SUMMARY PRODUCT CHARACTERISTICS (SmPC)

1. Name of Medicinal Product

NASO B12 (Methylcobalamin Nasal Spray 250 mcg/spray)

2. Qualitative and quantitative composition

For nasal use only

Each 0.1 ml contains :

Mecobalamin JP……500 mcg

Each spray delivers :

Mecobalamin JP 250 mcg; 2.3 ml (46 sprays)

For the full list of excipients, see section 6.1

3. Pharmaceutical Form:

Nasal spray

Clear red coloured solution, free from visible particulate matters.

4. Clinical Particulars:

4.1 Therapeutic indications

Treatment of vitamin B12 deficiency in patients without having neurological involvement.

4.2 Posology and method of administration

One dose comprises of two sprays administered as one spray in each nostril.

Adults

For treatment, instill one spray in each nostril every alternate day for 2 weeks (7 doses in 14 days).

Thereafter, for maintenance, instill one spray in each nostril once every week for 4 weeks.

The maintenance dosing should start after 7 days of the last treatment dose.

Nasal Spray should be administered at least one hour before or one hour after ingestion of hot foods or liquids as these may cause nasal secretions leading to loss of medication. Estimation of serum B12 levels should be made on completion of treatment & maintenance dosing to establish adequacy of therapy.

Pediatric use

As methylcobalamin nasal spray has not been studied in children, safety and effectiveness have not been established in pediatric patients

Method of Administration:

Always take this medicine as prescribed by your doctor. Check with your doctor or pharmacist if you are not sure.

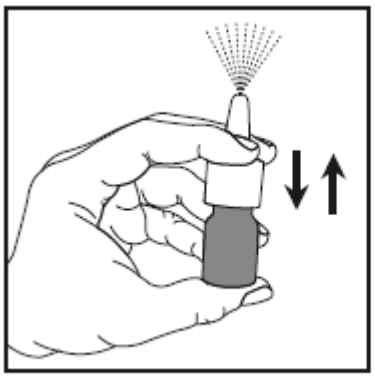


Fig. 1

Fig. 2

Fig. 3

a. Preparing the NASO B12 nasal spray:

- **Before First time use**

  Remove the cover from the nozzle and, while holding as shown above in Fig.1 press down firmly and quickly to pump 6 times in air for a fine mist to appear.

- **Before Subsequent uses (alternate day or weekly)**

  Remove the cover from the nozzle and, while holding as shown above in Fig.1 press down firmly and quickly to pump twice in air.

b. Instructions for using NASO B12 nasal spray

- Blow your nose gently to clear both nostrils.
- While holding the spray bottle as shown above in Fig.2, gently insert the nozzle (about 1 cm) into one nostril, pointing the tip towards the back of the nose.
- With your other nostril closed and head slightly tilted forward, firmly and quickly press down the plastic pump (arms) of the nasal spray bottle once while holding your breath to deliver 1 spray. Repeat these steps for the other nostril as shown above in Fig. 3.
- After use, clean the nozzle with a cloth, replace the cover on the nozzle and keep the bottle back in its box. Store in an upright position at a temperature not exceeding 30°C. Protect from light by putting the bottle back in the carton. DO NOT freeze.

c. After use of NASO B12

- Your nose may feel wet inside, and you may notice a slight taste in the throat, this is normal and will soon pass.

  NASO B12 solution is deep red in colour. Some amount of the deep red solution may trickle

out of the nostril and some amount may trickle into the mouth, causing red colouration of saliva.

4.3 Contraindications

This medication is contraindicated in the following situations:

- Sensitivity to cobalt, vitamin B12, or any component of this product
- Methylcobalamin should not, if possible, be given to patients or used to treat megaloblastic anaemia of pregnancy without first confirming the diagnosis

4.4 Special warnings and precautions for use

Laboratory tests

Hematocrit, reticulocyte count, vitamin B12, folate, and iron levels should be obtained prior to treatment. If folate levels are low, folic acid should also be administered.

Periodic monitoring of serum vitamin B12 concentrations must be obtained to confirm adequacy of therapy. Vitamin B12 concentrations and complete blood counts should be monitored one month after starting nasal spray and then at 3 to 6 month intervals thereafter. Patients with borderline-low vitamin B12 concentrations should also undergo measurement of methylmalonic acid and homocysteine concentrations, which are more sensitive measures of vitamin B12 deficiency in this setting.

