SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NOROGRIZOVIM Solution for IM Injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance(s):

Ampoule Type I
Each 1 mL solution for injection contains:
Hydroxocobalamin (Vitamin B_{12}) ..... 1 mg

Ampoule Type II
Each 2 mL solution for injection contains:
Pyridoxine hydrochloride (Vitamin B_6) ..... 100 mg
Thiamine hydrochloride (Vitamin B_1) ..... 100 mg
Lidocaine hydrochloride ..... 10 mg

Excipient(s) with known effect:

Ampoule Type I
Each 1 mL solution for injection contains:
Sodium tartrate ..... 2 mg
Benzyl alcohol ..... 10 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ampoule Type I
Solution for injection.
Red, clear, 1 mL solution for injection with a characteristic odor.

Ampoule Type II
Solution for injection.
Almost colorless to pale yellow, clear, 2 mL solution for injection with a characteristic odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NOROGRIZOVIM enables parenteral use in cases of vitamin B deficiencies where rapid distribution of these vitamins to tissues is required and gastrointestinal absorption is inadequate.

NOROGRIZOVIM is used in pre- and post-operative conditions, severe illnesses, multiple fractures, burn cases, neuritis, polyneuritis, neuralgia, peripheral-type facial paralyses, post-infectious paralyses, alcohol- and drug-induced toxic psychosis, drug intoxications of tuberculosis patients, anemia, convalescence, and to prevent vitamin deficiencies caused by high-dose or long-term drug therapies.

4.2. Posology and method of administration

NOROGRIZOVIM dose is adjusted based on its use for prophylactic or therapeutic purposes.

Posology / Frequency of administration and duration
As an initial dose, injecting a combination of Ampoule Type I and Type II once daily is generally sufficient. The treatment is continued with the same dose, given 2-3 times per week.

Method of administration
Administered intramuscularly (IM). In a sterile syringe, draw Ampoule Type II (colorless) first,

followed by Ampoule Type I (red solution), and administer intramuscularly to the patient.

Additional Information on Special Populations

Renal failure

Safety and efficacy of NOROGRIZOVIM in patients with renal failure have not been studied.

Hepatic failure

The degradation rate of pyridoxine increases in cases of liver dysfunction.

Pediatric population

It should not be given to premature or newborn infants. Its use in children is not recommended.

Geriatric population

Safety and efficacy of NOROGRIZOVIM in elderly patients have not been studied.

4.3. Contraindications

- Patients with known hypersensitivity to hydroxocobalamin, cyanocobalamin, cobalt, thiamine hydrochloride, pyridoxine hydrochloride, or any of the excipients in NOROGRIZOVIM.
- NOROGRIZOVIM is contraindicated during pregnancy and breastfeeding.

4.4. Special warnings and precautions for use

Megaloblastic anemia due to severe vitamin B_{12} deficiency, associated with intracellular potassium shifts following anemia resolution, can sometimes result in thrombocytosis and severe hypokalemia, which may be fatal. Therefore, monitoring serum potassium levels during the initial phase of vitamin B_{12} therapy is recommended. Potassium supplementation should be provided if necessary.

Vitamin B_{12} deficiency may mask the symptoms of polycythemia vera. This condition can become apparent during treatment with cyanocobalamin or hydroxocobalamin.

NOROGRIZOVIM treatment should not be used unless subacute degeneration of the spinal cord is fully diagnosed, as it may mask the symptoms of this condition.

Injection solutions containing thiamine hydrochloride for intravenous or intramuscular use may cause allergic or anaphylactic reactions. Extreme caution should be exercised before using NOROGRIZOVIM in patients with any history of sensitivity.

This medicinal product contains 10 mg of benzyl alcohol in 3 mL. It should not be administered to premature infants and newborns. It may cause toxic and anaphylactoid reactions in infants and children under 3 years old.

This medicinal product contains less than 1 mmol (23 mg) of sodium per 3 mL, meaning it is essentially "sodium-free".

Store protected from light.

