are well-known active substances and their use in the licensed indications is well established, the applicant has presented data from the scientific literature. The literature provided has confirmed the efficacy and safety of the active substances for use in the licensed indications.

What are the possible side effects of Vitamin B Compound Strong Tablets?
Like all medicines, this medicine can cause side effects, although not everybody gets them.
For the full list of side effects reported with Vitamin B Compound Strong Tablets, see section 4 of the package leaflet, available on the MHRA website

For the full list of restrictions, see the package leaflet.

**Why were Vitamin B Compound Strong Tablets approved?**
The MHRA concluded that, in accordance with EU requirements, the benefits of Vitamin B Compound Strong Tablets outweigh the identified risks and recommended that the product be approved for use.

**What measures are being taken to ensure the safe and effective use of Vitamin B Compound Strong Tablets?**
A risk management plan has been developed to ensure that Vitamin B Compound Strong Tablets are used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Vitamin B Compound Strong Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

**Other information about Vitamin B Compound Strong Tablets**
A Marketing Authorisation was granted in the UK on 19 January 2017.

The full PAR for Vitamin B Compound Strong Tablets follows this summary. For more information about treatment with Vitamin B Compound Strong Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2017.
SCIENTIFIC DISCUSSION

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Vitamin B Compound Strong Tablets (PL 33831/0025) could be approved.

This product is a General Sales List medicine (legal status GSL).

This application was made under the National Procedure, according to Article 10a of Directive 2001/83/EC, as amended, for products containing an active substance of well-established use.

Vitamin B Compound Strong Tablets are indicated for the treatment of clinical and sub-clinical vitamin B deficiency states (manifestations of which include glossitis, stomatitis, cheilosis, the heart manifestations of beriberi, the skin manifestations of pellagra, corneal vascularisation and polyneuritis).

This product contains the active substances nicotinamide, pyridoxine hydrochloride (vitamin B6), riboflavin (vitamin B2) and thiamine mononitrate (vitamin B1). These active substances are water-soluble vitamins. It is known that nearly every vitamin of the B-complex forms part of a co-enzyme that is essential for the metabolism of proteins, carbohydrates and fatty acids.

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

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application that are satisfactory.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

A national licence was granted in the UK on 19 January 2017.
II  QUALITY ASPECTS

II.1  Introduction
Vitamin B Compound Strong Tablets are brown coloured, circular, film coated tablets, debossed with ‘BP’ on one side and ‘2’ on other side.

Each film-coated tablet contains 20 mg nicotinamide, 2 mg pyridoxine hydrochloride, 2 mg riboflavin and 4.85 mg thiamine mononitrate.

Other ingredients consist of the pharmaceutical excipients, as follows:

Tablet core: lactose monohydrate, microcrystalline cellulose, pregelatinised starch, colloidal silicon dioxide, magnesium stearate.

Film coat: hypromellose (E464), hydroxy propyl cellulose, black iron oxide (E172), red iron oxide (E172), macrogol (E1521), titanium dioxide (E171), medium chain triglycerides.

The finished product is packaged in a clear aluminium/polyvinylchloride/polyvinylidene chloride blister pack, in a pack size of 28 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2  Drug substance

**Nicotinamide**

rINN/INN: Nicotinamide

Chemical name: Nicotinamide
Niacinamide
3-Pyridinecarboxamide

Structure:

![Nicotinamide Structure](image)

Molecular formula: $C_6H_6N_2O$
Molecular weight: 122.127
Appearance: White or almost white crystalline powder or colourless crystals
Solubility: Freely soluble in water and in ethanol

All aspects of the manufacture and control of the active substance nicotinamide from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
Riboflavin
rINN/INN: Riboflavin
Chemical name: Riboflavin
Vitamin B2

Structure:

![Riboflavin Structure](image)

Molecular formula: C_{17}H_{20}N_{4}O_{6}
Molecular weight: 376.369
Appearance: Yellow or orange-yellow crystalline powder
Solubility: Very slightly soluble in water, practically insoluble in ethanol (96%)

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

Pyridoxine hydrochloride
rINN/INN: Pyridoxine hydrochloride
Chemical name: Pyridoxine hydrochloride
Vitamin B6

Structure:

![Pyridoxine Hydrochloride Structure](image)

