BENERVA 50MG TABLETS
PL 00010/0610

BENERVA 100MG TABLETS
PL 00010/0611

UKPAR

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BENERVA 50MG TABLETS
PL 00010/0610

BENERVA 100MG TABLETS
PL 00010/0611

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Bayer plc Marketing Authorisations (licences) for the medicinal products Benerva 50mg Tablets (PL 00010/0610) and Benerva 100mg Tablets (PL 00010/0611). These are pharmacy-only medicines (P) used to treat thiamine deficiency.

Benerva Tablets contains the active ingredient thiamine hydrochloride (vitamin B_1). Thiamine is found naturally in many foods (especially in yeast, wholegrain cereals, meats and beans), however sometimes the body requires it as a supplement. This may be because there are insufficient amounts in the diet or an inability to absorb thiamine from the diet.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Benerva 50mg and 100mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

BENERVA 50MG TABLETS
PL 00010/0610

BENERVA 100MG TABLETS
PL 00010/0611

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Benerva 50mg Tablets (PL 00010/0610) and Benerva 100mg Tablets (PL 00010/0611) on 13th August 2008. The products are pharmacy-only medicines.

These are two strengths of Benerva, submitted as abridged applications according to Article 10(a) of Directive 2001/83/EC as amended, claiming a well established use application to the 300mg presentation which is already licensed in the UK (PL 00010/0312).

Thiamine Hydrochloride, also known as vitamin B_1, is a water-soluble B-complex vitamin. It is an essential nutrient and an important component of all cells. The active form of thiamine, thiamine pyrophosphate, is required for the synthesis of neurotransmitters and pentose sugars, the generation of factors which protect against cell damage due to reactive oxygen species, and is key in cellular energy production via the Krebs cycle.

The use of thiamine supplements to prevent and treat thiamine deficiency is well established. In the UK, all white and brown flour is fortified with thiamine (0.24mg/100g) to reduce thiamine deficiency in the community. The initiative to start flour fortification with thiamine began in the 1940s and the Bread and Flour Regulations 1998 made it mandatory (FSA, 2003). In addition, the use of oral thiamine is also well-established practice in the UK, both as a medicine and food supplement, as demonstrated by products in the market place.

Thiamine is a B vitamin indicated for populations in whom thiamine deficiency is a risk. This includes: regular heavy drinkers/chronic alcoholics; those with a high carbohydrate intake (relative to other calorie intake); those who undertake heavy physical exertion; those with a compromised nutritional status; patients receiving high dose diuretics; and diabetics

These applications were submitted at the same time and consequently, all sections of this Scientific Discussion refer to both 50mg and 100mg products.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Thiamine Hydrochloride

Nomenclature

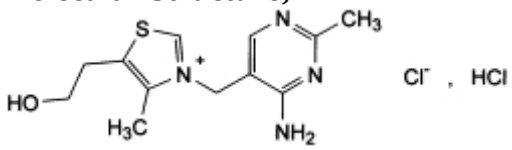
INN: Thiamine Hydrochloride

Chemical Name:

3-[(4-Amino-2-methylpyrimidin-5-yl]-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochloride.

Structure

Molecular Structure;



MW: 337.3

CAS Number: 67-03-8

Molecular Formula: $C_{12}H_{18}Cl_2N_4OS$

3.1.3. General Properties

White or almost white, crystalline powder or colourless crystals freely soluble in water, soluble in glycerol and slightly soluble in alcohol.

All aspects of the manufacture, in-process controls, validation and active substance specification are covered by a certificate of suitability for the active substance manufacturer.

An appropriate specification is provided for the active substance thiamine hydrochloride.

Batches of the active substance are stored in laminated pouches from outside to inside: polyethylene terephthalate (PET)-Aluminium-low density polyethylene (LDPE). The secondary packaging used consists of corrugated cardboard boxes. Suitable specifications have been provided for all packaging and primary packaging has been shown to be suitable for contact with food.

Batch analysis data are provided and comply with the proposed specification. Certificates of analysis have been provided for any working standards used.

Suitable stability data have been generated supporting a retest period of 36 months at 25^{o}C when stored in unopened containers.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, sucrose, pre-gelatinised maize starch, maize starch, purified talc and magnesium stearate. All excipients used comply with their respective Ph.Eur monograph.

Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all excipients.
With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Dissolution profiles

Dissolution profiles for both strengths of drug product were provided. The Benerva 100mg Tablets were compared to the relevant 100mg Food Supplement, demonstrating that both products comply with Ph.Eur monograph for dissolution of immediate release tablets. The Benerva 50mg Tablets were also tested for compliance with the Ph. Eur. monograph and were found to comply. In addition to comparative studies with food supplement tablets, the proposed products were tested across a range of physiological pHs to demonstrate rapid and similar dissolution profiles between the proposed 50mg and 100mg tablets.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on three full scale batches of each tablet strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in high density polyethylene (HDPE) bottle with a child-proof closure. Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 100 tablets.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are “Store below 25 degrees” and “Store in original package”.