A decline in the serum levels of B12 after one month of treatment with B12 nasal spray may indicate that the dose may need to be adjusted upward. Vitamin B12 deficiency that is inadequately treated for longer than three months may produce irreversible neurological damage.

Patients with pernicious anaemia have about 3 times the incidence of carcinoma of the stomach as in the general population, so appropriate tests for this condition should be carried out when indicated.

Patients with nasal pathology

Methylcobalamin nasal spray has not been evaluated in patients with nasal pathology. The effectiveness of nasal spray in patients with nasal congestion, allergic rhinitis and upper respiratory infections has not been determined. Treatment with nasal spray should be deferred until nasal symptoms have subsided. Patients with chronic nasal symptoms or significant nasal pathology are not ideal candidates for intranasal vitamin B12 therapy. If nasal spray therapy is attempted in these patients, vitamin B12 concentrations should be monitored more frequently than in patients without nasal pathology because of the potential for blunted absorption.

The dosing of methylcobalamin nasal spray and other intranasal medications should be separated

by several hours, and these patients should have more frequent monitoring of vitamin B12 concentrations because of the potential for erratic absorption.

Megaloblastic Anemia

Megaloblastic anemia has many causes, including vitamin B12 deficiency and folate deficiency. Folic acid may result in a hematological response in patients with vitamin B12 deficiency, but will not prevent irreversible neurological manifestations. Vitamin B12 is not an appropriate treatment for folate deficiency.

Doses of folic acid greater than 0.1 mg per day may result in hematologic remission in patients with vitamin B12 deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B12, irreversible damage will result.

Doses of vitamin B12 exceeding 10 mcg daily may produce hematologic response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.

The validity of diagnostic vitamin B12 or folic acid blood assays could be compromised by medications, and this should be considered before relying on such tests for therapy.

Hypokalaemia, thrombocytosis, and sudden death may occur when severe megaloblastic anemia is treated intensely with vitamin B12 due to conversion of severe megaloblastic to normal erythropoiesis. Serum potassium and the platelet count should be carefully monitored in this setting.

Vitamin B12 deficiency may suppress the signs of polycythemia vera. Treatment with vitamin B12 may unmask this condition.

Blunted response to vitamin B12 therapy

Infections, uremia, concurrent iron or folic acid deficiency, and drugs with bone marrow suppressantproperties (e.g., chloramphenicol) may blunt the therapeutic response to vitamin B12.

4.5 Interaction with other medicinal products and other forms of interaction

Persons taking most antibiotics, methotrexate and pyrimethamine invalidate folic acid and vitamin B12 diagnostic blood assays.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Animal reproduction studies have not been conducted with vitamin B12. It is also not known whether vitamin B12 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B12 is an essential vitamin and requirements are increased during

pregnancy. Megaloblastic anaemia occurring during pregnancy is usually due to folic acid deficiency rather than vitamin B12 deficiency. Methylcobalamin should not be used for the treatment of megaloblastic anaemia of pregnancy caused by folic acid deficiency. Methylcobalamin nasal spray should be given to a pregnant woman only if clearly needed.

Breast Feeding

Vitamin B12 is known to be excreted in human milk in concentrations which approximate the mother's vitamin B12 blood level. Caution should be exercised when Methylcobalamin nasal spray is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effect

Summary of the safety profile

Clinical study experience

No serious or severe Treatment Emergent Adverse Events (TEAEs) were reported during the study. Most of the TEAEs were of mild severity and were unlikely to be caused due to study drug. No clinically relevant changes were noted in clinical laboratory, vital signs, and physical examination. Treatment with intranasal Methylcobalamin appeared to be well-tolerated for 6 weeks in patients with vitamin B12 deficiency.

