

SmPC
BULTAMIN INJECTION

1. NAME OF THE MEDICINAL PRODUCT

BULTAMIN INJECTION [Vitamin B-Complex Injection]

2.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vitamin B1 (Thiamine Hydrochloride).....10mg
Vitamin B2 (Ribofavin Sodium Phosphate)...1.37mg
Vitamin B6 (Pyridoxine Hydrochloride).....1mg
Sodium-D-Pantothenate.....0.5mg

1ml of solution for injection contains:

50mg pyridoxine hydrochloride (vitamin B₆),
50mg thiamine hydrochloride (vitamin B₁),
0.5mg cyanocobalamin (vitamin B₁₂),
10mg lidocaine hydrochloride.

One ampoule (2ml) contains:

100mg pyridoxine hydrochloride (vitamin B₆),
100mg thiamine hydrochloride (vitamin B₁),
1mg cyanocobalamin (vitamin B₁₂),
20mg lidocaine hydrochloride.

Excipients with known effect:

Vitamin B1 (Thiamine Hydrochloride).....10mg
Vitamin B2 (Ribofavin Sodium Phosphate)...1.37mg
Vitamin B6 (Pyridoxine Hydrochloride).....1mg
Sodium-D-Pantothenate.....0.5mg

1. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear solution, free from visible particles. pH of solution is 4.4–4.8.

2. CLINICAL PARTICULARS

Therapeutic indications

Adults and children over 12 years

Treatment of haematologic and neurologic symptoms caused by continuous deficiency of vitamins B₁, B₆ and B₁₂.

Posology and method of administration

Posology

In case of severe and acute symptoms one injection (2ml) is usually administered once a day to achieve high levels of active substances in blood. When the acute phase has subsided and for less serious symptoms one injection is administered 2-3 times a week.

Solution for injection should not be administered to children under 12 years old.

Method of administration For intramuscular use.

Solution for injection is injected deeply into muscle tissue to avoid cardiovascular adverse effects.

Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.-
The use of the medicinal product is not recommended in case of severe cardiac conduction disorders and acute decompensated cardiac failure.
- Due to benzyl alcohol content the medicinal product must not be administered to new born babies, especially to premature new born babies.
- The medicinal product must not be used during pregnancy and breast-feeding.

Special warnings and precautions for use

Administration limits are 90mg and more benzyl alcohol per day: children under 3 years of age may develop toxic and anaphylactoid reactions.

Solution for injection

Should be injected only intramuscularly (i.m.), not intravenously (i.v.), to avoid cardiovascular adverse effects.

In case of inadvertent intravenous injection, the patient's heart activity should be monitored (ECG) or the patient should be hospitalized depending on the severity of cardiovascular symptoms (arrhythmias, bradycardia).

Interaction with other medicinal products and other forms of interaction

Thiamine is degraded by solutions containing sulphites. Other vitamins may be inactivated in the presence of vitamin B₁ degradation products. Therapeutic doses of vitamin B₆ may reduce the effect of L-dopa. Interactions occur with INH, D-penicillamine and cycloserine.

Cardiac adverse effects may increase when parenteral lidocaine is administered simultaneously with epinephrine or norepinephrine. Interactions also occur with sulphonamides.

In case of overdosage of local anaesthetics epinephrine or norepinephrine should not be used concomitantly.

Fertility, pregnancy and lactation

The safe daily dose of vitamin B₆ during pregnancy and breast-feeding is up to 25mg. As the vitamin B₆ content of this medicinal product is 100mg in one 2ml ampoule, it must not be used during pregnancy and breast-feeding.

Effects on ability to drive and use of machines

Has negligible influence on the ability to drive and use of machines.

Undesirable effects

Adverse reactions are presented according to the Med DRA system organ classes and on the basis of their frequency as follows:

Very common: $\geq 1/10$ ($\geq 10\%$)

Common: $\geq 1/100$ to $< 1/10$ ($\geq 1\%$ to $< 10\%$)

Uncommon: $\geq 1/1000$ to $< 1/100$ ($\geq 0.1\%$ to $< 1\%$) Rare:

$\geq 1/10000$ to $< 1/1000$ ($\geq 0.01\%$ to $< 0.1\%$)

Very rare: $< 1/10000$ ($< 0.01\%$), including isolated cases

Not known (cannot be estimated from the available data)

Immune system disorders:

Rare: hypersensitivity reactions (e.g. skin rash, respiratory inhibition, shock, angioedema).

Benzylalcohol: hypersensitivity reactions.

Nervous system disorders:

Not known: vertigo, clouding of consciousness.

Cardiac disorders: Very

rare: tachycardia.

Not known: bradycardia, arrhythmia.

Gastrointestinal disorders:

Not known: vomiting.

Skin and subcutaneous tissue disorders:

Very rare: severe sweating, acne, skin reactions with pruritus and urticaria.