Summary of Product Characteristics
This is acceptable.

Patient Information Leaflet
A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. 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 it contains.

Label
This is acceptable.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1.1 CLINICAL BACKGROUND

Thiamine Hydrochloride, also known as vitamin B1, is a water-soluble B-complex vitamin. It is an essential nutrient and an important component of all cells. The active form of thiamine, thiamine pyrophosphate, is required for the synthesis of neurotransmitters and pentose sugars, the generation of factors which protect against cell damage due to reactive oxygen species, and is key in cellular energy production via the Krebs cycle.

The use of thiamine supplements to prevent and treat thiamine deficiency is well established. In the UK, all white and brown flour is fortified with thiamine (0.24mg/100g) to reduce thiamine deficiency in the community. The initiative to start flour fortification with thiamine began in the 1940s and the Bread and Flour Regulations 1998 made it mandatory (FSA, 2003). In addition, the use of oral thiamine is also well-established practice in the UK, both as a medicine and food supplement, as demonstrated by products in the market place.

With regards to the current application, it is worth noting that the applicant already has 55mg and 110mg tablet preparations which are marketed under GSL as UK food supplements.

1.2 INDICATIONS

Benerva 50mg and 100mg Tablets are indicated for the treatment of thiamine deficiencies due to increased dietary requirements, reduced intakes, reduced absorption or increased excretion. Also for treatment of Wernicke-Korsakoff syndrome, Beriberi and thiamine deficiency related to chronic alcoholism.

Situations often accompanied by marginal thiamine deficiency and requiring supplementation include but are not limited to:

- Regular heavy drinking / chronic alcohol consumption
- High carbohydrate intakes
- Heavy physical exertion
- Compromised nutritional status
- High dose diuretics
- Type I and Type II diabetes mellitus

Assessor's comments: These indications are appropriate.

1.3 DOSE AND DOSE REGIMEN

50mg to 100mg per day for mild deficiency,
200mg to 300mg per day for severe deficiency.

Assessor's comments: The dosing regimens are satisfactory.

1.4 GCP ASPECTS

Not applicable.

1.5 ORPHAN MEDICINAL PRODUCTS

Not applicable

1.6 PAEDIATRIC DEVELOPMENT PROGRAMME

The applicant has stated that Benerva 50mg and 100mg Tablets are not suitable for children under the age of twelve. There are no plans to conduct paediatric studies.

1.7 SCIENTIFIC ADVICE

None sought or given.

1.8 LEGAL STATUS

The applicant proposes that Benerva 50mg and 100mg Tablets be classified as Pharmacy Sale (P).

Assessor's comments: This is satisfactory.

2 CLINICAL PHARMACOLOGY

Since this application is being made under Article 10a of Directive 2001/83/EC, and due to the fact that the clinical pharmacology is extensively and comprehensively detailed in the literature, no new pharmacokinetic or pharmacodynamic studies have been performed by the applicant.

2.1 PHARMACOKINETICS

2.1.1 Introduction and overview

Ingested thiamine is fairly well absorbed, rapidly converted to phosphorylated forms, and excreted in the urine in a variety of hydrolyzed and oxidized products. It is poorly stored in the body and excess amounts to the body's requirements are excreted.

2.2 BIOEQUIVALENCE

No bioequivalence study data have been submitted. The applicant has provided a suitable justification for the exemption of the bioequivalence study.

2.3 PHARMACODYNAMICS

The functions of thiamine can be categorised into established and plausible functions. The established functions of thiamine are biochemical functions of which thiamine pyrophosphate serves as the coenzyme of biochemical reactions, whereas the plausible functions are neurophysiological functions.

Thiamine is practically devoid of discernable pharmacodynamic actions when given in the usual therapeutic doses.

3 CLINICAL SAFETY

3.1 INTRODUCTION

The applicant has provided adequate literature reviews regarding the safety of thiamine. No new safety issues have been identified.

4 EXPERT REPORTS

The clinical overview has been written by an appropriately qualified person. The report refers to 47 publications up to year 2007.

5 OVERALL CONCLUSION

Vitamin preparations, including thiamine, have been available in the UK for many years. Their use is well established. Thiamine has recognised efficacy and acceptable safety. When used as indicated, thiamine has a favourable benefit to risk ratio.

6 PRODUCT LITERATURE

6.1 SPC

Assessors' comment: The proposed SmPC for these products are considered satisfactory.

6.2 PATIENT INFORMATION LEAFLET

Assessors' comment: The proposed Patient Information Leaflets for these products are considered satisfactory.

6.3 LABEL

The labelling text is medically satisfactory, including full colour mock-ups.

6.4 APPLICATION FORM

The application form is medically acceptable.

7 OVERALL CONCLUSION

7.1 PHARMACOKINETICS

The applicant believes it is appropriate to maintain the indication of treatment of severe thiamine deficiency for the lower tablet strengths as a split dose approach to the treatment of severe deficiency. 100mg two or three times a day is a recommended posology and is currently in use within the NHS for the treatment of alcoholics with thiamine deficiency and the maximum total dosage (300mg) is currently approved for the indication of thiamine deficiency for Benerva Tablets 300mg.