Table: Adverse events by body system, number of patients and number of occurrences by treatment with methylcobalamin nasal spray

System Organ Class Preferred Term	Total (N=103) n (%)
Number of patient with at least one event	5 (4.9)
Gastrointestinal disorders	1 (1.0)
Dyspepsia	1 (1.0)
General disorders and administration site conditions	1 (1.0)
Peripheral swelling	1 (1.0)
Infections and infestations	1 (1.0)
Bacterial infection	1 (1.0)
Metabolism and nutrition disorders	3 (2.9)
Iron deficiency anaemia	3 (2.9)
Nervous system disorders	1 (1.0)

Headache	1 (1.0)
Hypoaesthesia	1 (1.0)
Paraesthesia	1 (1.0)
Respiratory, thoracic and mediastinal disorders	1 (1.0)
Rhinorrhoea	1 (1.0)
Skin and subcutaneous tissue disorders	1 (1.0)
Pruritus	1 (1.0)
Note: Patients having multiple events within same System Organ Class were counted only once in respective system organ class under any event.	

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System.

4.9 Overdose

No overdosage has been reported with this drug.

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: This medicine contain cyanocobalamin vitamin B 12, which is used for the treatment of pernicious anaemia, and nutritional deficiencies of vitamin B 12 which results in macrocytic anaemia.

ATC code: B03BA01

Vitamin B12 is essential to growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis. Cells characterized by rapid division (e.g., epithelial cells, bone marrow, myeloid cells) appear to have the greatest requirement for vitamin B12. Vitamin B12 can be converted to coenzyme B12 in tissues, and as such is essential for conversion of methylmalonate to succinate and synthesis of methionine from homocysteine, a reaction which also requires folate.

In the absence of coenzyme B12, tetrahydrofolate cannot be regenerated from its inactive storage form, 5-methyltetrahydrofolate, and a functional folate deficiency occurs. Vitamin B12 also may be involved in maintaining sulfhydryl (SH) groups in the reduced form required by many SH-activated enzyme systems. Through these reactions, vitamin B12 is associated with fat and carbohydrate metabolism and protein synthesis. Vitamin B12 deficiency results in megaloblastic anemia, GI lesions, and neurologic damage that begins with an inability to

produce myelin and is followed by gradual degeneration of the axon and nerve head.

Methylcobalamin is the metabolically active coenzyme forms of vitamin B12 in the body. The other forms of cobalamin can be converted to the methylcobalamin required for vitamin B12 dependent enzyme function. The quantity of cobalamin detected following a small oral dose of methylcobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of methylcobalamin.

Human urinary excretion of methylcobalamin is about one-third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention. Thus, methylcobalamin has greater utility over cyanocobalamin.

5.2 Pharmacokinetic properties

Absorption:

A dose of 500 mcg of Methylcobalamin was administered intranasal as one spray (250 mcg) of NASO B12 in each nostril to 18 fasting healthy subjects having baseline mean serum vitamin B12 value of 396.14 pg/ml. The time to reach maximum serum vitamin B12 levels (C_{max} = 19779.47 pg/ml) after max administration of the dose was 12 minutes. The area under the serum vitamin B12 concentration-time curves AUC_{0-t} and AUC_{0-inf} after administration was 123399.31 pg*hr/ml and 243363.97 pg*hr/ml, respectively.

Pharmacokinetic parameters after a single dose administration of 500 mcg Methylcobalamin nasal spray (NASO B12):

T_{max}(hr)#	**C_{max}(pg/ml)#**	**AUC_{0-t} (pg*hr/ml)#**	**AUC_{0-inf} (pg*hr/ml)#**
0.20 ± 0.06	19779.47 ± 6726.28	123399.31 ± 31342.86	243363.97 ± 120348.80

#Mean ± S.D.

Distribution:

In the blood, B12 is bound to transcobalamin-II, a specific beta-globulin carrier protein, and is distributed and stored primarily in the liver and bone marrow.

