SMPC OF CLIMAX CLINDAZOLE

Clindazole Vitamin B Complex Injection 10mlx50 vials I.M./IV.

1. NAME OF THE MEDICINAL PRODUCT

{Product name} Clindazole 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

1 ml of solution for injection contains: 50 mg pyridoxine hydrochloride (vitamin B_6), 50 mg thiamine hydrochloride (vitamin B_1), 0.5 mg cyanocobalamin (vitamin B_{12}), 10 mg lidocaine hydrochloride.
One ampoule (2 ml) contains: 100 mg pyridoxine hydrochloride (vitamin B_6), 100 mg thiamine hydrochloride (vitamin B_1), 1 mg cyanocobalamin (vitamin B_{12}), 20 mg 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

For the full list of excipients, see section 6.1.

1. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear red 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 B_1, B_6 and B_{12}.

Posology and method of administration

Posology
In case of severe and acute symptoms one injection (2 ml) 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.

Elderly

Dose adjustments are not required.

Paediatric population

{Product name} 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 (see sections 4.4 and 4.8).

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 newborn babies, especially to premature newborn babies (see section 4.4).
- The medicinal product must not be used during pregnancy and breast-feeding (see section 4.6).

Special warnings and precautions for use

Administration limits are 90 mg 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 (see section 4.8). In case of inadvertent intravenous injection the patient's heart activity should be monitored (ECG) or the patient should be hospitalised 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 B_1 degradation products. Therapeutic doses of vitamin B_6 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 B_6 during pregnancy and breast-feeding is up to 25 mg. As the vitamin B_6 content of this medicinal product is 100 mg in one 2 ml ampoule, it must not be used during pregnancy and breast-feeding.

Effects on ability to drive and use machines

{Product name} has no or negligible influence on the ability to drive and use machines.

Undesirable effects

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

Very common: ≥1/10 (≥ 10%)
Common: ≥1/100 to <1/10 (≥ 1% to < 10%)
Uncommon: ≥1/1000 to <1/100 (≥ 0.1% to < 1%)
Rare: ≥1/10 000 to < 1/1000 (≥ 0.01% to < 0.1%)
Very rare: < 1/10 000 (< 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). Benzyl alcohol: 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.

Musculoskeletal and connective tissue disorders:
Not known: seizures.

General disorders and administration site reactions:
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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

[To be completed nationally]

Overdose

The toxicity of thiamine, pyridoxine or cyanocobalamin may be rated as very low. Development of more serious adverse effects caused by overdose may be expected only if about 1 g of these substances is administered. Reactions caused by lidocaine overdose (high plasma 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

Pharmacodynamic properties

Pharmacotherapeutic group: vitamin B_1 and its combinations with vitamin B_6 and/or vitamin B_{12}. ATC code: A11DB

The neurotropic vitamins of B-complex have beneficial effect to inflammatory and degenerative diseases of nerves and motion apparatus.
Vitamin B_1 is called an antineuritic vitamin. Its phosphorylated form thiamine pyrophosphate (TPP) regulates the breakdown of carbohydrates as a cofactor of carboxylase and is used in case of metabolic acidosis.
Vitamin B_6 regulates the breakdown of proteins, fats and carbohydrates.
Vitamin B_{12} is required for cellular metabolism, erythrocyte development and function of nervous system. Vitamin B_{12} 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 1 mg of thiamine. Excess thiamine is excreted with urine. The determination of the activity of a TPP-dependent ensyme - transketolase - is used to determine the B_1 status. Plasma concentration is 2-4 μg/100 ml.

Pyridoxine, pyridoxal and pyridoxamine are phosphorylated and oxidated to pyridoxal-5 phosphate (PALP). The main excreted metabolite is 4-pyridoxic acid. Tryptophan test is suitable for the determination of B_6. In adults the average serum PALP value is 1.2 μg/100 ml.

The daily requirement of vitamin B_{12} is 1 μg. An average of 1.5-3.5 μg of vitamin B_{12} is absorbed from food.
Normal vitamin B_{12} plasma concentration is 200-900 μg/ml, value below 200 μg/ml is regarded as deficit. Circulating vitamin B_{12} corresponds to about 0.1 % of total vitamin amount.

Intramuscular injection of 200 mg 10% lidocaine is reported to give serum concentrations 1.3-1.9 μg/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 1.5-2 hours.

Preclinical safety data

When lidocaine is administered to rats the formed metabolism product 2,6-xylidine may have mutagenic effect. The results are derived from *in vitro* 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 2 years, 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 {Product name} doses should not be used for longer periods.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Benzyl alcohol
Sodium triphosphate pentabasic
Sodium hydroxide (for pH adjustment)
Potassium hexacyanoferrate (III)
Water for injections

Incompatibilities

Thiamine is incompatible with oxidising 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 (>pH 3).

Vitamin B_{12} is incompatible with oxidising and reducing agents and heavy metal salts. In solutions containing thiamine vitamin B_{12} 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.

Shelf life

2 years.

Special precautions for storage

Store in a refrigerator (2 °C – 8 °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 2 ml.
5 ampoules are placed into a PVC liner. 1, 2 or 5 liners are placed into a cardboard box.

Pack size: 5, 10 or 25 ampoules.
Not all pack sizes may be marketed.

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: CLIMAX PHARMACY AND CHEMIST LIMITED
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Manufactured by: GREENFIELD PHARMACEUTICAL
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