The applicant has demonstrated that Benerva follows linear kinetics between 50mg and 200mg. As the applicant is specifying a therapeutic dose of up to 300mg doses that are of 200mg or greater are divided i.e a split-dose regimen; this means that any individual dose falls within the therapeutic range for which linear kinetics has been demonstrated.

7.2 PHARMACODYNAMICS

The functions of thiamine can be categorised into established and plausible functions. The established functions of thiamine are biochemical functions of which TPP serves as the coenzyme of biochemical reactions, whereas the plausible functions are neurophysiological functions.

The literature submitted is adequate to support the application. There are no objections from the medical point of view.

7.3 EFFICACY

In line with clinical guidance given by the Royal College of Physicians, Scottish Intercollegiate Guidelines Network, National Treatment Agency for Substance Misuse and Clinical Knowledge Summaries, a posology of 50mg to 100mg per day is proposed for the treatment of mild thiamine deficiency on the basis that it exceeds the minimum requirement (10mg to 25mg) and has a safety profile which allows safe chronic use at the proposed levels.

The literature presented to support the application is sufficient.

7.4 SAFETY

The safety profile of Benerva 300mg Tablets is a well-established since being first granted in 4 August 1989. The new formulations, Benerva 50mg Tablets and Benerva 100mg Tablets, is considered safe for use when used for the

proposed indication and according to the advice and information in the product literature.

7.5 RISK BENEFIT

At present, the risk benefit for both Benerva 50mg and 100mg Tablets is considered to be positive.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Benerva 50mg and 100mg 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.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Thiamine hydrochloride is a well known dietary supplement and has been used to treat thiamine/vitamin B1 deficiency for many years. Linear kinetics apply between the 50mg and 100mg tablets; proportional formulae for the tablets have been used and similar dissolution results have been shown for the two strengths.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with thiamine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

BENERVA 50MG TABLETS
PL 00010/0610

BENERVA 100MG TABLETS
PL 00010/0611

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 23rd November 2007.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 10th January 2008.
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 11th February 2008 and 2nd June 2008 and further information relating to the quality dossiers on 3rd March 2008.
4	The applicant responded to the MHRA's requests, providing further information on 23rd May 2008 and 12th June 2008 for the clinical sections, and again on 5th June 2008 for the quality sections.
5	The applications were determined on 13th August 2008.

BENERVA 50MG TABLETS
PL 00010/0610

BENERVA 100MG TABLETS
PL 00010/0611

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Benerva 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Benerva 50mg Tablets are a thiamine (vitamin B1)-containing monovitamin product.

Each tablet contains thiamine hydrochloride, 50mg.

This product contains lactose and sucrose, see section 4.4.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Round, white or almost white, biplanar tablets with bevelled edges embossed '50 Benerva' on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of thiamine deficiencies due to increased dietary requirements, reduced intakes, reduced absorption or increased excretion. Also for treatment of Wernicke-Korsakoff syndrome, Beriberi and thiamine deficiency related to chronic alcoholism.

Situations often accompanied by marginal thiamine deficiency and requiring supplementation include but are not limited to:

- Regular heavy drinking / chronic alcohol consumption
- High carbohydrate intakes
- Heavy physical exertion
- Compromised nutritional status
- High dose diuretics
- Type I and Type II diabetes mellitus

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Treatment:

Adults and adolescents from 12 years of age:

Mild deficiency: 50-100mg per day

Severe deficiency: 200-300mg per day in divided doses

Not recommended for children under 12 years.

Route of Administration

Oral

4.3 CONTRAINDICATIONS

Known allergy or hypersensitivity to thiamine or to any of the excipients in Benerva 50mg Tablets (see section 6.1).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The thiamine antagonists thiosemicarbazone and 5-fluorouracil can neutralise the effect of thiamine. Patients using any of these treatments may need their thiamine dose adjusted.

Thiamine could give false positive results for urobilinogen determination by the Ehrlich's reaction. High doses of thiamine may interfere with spectrophotometric assays of theophylline plasma concentration.

4.6 PREGNANCY AND LACTATION

This product is not intended for use in pregnant or lactating women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effect on the ability to drive and use machines have been performed. However, patients should be cautioned to see how they react before driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

Gastrointestinal disorders:

Mild gastrointestinal events such as nausea, vomiting, diarrhoea, and abdominal pain have been reported. Frequency not known (cannot be estimated from data).

Immune system disorders:

Allergic and anaphylactic reactions, with symptoms of pruritus, urticaria, itching, hives, angioedema, abdominal pain, respiratory distress, tachycardia, palpitations, and shock have been reported in single cases. Frequency not known (cannot be estimated from data).

4.9 OVERDOSE

Overdose with this route of administration is unlikely. A suspected overdose should be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Vitamin B1, Plain

ATC code: A11DA01.