Molecular formula: C_{8}H_{12}ClNO_{3}
Molecular weight: 205.638
Appearance: White or almost white crystalline powder
Solubility: Freely soluble in water, slightly soluble in ethanol (96%)

The manufacture and control of the active substance pyridoxine hydrochloride from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.
Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**Thiamine mononitrate**

rINN: Thiamine nitrate  
Chemical name: Thiamine nitrate  
Thiamine mononitrate  
Vitamin B1 mononitrate  

Structure:

![structure](image)

Molecular formula: $C_{12}H_{17}N_{5}O_{4}S$  
Molecular weight: 327.359  
Appearance: White or almost white crystalline powder or small colourless crystals  
Solubility: Sparingly soluble in water, freely soluble in boiling water, slightly soluble in 98% ethanol and in methanol.

The manufacture and control of the active substance thiamine mononitrate from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

**II.3 Medicinal Product**

**Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious and stable tablets.

A satisfactory account of the pharmaceutical development has been provided.

With the exception of the film-coating, which complies with a suitable in-house specification, all excipients comply with their respective European Pharmacopoeia monographs. With the exception of the lactose monohydrate, none of the excipients are sourced from animal or human origin. The lactose is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. The manufacturing process has been validated using three commercial scale batches and has shown satisfactory results.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Stability of the products**
Stability studies were performed, in accordance with current guidelines, on batches of the finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 24 months, with the special storage conditions of “Store below 25°C in original package in order to protect from moisture”.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted for Vitamin B Compound Strong Tablets.

**II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

The approved text version of the labelling is shown below. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before those packs are commercially marketed.
MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Vitamin B Compound Strong Tablets

2. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Blue Bio Pharmaceuticals Limited,
5th Floor
Beaux Lane House,
Mercer Street Lower,
Dublin 2
Ireland

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton for Aluminium/PVC/PVDC Blister

1. NAME OF THE MEDICINAL PRODUCT

Vitamin B Compound Strong Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film coated tablet contains
- Nicotinamide: 20 mg
- Pyridoxine hydrochloride: 2 mg
- Riboflavin: 2 mg
- Thiamine mononitrate: 4.85 mg

3. LIST OF EXCIPIENTS

Also contains Lactose
See enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
9. SPECIAL STORAGE CONDITIONS

Store below 25°C in original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

No special conditions.

11. NAME AND ADDRESS OF THE MARKETING AUTHORITY HOLDING

Blue Bio Pharmaceuticals Limited,
5th Floor
Beaux Lane House,
Mercer Street Lower,
Dublin 2
Ireland

Distributed by:
Alissa Healthcare Research Limited,
Unit 5, Fulcrum 1, Solent way, Whitely, Fareham,
Hampshire, PO 15 7FE England.

12. MARKETING AUTHORIZATION NUMBER(S)

PL No. 33831/0025

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.

15. INSTRUCTIONS ON USE

Read the package leaflet before use.

16. INFORMATION IN BRAILLE

Vitamin B Compound Strong Tablets
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of the active substances are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2 Pharmacology
Nicotinamide, also known as niacinamide, is a water-soluble amide of nicotinic acid. Nicotinamide is the active form, which functions as a constituent of two coenzymes, namely, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes in their reduced states (NADH/NADPH) are the principal forms of niacin that exist in animal tissues.

Pyridoxine is a water-soluble vitamin. Pyridoxine is composed of three forms (vitamers), pyridoxine, pyridoxal and pyridoxamine. The cofactor forms of pyridoxine are pyridoxal-5’-phosphate and pyridoxamine-5’-phosphate. Pyridoxal phosphate is involved as a cofactor particularly in the metabolic transformation of amino acids, including decarboxylation, transamination and racemisation.

Thiamine (vitamin B1) is a relatively heat- and acid-stable, water-soluble compound, containing a pyrimidine and a thiazole nucleus linked by a methylene bridge. Derivatives of thiamine include the mono-, pyro- and triphosphate forms and the synthetic hydrochloride and slightly less water soluble mononitrate salt. Thiamine pyrophosphate (TPP) is a co-enzyme in several enzymatic reactions. TPP may also have a non-co-enzymic function during stimulation of neuronal cells and other excitable tissues, such as skeletal muscle.

Riboflavin, commonly known as vitamin B2, is the precursor of flavin cofactors. It is present in a typical diet, and inside the cells it is metabolised to flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). As a result of their rather unique and flexible chemical properties these flavins are among the most important redox cofactors present in a large series of different enzymes.