Musculo-skeletal and connective tissue disorders:

Not known: seizures.

General disorders and administrations interactions:

Not known: systemic reactions, including central nervous system excitement and/or depression (balance disorder, nervousness, feeling of danger, euphoria, confusion, dizziness, clouding of consciousness, tinnitus, blurred or double vision, vomiting, feeling of cold or hot, numbness), may occur as a result of rapid injection (inadvertent intravenous injection, injection into tissues with good blood supply) or overdose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Overdose

The toxicity of thiamine, pyridoxine or cyanocobalamin maybe rated as very low. Development of more serious adverse effects caused by overdose may be expected only if about 1g of these substances is administered. Reactions caused by lidocaine overdose (highplasma level) are systemic and involve central nervous system and cardiovascular system. The adverse reactions include medullar depression, tonic and clonic seizures and cardiovascular collapse. Treatment of overdose is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

Pharmacodynamicproperties

Pharmacotherapeutic group: vitaminB₁ and its combinations with vitaminB₆ and/or vitaminB₁₂.

The neurotropic vitamins of B-complex have beneficial effect to inflammatory and degenerative diseases of nerves and motion apparatus.

Vitamin B₁ is called an antineuritic vitamin. Its phosphorylated form thiamine pyrophosphate (TPP) regulates the breakdown of carbohydrates as a cofactor of carboxylase and is used incase of metabolic acidosis.

Vitamin B₆ regulates the breakdown of proteins, fats and carbohydrates.

Vitamin B₁₂ is required for cellular metabolism, erythrocyte development and function of nervous system. Vitamin B₁₂ is a catalyst of the synthesis of nuclear acids and thus the building of new cellular nuclei.

Lidocaine hydrochloride is added to alleviate post procedural pain.

Pharmacokinetic properties

The daily requirement is about 1mg of thiamine. Excess thiamine is excreted with urine. The determination of the activity of a TPP-dependent enzyme-transketolase- is used to determine the B₁ status. Plasma concentration is 2-4µg/100ml.

Pyridoxine, pyridoxal and pyridoxamine are phosphorylated and oxidated to pyridoxal-5phosphate (PALP). The main excreted metabolite is 4-pyridoxicacid. Tryptophan test is suitable for the determination of B₆. In adults the average serum PALP value is 1.2µg/100ml.

The daily requirement of vitaminB₁₂ is 1µg. An average of 1.5-3.5µg of vitamin B₁₂ is absorbed from food.

Normal vitamin B₁₂ plasma concentration is 200-900µg/ml, value below 200µg/ml is regarded as deficit. Circulating vitamin B₁₂ corresponds to about 0.1% of total vitamin amount.

Intramuscular injection of 200mg 10% lidocaine is reported to give serum concentrations 1.3-1.9µg/ml.

Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Although unchanged lidocaine is excreted into the urine, it is a minor route of excretion and account for less than 11%. Lidocaine has an initial half-life

Of 7-30 minutes and a terminal half-life of 1.5-2hours.

Predlinical safety data

When lidocaine is administered to rats the formed metabolism product 2,6-xylidine may have mutagenic effect. The results are derived from invitro tests where this metabolite was used in very large, almost toxic, concentrations. Therefore there is no basis to believe that the parent product lidocaine would be mutagenic.

In carcinogenicity studies, where 2,6-xylidine was administered to rats during pregnancy and after birth for more than 2years, both benign as well as malignant tumours, especially in nasal cavity, were found using controls. The importance of these findings for humans cannot be completely excluded. Therefore high doses should not be used for longer periods.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Benzylalcohol
Sodium triphosphate penta basic
Sodium hydroxide (for pH adjustment)
Potassium hexacyanoferrate(III)
Water for injections

Incompatibilities

Thiamine is incompatible with oxidizing and reducing agents, mercury chloride, iodine, carbonate, acetate, ferric sulfate, tannic acid, ferric ammonium citrate, Phenobarbital sodium, riboflavin, benzylpenicillin, glucose and metabisulphite. Copper accelerates the breakdown of thiamine; in addition thiamine loses its effect at increased pH level (>pH3).

Vitamin B₁₂ is incompatible with oxidizing and reducing agents and heavy metal salts. In solutions containing thiamine vitamin B₁₂ as well as other B-complex factors are destroyed by thiamine degradation products (low concentration of ferric ions may hinder this). Also riboflavin (especially with concomitant effect of light) has degrading effect. Nicotinamide accelerates phytolysis, at the same time antioxidants have inhibiting effect.

Shelflife

2years.

Special precautions for storage

Store below 30°C. Do not freeze. Store in the original package in order to protect from light. Once ampoule has been opened, the content should be used immediately.

Nature and contents of container

Type I amber glass ampoules of 2ml.

10 ampoules are placed into a transparent PVC tray and placed into a cardboard box.

Packsize:2ml X 10 Ampoules

Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Marketed by:

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Manufactured by:

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