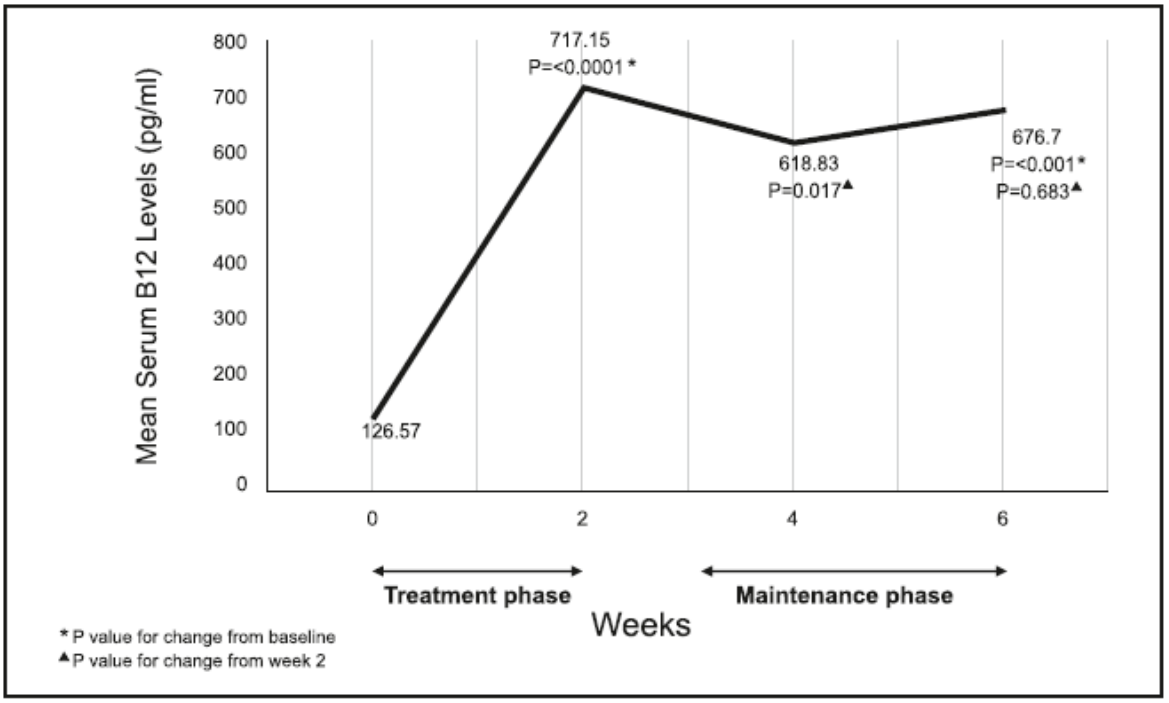
Elimination:

About 3-8 mcg of vitamin B12 is secreted into the gastrointestinal tract daily via the bile. In subjects with sufficient intrinsic factor, all but about 1 mcg is reabsorbed. When vitamin B12 is administered in doses that saturate the binding capacity of plasma proteins and the liver, the unbound vitamin B12 is rapidly eliminated in the urine.

Clinical Study Summary:

NASO B12 (Methylcobalamin) was administered as nasal spray to 103 patients with vitamin

B12 deficiency at a dose of 500mcg on each alternate day during treatment phase of the trial for 2 weeks and then continued to maintenance phase with the same treatment once a week for 4 weeks. The proportion of patients achieving serum vitamin B12 level at the end of 2 weeks of treatment was 97.78% (88/90) and at the end of 6 weeks was 95.06% (77/81). Thus, Methylcobalamin nasal spray demonstrated statistically significant increase in vitamin B12 levels (>200 pg/mL) and thereby the same were maintained at the end of six weeks of treatment. The nasal spray was well tolerated and depicted excellent safety and efficacy profile. Therefore, NASO B12 spray formulation can be beneficial for treatment and maintenance of serum vitamin B12 levels in deficient patients.



5.3 Preclinical safety data

No details available.

6. Pharmaceutical particulars

6.1 List of excipients

Glycerol (Non Parenteral)

Glycofurol (Stabilizer-1)

Benzalkonium Chloride

Sodium Glycocholate

Sodium Citrate

Citric Acid Anhydrous

Purified Water

6.2 Incompatibilities

Physical or chemical incompatibilities not known, however it is recommended not to co-administer NASO B12 with other nasal sprays.

6.3 Shelf-life: 24 months

6.4 Special precautions for storage: Store upright at a temperature not exceeding 30°C. Do not freeze. Protect from light.

6.5 Nature and contents of container

Primary Packing: 5 ml amber glass vial mounted with spray pump and actuator with protecting cap.

Secondary Packing: Such 1 labelled vial packed in printed carton along with booklet.

6.6 Special precautions for disposal and other handling

None

7. Marketing Authorization Holder and Manufacturing Site Addresses

Marketing Authorization Holder:

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8. Marketing authorization number: H2021/CTD8415/18534

9. Date of first authorisation/renewal of the authorisation: 01st September 2021

10. Date of revision of text: 19th September 2024