The primary and secondary pharmacology of nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine mononitrate have been reviewed adequately in the applicant’s non-clinical overview. However, the combined use of these active substances within the product and the contribution of each component were not discussed. As the combination has been in use for many years, further discussion of non-clinical data is not warranted.

III.3 Pharmacokinetics
The pharmacokinetic properties of nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine mononitrate have been reviewed adequately in the applicant’s non-clinical overview. As these components have been used extensively in the clinic the findings from non-clinical species are superceded by the human findings.

Nicotinamide is readily absorbed from skin, blood, and the intestines and is widely distributed throughout the body. The mode of transport is thought to be carrier-mediated facilitated diffusion at lower concentrations, masked by passive diffusion at higher concentrations. Nicotinamide is transported, mainly by simple diffusion, into the brain and heart, where it is metabolised into hydrophilic compounds and trapped. There is evidence to suggest it is accumulated in the small intestine, probably due to bile duct excretion of the tracer and its metabolites.
In rat liver, increased amounts of the methyl metabolite were found after repeated administration of nicotinamide. Methylation may lead to methyl deficiency as is reflected in low levels of choline as a methyl source found in the liver. In mice nicotinamide-N-oxide was found to be the main metabolite in plasma. Excretion is primarily through the urinary tract.

Nicotinamide has the potential to alter the pharmacokinetics and pharmacodynamics when administered with anticancer drugs.

Pyridoxine hydrochloride is absorbed rapidly from the upper intestine regardless of the size of the dose given. Absorption may also occur from the ileum and to a small extent from the colon. There is a linear relationship between oral dose and the amount absorbed in normal animals and in those in which the distal small intestine has been resected. These observations suggest the possibility that pyridoxine may be absorbed by diffusion. Labelled pyridoxal, pyridoxal phosphate and pyridoxine phosphate were found in the intestine and liver, although labelled pyridoxine could not be detected in the peripheral blood but substantial amounts of labelled pyridoxal and pyridoxal-phosphate were found in the blood. The results suggest that the liver and intestine play major role in converting dietary pyridoxine to circulating pyridoxal which is taken up and phosphorylated by other organs. Most of blood pyridoxal was shown to be located in the plasma.

Pyridoxine is rapidly converted in the liver to pyridoxine phosphate, pyridoxal phosphate and pyridoxamine phosphate via oxidation. This causes the release of pyridoxal and some pyridoxal phosphate to the general circulation where it reaches other organs chiefly as circulating pyridoxal. The biliary excretion studies of vitamin B6 in the intact rat and isolated perfused rat liver suggest that pyridoxine and its metabolites are released separately by the hepatocytes into the bile and the perfusate, and that paracellular transport of vitamin B6 is not the predominant pathway for the biliary excretion of this vitamin. In urine, pyridoxine was excreted primarily unchanged with a small amount of only one metabolite, most likely 4-pyridoxic acid.

It has been demonstrated in a rat intestinal absorption model that the intestinal absorption of isoniazid could be significantly inhibited by pyridoxine, although the pharmacokinetics do not appear to be adversely affected.

Studies in rats showed that the main site of absorption of thiamine was the duodenum and proximal jejunum; in the remainder of the small intestine relatively little thiamine was absorbed, particularly in the low dietary thiamine treatments. Distribution in rats identified that labelled thiamine distributed to liver, brain, kidney and testes.

Metabolism of thiamine was examined in mice which demonstrated that thiamine catabolizes to thiochrome and 4-methyl-5 beta-oxyethylthiazole. These compounds are greatly eliminated from the organism during the first hour after thiamine injection. Studies in rats indicated that thiamine was not excreted in the urine until the tissue levels were 75% saturated. No reports of pharmacokinetic interactions were retrieved.

Absorption of riboflavin was investigated using labelled riboflavin perfused to anaethesised rats. The absorption was seen to be a dual process: at low substrate concentrations (< 2 μmol/L) a saturable component predominated; at higher concentrations simple diffusion was found to be the prevailing uptake mechanism. Distribution determined in Bcrp1(−/−) mice and wild-type mice revealed that there was 1.8-fold higher plasma and liver concentrations of labelled riboflavin in Bcrp1(−/−) mice than wild-type mice.
Metabolism occurs mainly in conjunction with endocrine glands. Hormones influence the metabolic utilisation of the vitamin, the magnitude of tissue concentrations, the rate of excretion in urine, and, in certain species, the transport of the vitamin in plasma. Disturbances in the metabolism of riboflavin have been seen to accompany endocrine disorders both in experimental animals and in man. Excretion is rapid via urine, followed on several hours later by faecal excretion. Alterations in various aspects of flavin metabolism have been observed following administration of certain drugs, namely, antimalarial, antimicrobial, anticancer, and some tricyclic antidepressant and antipsychotic agents.