4.5. Interaction with other medicinal products and other forms of interaction

In patients with vitamin B_{12} deficiency, co-administration of vitamin B_{12} and chloramphenicol may inhibit the hematopoietic response to vitamin B_{12}.

Although its clinical significance is unknown, thiamine has been reported to enhance the effect of neuromuscular blocking agents.

Pyridoxine hydrochloride accelerates the peripheral metabolism of levodopa, reducing its efficacy. This effect can only be prevented if levodopa is used in combination with carbidopa. Patients using levodopa alone are advised not to take more than 5 mg of pyridoxine.

Pyridoxine reduces the effects of the antineoplastic drug altretamine, the psycholeptic drug barbiturates, and the antiepileptic drug phenytoin.

When used with oral contraceptives, serum B_{12} levels may decrease.

4.6. Fertility, pregnancy and lactation
General principles
Pregnancy category "X".

Women of childbearing potential / Contraception in males and females
NOROGRIZOVIM is suspected to cause severe birth defects if administered during pregnancy.
It is contraindicated during pregnancy. Women of childbearing potential must use effective contraception during treatment.

Pregnancy
NOROGRIZOVIM is contraindicated during pregnancy due to its high-dose vitamin B_6 content that significantly exceeds the "Recommended Daily Allowance".

Lactation Period
NOROGRIZOVIM is contraindicated during lactation due to its high-dose vitamin B_6 content that significantly exceeds the "Recommended Daily Allowance".

Fertility
There are no clinical or non-clinical studies available regarding reproduction ability.

4.7. Effects on ability to drive and use machines
There are no known effects of NOROGRIZOVIM on the ability to drive and use machines.

4.8. Undesirable effects
The following terms and frequency classifications have been used for undesirable effects related to the use of NOROGRIZOVIM: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); and Not known (frequency cannot be estimated based on available data).

Immune system disorders
Rare : Allergic reactions
Very rare : Anaphylaxis

Endocrine disorders
Not known : Reduction in milk secretion, acidosis

Nervous system disorders
Not known : Headache, neuropathy, paresthesia

Gastrointestinal disorders
Not known : Nausea, moderate transient diarrhea

Hepatobiliary disorders
Not known : Increase in liver enzyme levels (AST)

Skin and subcutaneous tissue disorders
Not known : Exanthema (transient), itching

General disorders and administration site conditions
Not known : Pain at the injection site

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 national reporting system.

4.9. Overdose
No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group : Vitamin B-complex, plain
ATC Code : A11EA

Mechanism of Action
NOROGRIZOVIM is a combination of vitamins B_1, B_6, and B_{12}, which are well known for their antineuralgic and neurotrophic effects. The effects of these vitamins target nerve cells and fibers. The pharmacodynamic effects of each vitamin, which are dependent on their individual properties, are further enhanced when the dosage ratios are appropriate.

Vitamin B_{12} (hydroxocobalamin) acts as a coenzyme in the body, activating the biosynthesis of methionine, thymidine, and protoporphyrin, and plays a catalytic role in the formation of nucleoproteins and hemoglobin, ensuring normal erythropoiesis. Due to these effects, hydroxocobalamin rapidly corrects the condition in pernicious anemia and hyperchromic macrocytic anemia. Due to its role in nucleoprotein synthesis and efficacy in lipid metabolism, vitamin B_{12}, which plays a crucial role in the regeneration of myelin and the dysfunction of neurons, is effective against neuropathies. Hydroxocobalamin has a longer duration of pharmacological activity and greater efficacy compared to cyanocobalamin, as it stays in the body longer and reaches higher plasma concentrations when administered in equal doses.

Vitamin B_1 participates in cellular respiration through its important role in redox reactions. It is essential for carbohydrate metabolism. Its deficiency leads to the accumulation of pyruvic acid, destruction of nerve tissue, and peripheral neuropathy.

Vitamin B_6 plays a role in the decarboxylation and transamination of many amino acids in protein metabolism. It is also important in the nutrition of nerve tissue and in the metabolism of glutamic acid. Its deficiency leads to convulsions, hypochromic anemia, skin and oral lesions, and polyneuropathies.

