NA-RAZ-B12 (06-2021)

1. NAME OF THE MEDICINAL PRODUCT

VITAMINE B12 STEROP 1mg / ml

Solution for I.M or S.C injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Cyanocobalamin (vitamin B12) 1mg / ml
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Pernicious anemia and its neurological complications, subacute combined degeneration of the spinal cord.
Treatment of vitamin B12 deficiency states and macrocytic anemias associated with nutritional deficiencies, gastrectomy and abnormalities of, or malabsorption from, the gastrointestinal tract such as celiac disease, sprue and accompanying folic acid deficiency. Also suitable for use as the flushing dose in the schilling test for pernicious anemia.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Vitamine B12 Sterop 1mg/ml may be given by subcutaneous or intramuscular injection. Do not use intravenously.

Pernicious Anemia, Vitamin B12 Deficiency States and Macrocytic Anemias
The usual initial dose is 250-1000 micrograms on alternate days for 1-2 weeks, followed by 250 micrograms weekly until the blood count is normal. Thereafter, the maintenance dose is 1000 micrograms monthly. If there are neurological complications, the initial dose of 1000 micrograms is recommended on alternate days while improvement is occurring.

Maintenance
1000 micrograms monthly.

Schilling test
The flushing dose is 1000 micrograms.

4.3 CONTRAINDICATIONS

- Hypersensitivity to vitamin B12 or to any of the excipients listed in section 6.1.
- History of allergy to cobalamins (vitamins B12 and related substances) or to cobalt.
- Vitamin B12 must not be given to patients with Leber's disease or tobacco-induced amblyopia since these optical nerve neuropathies may continue to degenerate during treatment with vitamin B12.
- Malignant tumor: owing to the impact of vitamin B12 on the growth of tissues with a high cell turnover, the risk of acute exacerbation of the malignant disease must be taken into account.
- The cause of the anemia must be firmly established before vitamin B12 is administered.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- Anaphylactic reactions are very rare. Nonetheless, potentially severe immunoallergic reactions that have, in exceptional cases, resulted in the death of the patient have been reported after injection of cobalamin preparations (vitamin B12 and related substances); administration of this product to patients at risk for allergic reactions (patients with asthma or eczema) is to be avoided or a test dose should be injected intradermally (prick test).
- At the start of treatment with vitamin B12 for megaloblastic anemia, serum potassium levels should be assayed since megaloblastic anemia will revert to normal erythropoiesis and there will be an increased need for potassium created by the rise in erythrocyte count.
- Intravenous administration can result in an almost complete loss of the dose in the urine and should therefore be avoided.
- Treatment response should be monitored as an inadequate treatment continued for more than 3 months could result in irreversible neurological damage.
- The treatment with folic acid alone is not applicable in megaloblastic anaemia caused by vitamin B12 deficiency. Although folic acid administration can reverse haematological disorders, the neurological damage (due to vitamin B12 deficiency) can still progress in absence of vitamin B12 therapy and this can become irreversible. In this case, there is a risk of subacute degeneration of the spinal cord when high doses of folic acid (5mg or more) are administered, especially in the elderly. Furthermore, a pernicious anaemia caused by a vitamin B12 deficiency can be masked at the dose of 1mg of folic acid per day or more, while neurological deficiency can continue to progress. Any vitamin B12 deficiency, whether or not it is associated with folic acid deficiency, must be corrected.
- Do not use the solution if it is not clear.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The anesthetic nitrogen protoxide induces irreversible oxidation of reduced cobalamin and may cause megaloblastic hematopoiesis and concomitant neurological disorders.

4.6 FERTILITY, PREGNANCY AND LACTATION

Fertility
There are no data generated by animal studies concerning the effects of cyanocobalamin on fertility or reproductive performance (see section 5.3).

Pregnancy
There are no or limited amount of data from the use of cyanocobalamin in pregnant women. However, vitamin B12 needs are higher during pregnancy.
Studies in animals have shown teratogen effects after a daily exposition during organogenese (see section 5.3).
Cyanocobalamin crosses the placental barrier. This medicine will be used during pregnancy but only when the potential benefits of treatment outweigh the risks for the fetus.