Thiamine pyrophosphate (TPP), the coenzymatic form of thiamine, is involved in two main types of metabolic reactions: decarboxylation of α-ketoacids (e.g. pyruvate, α-ketoglutarate and branched-chain keto acids) and transketolation (e.g. among hexose and pentose phosphates). Therefore, the principal physiological role of thiamine is as a co-enzyme in carbohydrate metabolism, where TPP is required for several stages in the breakdown of glucose to provide energy.

Apart from its metabolic role as a coenzyme, thiamine plays a role in neurotransmitter function and in nerve conduction.

In high doses, thiamine suppresses the transmission of neural stimuli and thus can have an analgesic effect.

Early stages of thiamine deficiency may be accompanied by non-specific symptoms that may be overlooked or easily misinterpreted. The clinical signs of deficiency include anorexia; weight loss; mental changes such as apathy, decrease in short-term memory, confusion and irritability; muscle weakness; and cardiovascular effects such as an enlarged heart.

Cardiac failure, muscle weakness, peripheral and central neuropathy are functional consequences of severe thiamine deficiency. Clinical manifestations of beriberi (severe thiamine deficiency) vary with age. Adults may present with dry (paralytic or nervous), wet (cardiac), or cerebral (Wernicke-Korsakoff syndrome) forms of beriberi.

5.2 PHARMACOKINETIC PROPERTIES

Absorption: Thiamine is rapidly absorbed in humans, largely in the proximal small intestine. There are two mechanisms, one by a carrier mediated transport at low physiological concentrations (<2μM), one by passive diffusion at higher concentrations. Absorption is typically high, but intestinal absorption in humans is rate limiting.

Distribution: The average total amount of thiamine in an adult is approximately 30mg. In general the heart has the highest concentration (0.28-0.79mg per 100g), followed by kidney (0.24-0.58mg per 100g), liver (0.20-0.76mg per 100g), and brain (0.14-0.44mg per 100g). In the spinal cord and the brain, the thiamine level is about double that of peripheral nerves. The whole-blood thiamine content varies from 5 to 12μg per 100 ml, 90% of which is in the red cells and leukocytes. Leukocytes have a 10 fold higher concentration than red cells. Thiamine has a high turnover rate in the body and is not stored in large amounts for any period of time in any tissue. When intake is about 60μg per 100g body weight (or 42mg per 70kg) and the total body thiamine reaches 2μg/g (or 140mg per 70kg), a plateau is reached in most tissues.

Thiamine transport across the blood-brain barrier involves two different mechanisms. The saturable mechanism at the blood-brain barrier, however, differs from the energy-dependent mechanism described in the gut, and from the active transport system described in cerebral cortex cells, which may be dependent upon membrane-bound phosphatases.

The immunohistochemical distribution of TTP (thiamine triphosphate) suggests that it has a role in nerve conduction .

Metabolism: Thiamine is quickly converted to the diphosphate and to a smaller extent the triphosphate esters in the tissues. All thiamine in excess of tissue needs, as well as binding and storage capacity, is rapidly excreted in the urine in the free form. Stimulation of nerves causes the release of thiamine or the monophosphate with a concomitant decrease in the tri- and diphosphates.

Excretion: Thiamine is excreted in the urine. The half-life of thiamine in the body is 10-20 days. In addition to free thiamine and a small amount of thiamine diphosphate, thiochrome, and thiamine disulfide, about 20 metabolites of thiamine have been reported in the urine of rats and humans but only six have been conclusively identified. The relative proportion of metabolites to thiamine excreted increases with decreasing thiamine intake.

5.3 PRECLINICAL SAFETY DATA

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose Monohydrate
Sucrose
Pregelatinised Maize Starch
Maize Starch

Purified Talc
Magnesium Stearate

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.

Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
100 tablets in an HDPE bottle with a child resistant closure, composed of HDPE outer cap and polypropylene inner material with a fibreboard/aluminium induction heat seal liner over the mouth of the bottle, packaged in a carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Bayer plc
Bayer House
Strawberry Hill
Newbury, Berkshire
RG14 1JA
Trading as Bayer plc, Consumer Care Division

8 MARKETING AUTHORISATION NUMBER(S)
PL 00010/0610

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/08/2008

10 DATE OF REVISION OF THE TEXT
13/08/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Benerva 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Benerva 100mg Tablets are a thiamine (vitamin B1)-containing monovitamin product.

Each tablet contains thiamine hydrochloride, 100mg.

This product contains lactose and sucrose, see section 4.4.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Round, white or almost white, biplanar tablets with bevelled edges embossed '100 Benerva' on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of thiamine deficiencies due to increased dietary requirements, reduced intakes, reduced absorption or increased excretion. Also for treatment of Wernicke-Korsakoff syndrome, Beriberi and thiamine deficiency related to chronic alcoholism.