III.4 Toxicology

The toxicology properties of nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine mononitrate are discussed in detail in the applicant’s non-clinical overview. The summaries of these findings are presented below.

Studies of nicotinamide in rats at lower doses have not showed toxic effects, except induction of components of hepatic microsomal mixed function oxidase systems. However repeated administrations of nicotinamide in male rats revealed the toxicity signs as reduced body weight and food consumption. As an adaptive response liver weight was elevated. The no-observed-adverse-effect-level (NOAEL) derived from this study is 215 mg/kg.

Nicotinamide is considered not mutagenic in bacterial strains. No chromosomal effects in mammalian cells were reported, and in an in vivo micronucleus test no clastogenic effects were seen. Lifetime administration to mice of nicotinamide and isonicotinamide as 1% solutions in drinking water showed that these chemicals did not increase carcinogenic potential.

In animal reproduction toxicity studies, nicotinamide has been shown to cause growth retardation, which may in part be due to reduced food and water intake, due to the palatability, and in part due to a deficiency in methionine, which is expended during the methylation of nicotinamide into its metabolites. There is no evidence to describe effects on fertility, and the effects on reproductive and developmental toxicity are based on decreased placental and pup body weight (males only). No teratogenic effects were observed.

Acute and sub-acute toxicity studies of pyridoxine hydrochloride in dogs suggested the development of ataxia, degenerative histologic lesions in trigeminal ganglia and associated structures. Chronic toxicity studies revealed the loss of axons and myelin.

The pyrolysate of pyridoxine hydrochloride does not show any mutagenicity in the histidine-requiring mutants Salmonella typhimurium TA98 and TA100. No carcinogenicity data has been retrieved.

High doses of pyridoxine (500 and 1000 mg/kg) in male rats for 2 weeks showed decreased weights of reproductive organs like the epididymis and reduced spermatid counts. Six weeks of administration resulted in a similar decrease in reproductive organs being observed. Pyridines have also been shown to cross the placental barrier in rats and cause premature delivery, miscarriages and stillbirths.

Acute toxicity of thiamine is very low and adverse effects were not reported even after administration of high doses. No repeat dose studies were available.

Thiamine hydrochloride has been shown to be non-mutagenic in a range of bacterial mutagenicity and in vitro chromosomal aberration tests. Prolonged dietary administration to rats at dosages of 1000 and 10,000 ppm confirm low toxicity of this compound and an absence of carcinogenicity.

It has been shown that excess exposure of thiamine to female rats fed a white flour casein diet,
simulating a low-quality human diet, had no effect on growth, but adversely affected reproduction, as evidenced by high mortality and poor growth of the young. Acute toxic effects of riboflavin are low and LD<sub>50</sub> after intraperitoneal administration was found to be 560 mg/kg and death occurs by obstruction of the kidney by concretions. No toxic manifestations resulted after repeated daily administrations of riboflavin in rats.

On exposure to visible light, riboflavin and lumiflavin produced reactive oxygen species such as singlet oxygen and superoxide radicals. As a result both riboflavin and lumiflavin, upon illumination, showed mutagenic response in the umu test as well as in the Ames/Salmonella assay with Salmonella typhimurium TA102. No mutagenicity was observed if the compounds were not illuminated. The results suggested the involvement of superoxide radicals in light-induced mutagenicity of riboflavin as well as lumiflavin. Riboflavin has not been shown to be carcinogenic in a 22 month oral study in rats.

No data has been identified on the reproductive toxicity of riboflavin in animals. It has been shown that deprivation of riboflavin at the end of the middle-third of pregnancy in inbred mice results in skeletal malformations, and defects of the esophagus and brain.

### III.5 Ecotoxicity/Environmental risk Assessment (ERA)
The Marketing Authorisation Holder has provided adequate justification for not submitting an ERA.