5.2. Pharmacokinetic properties
General Properties
Associated with Hydroxocobalamin (Vitamin B_{12})
Absorption
Hydroxocobalamin is absorbed more slowly from the injection site compared to cyanocobalamin.

Distribution
When administered intramuscularly in healthy individuals and patients with vitamin B_{12} deficiency, hydroxocobalamin causes a more stable increase in plasma concentrations compared to cyanocobalamin. Hydroxocobalamin binds with a higher affinity to specific and non-specific binding proteins (transcobalamins) in tissues and blood compared to cyanocobalamin. Vitamin B_{12} is distributed to the liver, bone marrow, and tissues, including the placenta. Approximately 50-90% of the total vitamin B_{12} in the body is stored in the liver.

Biotransformation
The reabsorption of hydroxocobalamin from the liver may be higher compared to cyanocobalamin. It is hypothesized that vitamin B_{12} is converted into its coenzyme form in the liver, and this form is found in the tissues.

Elimination

When administered intramuscularly in healthy individuals and patients with vitamin B_{12} deficiency, the excretion of hydroxocobalamin in urine occurs more slowly compared to cyanocobalamin. About 16-66% of 0.5-1 mg of intramuscular hydroxocobalamin is excreted in the urine within 72 hours. It undergoes enterohepatic cycling and is also excreted in the bile. A significant portion of the drug is excreted within the first 24 hours.

Associated with Thiamine (Vitamin B_1)

Absorption

Thiamine is rapidly and completely absorbed following intramuscular administration.

Distribution

It is widely distributed throughout body tissues. The average amount of thiamine in the body is estimated to be around 30 mg, with a daily turnover of approximately 1 mg.

Biotransformation

Several metabolites of thiamine that are excreted in urine have been identified in humans.

Elimination

After physiological doses, the amount of thiamine excreted unchanged in the urine is either very small or none at all. After high doses, once tissue saturation is reached, thiamine, both in its unchanged and metabolite forms, can be excreted in the urine.

Associated with Pyridoxine (Vitamin B_6)

Absorption

Vitamin B_6 is well absorbed. It is primarily stored in the liver, with smaller amounts in the muscles and brain.

Distribution

The total amount of vitamin B_6 in the body is estimated to be around 167 mg.

Biotransformation

Pyridoxal and pyridoxal phosphate are the main forms of the vitamin in the blood, where they bind strongly to proteins. The biological half-life of pyridoxine is 15-20 days. Pyridoxal is oxidized to 4-pyridoxic acid in the liver and excreted in the urine. In patients with cirrhosis, the degradation rate may increase.

Elimination

Pyridoxal is removed from the body via hemodialysis.

5.3. Preclinical safety data

The active substances contained in NOROGRIZOVIM have been in clinical use for many years. Studies related to these substances have been completed. Possible adverse effects related to their use are mentioned in the relevant sections (see sections 4.4, 4.6, 4.8, and 4.9).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzyl alcohol
Sodium tartrate
Tartaric acid
Propyl gallate
Water for injections

6.2. Incompatibilities

If compatibility studies have not been conducted, this medicinal product should not be mixed with other medicinal products.

6.3. Shelf life
60 months.

6.4. Special precautions for storage
Store at room temperature below 25°C and protected from light.

6.5. Nature and contents of container
Type I Ampoule : 1 mL, printed, colorless, ringed ampoule (Type I)
Type II Ampoule : 2 mL, printed, amber-colored, ringed ampoule (Type II)

Each cardboard box contains 5 pieces of Type I ampoules and 5 pieces of Type II ampoules placed in a transparent PVC separator.

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORIZATION HOLDER
Licensed by Pfizer Inc./USA
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORISATION NUMBER(S)
144/75

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 03.05.1988
Date of latest renewal : 05.03.2008

10. DATE OF REVISION OF THE SPC
29.03.2013