Situations often accompanied by marginal thiamine deficiency and requiring supplementation include but are not limited to:

- Regular heavy drinking / chronic alcohol consumption
- High carbohydrate intakes
- Heavy physical exertion
- Compromised nutritional status
- High dose diuretics
- Type I and Type II diabetes mellitus

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Treatment:

Adults and adolescents from 12 years of age:

Mild deficiency: 50-100mg per day

Severe deficiency: 200-300mg per day in divided doses

Not recommended for children under 12 years.

Route of Administration

Oral

4.3 CONTRAINDICATIONS

Known allergy or hypersensitivity to thiamine or to any of the excipients in Benerva 100mg Tablets (see section 6.1).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The thiamine antagonists thiosemicarbazone and 5-fluorouracil can neutralise the effect of thiamine. Patients using any of these treatments may need their thiamine dose adjusted.

Thiamine could give false positive results for urobilinogen determination by the Ehrlich's reaction. High doses of thiamine may interfere with spectrophotometric assays of theophylline plasma concentration.

4.6 PREGNANCY AND LACTATION

This product is not intended for use in pregnant or lactating women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effect on the ability to drive and use machines have been performed. However, patients should be cautioned to see how they react before driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

Gastrointestinal disorders:

Mild gastrointestinal events such as nausea, vomiting, diarrhoea, and abdominal pain have been reported. Frequency not known (cannot be estimated from data).

Immune system disorders:

Allergic and anaphylactic reactions, with symptoms of pruritus, urticaria, itching, hives, angioedema, abdominal pain, respiratory distress, tachycardia, palpitations, and shock have been reported in single cases. Frequency not known (cannot be estimated from data).

4.9 OVERDOSE

Overdose with this route of administration is unlikely. A suspected overdose should be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Vitamin B1, Plain

ATC code: A11DA01.

Thiamine pyrophosphate (TPP), the coenzymatic form of thiamine, is involved in two main types of metabolic reactions: decarboxylation of α-ketoacids (e.g. pyruvate, α-ketoglutarate and branched-chain keto acids) and transketolation (e.g. among hexose and pentose phosphates). Therefore, the principal physiological role of thiamine is as a co-enzyme in carbohydrate metabolism, where TPP is required for several stages in the breakdown of glucose to provide energy.

Apart from its metabolic role as a coenzyme, thiamine plays a role in neurotransmitter function and in nerve conduction.

In high doses, thiamine suppresses the transmission of neural stimuli and thus can have an analgesic effect.

Early stages of thiamine deficiency may be accompanied by non-specific symptoms that may be overlooked or easily misinterpreted. The clinical signs of deficiency include anorexia; weight loss; mental changes such as apathy, decrease in short-term memory, confusion and irritability; muscle weakness; and cardiovascular effects such as an enlarged heart.

Cardiac failure, muscle weakness, peripheral and central neuropathy are functional consequences of severe thiamine deficiency. Clinical manifestations of beriberi (severe thiamine deficiency) vary with age. Adults may present with dry (paralytic or nervous), wet (cardiac), or cerebral (Wernicke-Korsakoff syndrome) forms of beriberi.

5.2 PHARMACOKINETIC PROPERTIES

Absorption: Thiamine is rapidly absorbed in humans, largely in the proximal small intestine. There are two mechanisms, one by a carrier mediated transport at low physiological concentrations (<2μM), one by passive diffusion at higher concentrations. Absorption is typically high, but intestinal absorption in humans is rate limiting.

Distribution: The average total amount of thiamine in an adult is approximately 30mg. In general the heart has the highest concentration (0.28-0.79mg per 100g), followed by kidney (0.24-0.58mg per 100g), liver (0.20-0.76mg per 100g), and brain (0.14-0.44mg per 100g). In the spinal cord and the brain, the thiamine level is about double that of peripheral nerves. The whole-blood thiamine content varies from 5 to 12μg per 100 ml, 90% of which is in the red cells and leukocytes. Leukocytes have a 10 fold higher concentration than red cells. Thiamine has a high turnover rate in the body and is not stored in large amounts for any period of time in any tissue. When intake is about 60μg per 100g body weight (or 42mg per 70kg) and the total body thiamine reaches 2μg/g (or 140mg per 70kg), a plateau is reached in most tissues.

Thiamine transport across the blood-brain barrier involves two different mechanisms. The saturable mechanism at the blood-brain barrier, however, differs from the energy-dependent mechanism described in the gut, and from the active transport system described in cerebral cortex cells, which may be dependent upon membrane-bound phosphatases.

The immunohistochemical distribution of TTP (thiamine triphosphate) suggests that it has a role in nerve conduction .

Metabolism: Thiamine is quickly converted to the diphosphate and to a smaller extent the triphosphate esters in the tissues. All thiamine in excess of tissue needs, as well as binding and storage capacity, is rapidly excreted in the urine in the free form. Stimulation of nerves causes the release of thiamine or the monophosphate with a concomitant decrease in the tri- and diphosphates.

Excretion: Thiamine is excreted in the urine. The half-life of thiamine in the body is 10-20 days. In addition to free thiamine and a small amount of thiamine diphosphate, thiochrome, and thiamine disulfide, about 20 metabolites of thiamine have been reported in the urine of rats and humans but only six have been conclusively identified. The relative proportion of metabolites to thiamine excreted increases with decreasing thiamine intake.