In accordance with the EU guideline (EMEA/CHMP/SWP/4447/00 corr 1), an ERA is not required for this product as the active substances are vitamins and are thus exempt. No change in the environmental risk assessment of Vitamin B Compound Strong Tablets (nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine mononitrate) is anticipated.

### III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Vitamin B Compound Strong Tablets.

### IV. CLINICAL ASPECTS

#### IV.1 Introduction
No new clinical data have been submitted and none are required for an application of this type. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of the active substances. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

#### IV.2 Pharmacokinetics
Nicotinamide is readily absorbed from the gastrointestinal tract following oral administration and is widely distributed in the body tissues. Small amounts of nicotinamide are excreted unchanged in urine following therapeutic doses, however, the amount excreted unchanged is increased with larger doses.

Pyridoxine is absorbed from the gastrointestinal tract and is converted to the active form pyridoxal phosphate. It is excreted in the urine as 4-pyridoxic acid.

Riboflavin is absorbed from the gastrointestinal tract and in the circulation is bound to plasma proteins. Although widely distributed, little is stored in the body, and amounts in excess of requirements are excreted in the urine.

Thiamine is absorbed from the gastrointestinal tract and is widely distributed to most body tissues. It is not stored to any appreciable extent in the body and amounts in excess of requirements are excreted in the urine as unchanged thiamine or metabolites.
IV.3 Pharmacodynamics
B vitamins are a group of water-soluble vitamins that play important roles in cell metabolism. The B vitamins maintain and increase the metabolic rate, preserve muscle tone, guarantee the good condition of the skin, improve the functions of the nervous and immune system and promote growth and cell division.

IV.4 Clinical efficacy

Nicotinamide
Studies on efficacy of nicotinamide on incidence of cardiovascular risks demonstrated that it reduces the composite endpoint of cardiovascular disease events. No association was found on the incidences of stroke. Nicotinamide plays an integral role in reducing the risk of gastrointestinal cancers in certain populations. It has shown efficacy in preventing UV induced immunosuppression in humans. A lack of cellular NAD content may increase genomic instability. Hence supplementation with nicotinamide may show a preventive role in cancer. Also in combination with coenzyme 10 and riboflavin, nicotinamide is effective in treatment of breast cancer when used along with tamoxifen.

Pyridoxine hydrochloride
As shown by several studies, there is a relationship between arterial blood pressure and pyridoxine status. Pyridoxine supplementation resulted in reduction of both systolic and diastolic blood pressure in hypertensive subjects, probably by correcting membrane abnormality and calcium channel blocking action. Hypercholesterolemia plays a pathological role in glucose intolerance in diabetics. Supplementation with pyridoxine is found to be effective in reducing serum cholesterol levels in diabetics. Also pyridoxine in combination with leucine elevated insulin sensitivity and oxidation of fat in obese subjects.

Thiamine mononitrate
Thiamine is an essential cofactor in carbohydrate metabolism. Thiamine supplementation is positively associated with metabolic diseases including diabetes. Thiamine is found efficacious in the reduction of glucose levels in Type 2 diabetic patients and hence may be a useful adjunct therapy in treating diabetes. Thiamine can reduce harmful by-products of glucose metabolism and also oxidative stress, as well as cardiovascular risks. Arterial smooth muscle cells are involved in the development of atherosclerosis, particularly in diabetic patients. Thiamine supplementation inhibits arterial smooth muscle cell proliferation and hence is beneficial in preventing atherosclerosis in diabetic patients.

Riboflavin
Riboflavin deficiency could significantly affect oxidative folding, cell damage and heme biosynthesis. Hence riboflavin supplementation could reverse these conditions effectively. Riboflavin intake is positively associated with anaemia hence deficiency will result in anaemia. Riboflavin is also essential for normal erythropoiesis hence riboflavin supplement can enhance erythropoiesis and is effective in sickle cell disease.

IV.5 Clinical Safety
B vitamins are water soluble and so adverse effects are usually observed only when consumed in excess. The literature review showed that adverse effects are reported only when associated with administration of high doses.

Nicotinamide
No adverse effects were observed when nicotinamide was administered at a dose of 3000 mg per day in Type 1 diabetic patients. In another single blinded study, where a 1000 mg dose was administered for 45 days, no adverse effects were observed. In another other study the range of adverse effects observed were headaches, heartburn, nausea, gastrointestinal disturbances and fatigue at a dose of 3000 mg/day.
for 3–36 months. Adverse effects such as flushing and gastrointestinal effects were observed at and above the dose of 50 mg/day. Also serum phosphorus levels were decreased in heart disease patients and nicotinamide abates triglycerides and elevates HDL.