Breastfeeding
Vitamin B12 is excreted in the breast milk.
The effects of cyanocobalamin on neonates/infants are not known. The decision must be taken whether to stop breastfeeding or to interrupt/ to abstain from treatment with vitamin B12, weighing the benefits of breastfeeding for the infant versus those of treatment for the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Vitamin B12 has no influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Some undesirable effects were observed only after parenteral administration: pain at the injection site, pruritus, urticaria, transient diarrhea, anaphylactic shock.

The undesirable effects encountered with cyanocobalamin are presented in the table below by organ system class and frequency. The frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table: Known undesirable effects		
Organ system	**Undesirable effects**	**Frequency**
Immune system disorders	Allergic reactions: pruritus, urticaria, eczema, erythema, oedema that can be severe.	Not known
	Anaphylactic shock	Rare
Gastrointestinal disorders	Transient diarrhea	Not known
Skin and subcutaneous tissue disorders	Acne	Not known
Renal and urinary disorders	Red coloration of urine (corresponding to urinary elimination of vitamin B12)	Common
General disorders and administration site conditions	Pain at the injection site	Not known

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il .

4.9 OVERDOSE

As vitamin B12 is a hydrosoluble vitamin, the excess administered is eliminated in the urine and bile. An overdose is therefore not to be feared.
The very rare cases of anaphylactic shock should be treated with injectable adrenomimetics and corticosteroids.
No cases of acute or chronic (overdose) intoxication have been reported.
In case of administration of doses in excess, stop treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Vitamin
ATC code: B03BA

Vitamin B12 plays an essential role in the synthesis of DNA. It is therefore indispensable for all high cell turnover tissues (hematopoietic tissues, small bowel, uterus, etc). A vitamin B12 deficiency (most often caused by resorption disorders but also by a strict vegetarian diet) may cause macrocytic anemia and neurological disorders, for instance pernicious anemia. One possible effect is demyelinisation which causes nervous tissue degradation.

5.2 PHARMACOKINETIC PROPERTIES

Vitamin B12 undergoes first-pass metabolism; Excreted mainly in the bile, two-thirds or three quarters is reabsorbed in the intestine in patients with intrinsic factor. After injection of high doses of vitamin B12, a large proportion, 50 to 70% of the dose administered within the first 18 hours depending on the state of the reserves, is excreted in the urine via glomerular filtration.
After intramuscular or subcutaneous injection, resorption is slow resulting in long-lasting concentrations in the blood and high serum and tissue binding, particularly in the liver parenchyma. After intravenous injection, resorption is more rapid and about 90% of the dose administered is excreted in the urine.

5.3 PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Toxicity for the foetus development, including teratogenicity, has been observed by rat and rabbit at doses of 150 mg/kg and more administrated per day throughout organogenesis.
There is no data available on male and female fertility neither on peri- and postnatal development.

The carcinogen potential of cyanocobalamin hasn't been evaluated.

However, cyanocobalamin's pharmacological effect on DNA synthesis makes it an indispensable agent for cell multiplication and it could therefore have a deleterious effect on the growth of pre-existing cancerous tissues (high cell turnover malignant tumors).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride.
Water for injections.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

The expiry date of the product is indicated on the packaging materials.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Store in the original package to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Carton boxes packed with 10 or 100 glass ampoules. Each ampoule contains 1 ml solution.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

- At the end of the infusion procedure, any remaining solution and parts of the infusion kit containing this solution must be disposed of in compliance with current legislation.
- When administered by injection, VITAMINE B12 STEROP 1mg/ml must be withdrawn from the ampoule as recommended in current good practices, using optimally aseptic technique, into a sterile syringe immediately after the ampoule is opened. The medicinal solution must be then administered immediately. Any unused or remaining medicinal solution must be disposed of as stipulated in current good practices.
- If the solution is administered by infusion, both the medicinal solution and the infusion kit will be maintained under sterile conditions throughout the procedure as described in current good practices. It is standard good clinical practice to use any prepared medicinal solution within 24 hours.
- VITAMINE B12 STEROP 1mg/ml does not contain any antimicrobial preservatives and will not prevent growth of microorganisms. The medicinal solution and any syringe containing this medicinal solution are for single and individual use only.

7. MARKETING AUTHORISATION HOLDER

RAZ Pharmaceutics Ltd., 6 Hamatechet St., Kadima, Israel.

8. MANUFACTURER:

Laboratoires STEROP NV, Belgium.

9. MARKETING AUTHORISATION NUMBER

163-11-35283-00

Revised in May 2021 according to MOHs guidelines.

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