5.3 PRECLINICAL SAFETY DATA

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose Monohydrate
Sucrose
Pregelatinised Maize Starch
Maize Starch
Purified Talc
Magnesium Stearate

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.

Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
100 tablets in an HDPE bottle with a child resistant closure, composed of HDPE outer cap and polypropylene inner material with a fibreboard/aluminium induction heat seal liner over the mouth of the bottle, packaged in a carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Bayer plc
Bayer House
Strawberry Hill
Newbury, Berkshire
RG14 1JA
Trading as Bayer plc, Consumer Care Division

8 MARKETING AUTHORISATION NUMBER(S)
PL 00010/611

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/08/2008

10 DATE OF REVISION OF THE TEXT
13/08/2008

PATIENT INFORMATION LEAFLET

Benerva®

50mg tablets

Thiamine Hydrochloride 50mg

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to take Benerva 50mg tablets carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve.
- If you have any unusual effects after using this product, tell your doctor or pharmacist.

IN THIS LEAFLET

1. WHAT ARE BENERVA® 50mg TABLETS AND WHAT ARE THEY USED FOR?

Benerva 50mg tablets are vitamin tablets which contain thiamine (vitamin B_1). They are used to treat thiamine deficiency (when your body does not have enough of the vitamin).

Even though thiamine is found naturally in many foods (especially in yeast, wholegrain cereals, meats and beans), sometimes your body requires a supplement. This may be because your diet does not contain enough thiamine or you may not be absorbing it from your diet effectively. You may also have a special need for extra thiamine, especially if you are excreting it quickly from your body (e.g. in your urine).

By taking Benerva 50mg tablets, you can make sure you have sufficient thiamine in your diet.

2. BEFORE YOU TAKE BENERVA® 50mg TABLETS

DO NOT take Benerva 50mg tablets if you are:

- Allergic (hypersensitive) to thiamine or any of the other ingredients in the product (*see section 6, Further Information*).
- Under 12 years of age.

Important information about some of the ingredients:
These tablets contain lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, speak to your doctor before taking this medicine.

Taking other medicines:
Tell your doctor or pharmacist if you are taking any other medicines, including those obtained without a prescription, such as vitamins or herbal preparations which you have bought yourself.

Certain medicines can reduce the effect of your thiamine tablets.

Tell your doctor if you are taking the following medicine because he/she may need to adjust your thiamine dose:

- fluorouracil (used to treat certain cancers and viral infections).

Having blood tests or other medical tests:
High concentrations of thiamine in the blood can affect certain medical tests. If you are having a blood test, scan, or any other medical test, tell your doctor that you are taking thiamine tablets.

Driving and using machines:
This medicine is not known to affect the ability to drive or use machines. However, if you feel you may be affected, do not drive or use machines and speak to your doctor.

Pregnancy and breast-feeding:
Do not take Benerva 50mg tablets if you are pregnant or breast-feeding unless under the direction of your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

3. HOW TO TAKE BENERVA® 50mg TABLETS

This product may have been prescribed for you by your doctor. If so, follow his/her directions carefully.

The usual dosage recommendations are as follows.

Adults and children over 12 years of age:

The tablets should be swallowed with water. Do not chew the tablets.

Mild deficiency:	1–2 tablets once a day
Severe deficiency:	2 tablets 2–3 times a day

The tablets can be taken as long as symptoms persist or a dietary supplement is required, follow the recommendation of your doctor or pharmacist.

If your condition does not improve, tell your doctor.

Children under 12 years of age: Do not use.

If you take too many Benerva 50mg tablets:
This is unlikely to be harmful, but if you have taken too many tablets tell your doctor or pharmacist immediately or contact your nearest Emergency Department.

If you forget to take your tablet:
Take your dose as soon as you remember, then carry on taking your tablets as usual. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Benerva 50mg tablets can cause side effects, although not everybody gets them. Side effects are unlikely at the recommended doses.

Very few people may experience an **allergic reaction** after taking this medicine, symptoms of this could be:

- Rash or skin irritation;
- Swelling of face, lips, throat or tongue;
- Stomach pain;
- Difficulty in breathing or swallowing;
- Rapid pulse;
- Heart pain.

Some people may experience a **mild stomach upset** after taking this medicine, symptoms of this could be:

- Nausea;
- Vomiting;
- Stomach pain;
- Diarrhoea.

If you experience these or any other unusual side effect after taking these tablets you should seek the advice of a doctor or pharmacist.

5. HOW TO STORE BENERVA® 50mg TABLETS

Keep out of the reach and sight of children.

Store below 25°C. This product should be stored in its original carton.

Do not use Benerva 50mg tablets after the expiry date which is stated on the carton and on the bottle. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Benerva 50mg tablets contain:
The **active substance** is thiamine hydrochloride (50mg per tablet).