Doses of up to 2000 mg/day of nicotinic acid have reportedly been administered during pregnancy to niacin deficient women in developing countries, without evidence of foetal toxicity.

**Pyridoxine hydrochloride**

Doses of pyridoxine above 500 mg/day for prolonged period may result in sensory nerve damage and doses below this are considered safe. However some data suggest that doses greater than 200 mg/day for prolonged periods may result in low serum folic acid levels, and doses above 2000 mg/day may result in nerve damage with symptoms of tingling in hands and feet, stumbling gait, perioral numbness, as well as lack of muscular coordination. However such reactions are reversible after discontinuation of therapy. Commonly observed adverse effects were indigestion and nausea. Pyridoxine supplementation causes slight elevation in urinary calcium, phosphate, magnesium, sodium, potassium and uric acid levels.

In an open study, 16 patients received 150 mg daily for 6 months for the treatment of diabetic neuropathy. It was reported that one patient developed increased photosensitivity with increased tanning on minimal exposure to sunlight, but this subject elected to remain in the study. The patients underwent a monthly clinical evaluation by a neurologist, including a detailed electrophysiological study of motor and sensory nerves. No deterioration of peripheral nerve function was observed, though examinations were completed after only 4 months of supplementation in 10 subjects and after 5 months in 5 subjects. The limitations of this study are the short duration of treatment, the small number of patients studied and the incomplete follow-up of symptoms.

**Thiamine mononitrate**

Thiamine is generally considered safe after administration. Most of the adverse effects were observed after parenteral administration. However excess oral dose of thiamine may result in headache, insomnia, irritability, rapid pulse as well as weakness which are reversible after cessation of treatment. A few case reports have suggested adverse effects from lower doses, for example a woman experienced rapid pulse and nervous irritability after daily doses of thiamine. In some individuals prolonged doses of pyridoxine may result in anaphylactic reactions which may prove fatal. Eczema may also result at a daily dose of 200 mg. Thiamine toxicity resulted in a 47 year old woman who ingested considerably large doses (10,000 mg daily for 2 ½ weeks). Overdose symptoms include headache, irritability, insomnia, rapid pulse, weakness and trembling.

The oral toxicity of thiamine and thiamine derivatives in humans is generally considered very low. High oral doses of thiamine hydrochloride (≥ 7000 mg) may cause headache, nausea, irritability, insomnia, rapid pulse and weakness. These symptoms are relieved following cessation of treatment or reduction of dose.

A feeling of warmth, pruritus, urticaria, weakness, sweating, nausea, restlessness, tightness of the throat, angioneurotic oedema, cyanosis, pulmonary oedema, haemorrhage into the gastrointestinal tract, collapse and death have been rarely reported, mainly following repeated I.V. administration.

**Riboflavin**

Toxic or adverse effects with riboflavin are relatively low. At high doses yellow discoloration of urine was observed. It is considered to be safe up to 400 mg/day for at least 3 months. At 400 mg/day few non-specific adverse effects were reported which cannot be directly attributed to the treatment. However anaphylaxis may result and hence caution is advised in this regard.
IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The applicant has submitted a risk management plan (RMP), 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 Vitamin B Compound Strong Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>SmPC includes: Contraindication in section 4.3 for patients with known hypersensitivity to any of the active constituents.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patient with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption</td>
<td>SmPC includes: Warning in section 4.4 with information that Vitamin B Compound Strong Tablets contains lactose monohydrate and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.</td>
<td>None</td>
</tr>
<tr>
<td>Use in lactation</td>
<td>SmPC includes: Fertility, pregnancy and lactation in section 4.6 where Vitamin B Compound Strong Tablets should only be used with caution in nursing mothers because in high doses, pyridoxine may interfere with prolactin release.</td>
<td>None</td>
</tr>
</tbody>
</table>

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Vitamin B Compound Strong Tablets.

V. USER CONSULTATION
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATIONS
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine mononitrate is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk assessment is therefore considered to be positive.
Annex 1  Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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</thead>
<tbody>
<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Y/N (version)</td>
</tr>
</tbody>
</table>