The **other ingredients** are lactose monohydrate, sucrose, pregelatinised maize starch, maize starch, purified talc and magnesium stearate.

See Section 2, 'Important information about some of the ingredients' for advice about lactose and sucrose.

What Benerva 50mg tablets look like and contents of the pack:
Benerva 50mg tablets are available in bottles containing 100 round white tablets marked with '50 Benerva' on one side.

Marketing Authorisation Holder:
Bayer plc
Consumer Care Division
Bayer House, Strawberry Hill
Newbury, Berkshire RG14 1JA
United Kingdom

Manufacturer:
Brunel Healthcare Manufacturing Ltd
William Nadin Way
Swadlincote
Derbyshire, DE11 0BB
United Kingdom

This leaflet was last approved in July 2008.

Remember: if you have any doubts about using Benerva 50mg tablets correctly, seek the advice of your doctor or pharmacist.

Bayer

Benerva is a Registered Trademark of Bayer AG, Germany.

Benerva®

100mg tablets

Thiamine Hydrochloride 100mg

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to take Benerva 100mg tablets carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve.
- If you have any unusual effects after using this product, tell your doctor or pharmacist.

IN THIS LEAFLET

1. WHAT ARE BENERVA® 100mg TABLETS AND WHAT ARE THEY USED FOR?

Benerva 100mg tablets are vitamin tablets which contain thiamine (vitamin B_1). They are used to treat thiamine deficiency (when your body does not have enough of the vitamin).

Even though thiamine is found naturally in many foods (especially in yeast, wholegrain cereals, meats and beans), sometimes your body requires a supplement. This may be because your diet does not contain enough thiamine or you may not be absorbing it from your diet effectively. You may also have a special need for extra thiamine, especially if you are excreting it quickly from your body (e.g. in your urine).

By taking Benerva 100mg tablets, you can make sure you have sufficient thiamine in your diet.

2. BEFORE YOU TAKE BENERVA® 100mg TABLETS

DO NOT take Benerva 100mg tablets if you are:

- Allergic (hypersensitive) to thiamine or any of the other ingredients in the product (*see section 6, Further Information*).
- Under 12 years of age.

Important information about some of the ingredients:

These tablets contain lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, speak to your doctor before taking this medicine.

Taking other medicines:
Tell your doctor or pharmacist if you are taking any other medicines, including those obtained without a prescription, such as vitamins or herbal preparations which you have bought yourself.

Certain medicines can reduce the effect of your thiamine tablets.

Tell your doctor if you are taking the following medicine because he/she may need to adjust your thiamine dose:

- fluorouracil (used to treat certain cancers and viral infections).

Having blood tests or other medical tests:
High concentrations of thiamine in the blood can affect certain medical tests. If you are having a blood test, scan, or any other medical test, tell your doctor that you are taking thiamine tablets.

Driving and using machines:
This medicine is not known to affect the ability to drive or use machines. However, if you feel you may be affected, do not drive or use machines and speak to your doctor.

Pregnancy and breast-feeding:
Do not take Benerva 100mg tablets if you are pregnant or breast-feeding unless under the direction of your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

3. HOW TO TAKE BENERVA® 100mg TABLETS

This product may have been prescribed for you by your doctor. If so, follow his/her directions carefully.

The usual dosage recommendations are as follows.

Adults and children over 12 years of age:

The tablets should be swallowed with water. Do not chew the tablets.

Mild deficiency:	1 tablet once a day
Severe deficiency:	1 tablet 2–3 times a day

The tablets can be taken as long as symptoms persist or a dietary supplement is required, follow the recommendation of your doctor or pharmacist.

If your condition does not improve, tell your doctor.

Children under 12 years of age: Do not use.

If you take too many Benerva 100mg tablets:
This is unlikely to be harmful, but if you have taken too many tablets tell your doctor or pharmacist immediately or contact your nearest Emergency Department.

If you forget to take your tablet:
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If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Benerva 100mg tablets can cause side effects, although not everybody gets them. Side effects are unlikely at the recommended doses.

Very few people may experience an **allergic reaction** after taking this medicine, symptoms of this could be:

- Rash or skin irritation;
- Swelling of face, lips, throat or tongue;
- Stomach pain;
- Difficulty in breathing or swallowing;
- Rapid pulse;
- Heart pain.

Some people may experience a **mild stomach upset** after taking this medicine, symptoms of this could be:

- Nausea;
- Vomiting;
- Stomach pain;
- Diarrhoea.

If you experience these or any other unusual side effect after taking these tablets you should seek the advice of a doctor or pharmacist.

5. HOW TO STORE BENERVA® 100mg TABLETS

Keep out of the reach and sight of children.

Store below 25°C. This product should be stored in its original carton.

Do not use Benerva 100mg tablets after the expiry date which is stated on the carton and on the bottle. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Benerva 100mg tablets contain:
The **active substance** is thiamine hydrochloride (100mg per tablet).

The **other ingredients** are lactose monohydrate, sucrose, pregelatinised maize starch, maize starch, purified talc and magnesium stearate.

See Section 2, 'Important information about some of the ingredients' for advice about lactose and sucrose.

What Benerva 100mg tablets look like and contents of the pack:
Benerva 100mg tablets are available in bottles containing 100 round white tablets marked with '100 Benerva' on one side.

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William Nadin Way
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Remember: if you have any doubts about using Benerva 100mg tablets correctly, seek the advice of your doctor or pharmacist.

Bayer

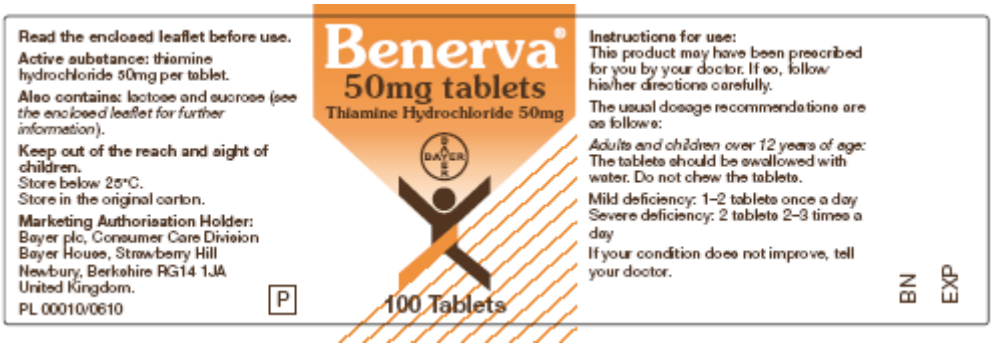
Benerva is a Registered Trademark of Bayer AG, Germany.

LABELLING

PL 00010/0610

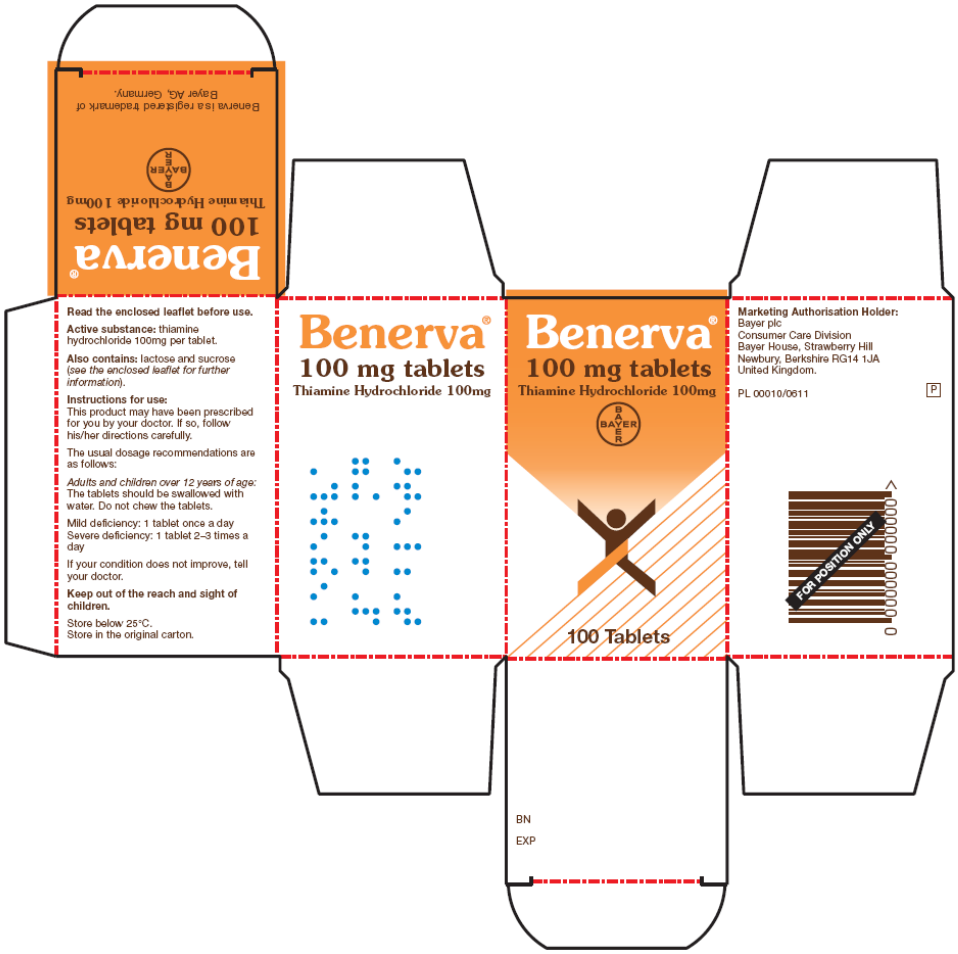
CARTON-
BENERVA 50MG TABLETS

LABEL-
BENERVA 50MG TABLETS



PL 00010/0611

CARTON-
BENERVA 100MG TABLETS



LABEL-
BENERVA 100MG TABLETS