To be sold by retail on the prescription of a RMP only

COBASWIFT NS

1. Generic Name:

Methylcobalamin Nasal Spray

2. Qualitative and quantitative composition:

Each spray (0.1 ml) contains:

Methylcobalamin IP…….. 250 mcg

Each ml contains:

Methylcobalamin IP……...…. 2.5 mg
Preservative:
Phenyl ethyl alcohol IP……..5 mg
Benzyl alcohol IP……5 mg
Excipients ……..…..... q.s

3. Dosage form and strength:

Dosage form: Nasal Spray

Strength: 250 mcg/Spray

4. Clinical particulars:

4.1 Therapeutic indication:

Treatment and maintenance therapy of vitamin B12 Deficiency.

4.2 Posology and method of administration:

Posology

Adults

Instill one spray in each nostril on day 0, 2 and 7. Thereafter, for maintenance instill one spray in each nostril once a week for 4 weeks.

Paediatric use

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

Method of Administration:

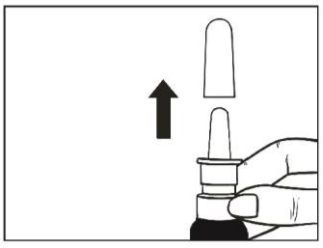


Fig. 1

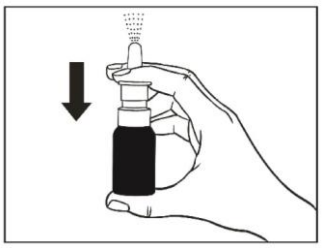


Fig. 2

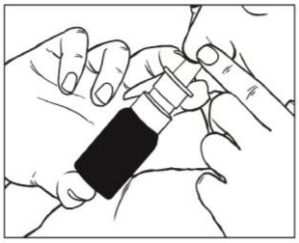


Fig. 3

- **Instruction for Handling and Storage:**

  COBASWIFT NS should be stored below 30ºC. Shake well before use.

- **Instructions for using COBASWIFT NS:**
  - Remove the plastic cap (see figure 1).
  - Before you use COBASWIFT NS for the first time, prime the pump by pressing downward on the shoulders of the white nasal applicator using your index finger and middle finger while holding the base of the bottle with your thumb 5 times (see figure 2).
  - Gently blow your nose to clear the nostrils. Close one nostril. Carefully insert the nasal applicator/tip (about 1 cm) into the other open nostril tilting the bottle slightly in a straight line with the nasal cavity (see figure 3). Press down and release the pump once.
  - Repeat above step for the other nostril.

  Do not breathe deeply after administration.

- **After use of COBASWIFT NS:**

  Your nose may feel wet inside, some amount may trickle out of the nostril and into the mouth and you may notice a slight taste in the throat, this is normal and will soon pass.

Cobaswift NS solution is pink to red color translucent solution and may give pink to red colouration to the secretion temporarily.

- **If you forget a dose:**

  Use the spray as soon as you remember, then take the next dose at the usual time. Do not take a double dose to make up for a missed dose.

4.3 Contraindications:

Sensitivity to cobalt and/or vitamin B12

4.4 Special warnings and precautions for use:

<u>Warnings</u>

- Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with vitamin B12 suffered severe and swift optic atrophy.
- Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B12. Folic acid is not a substitute for vitamin B12 although it may improve vitamin B12-deficient megaloblastic anemia. Exclusive use of folic acid in treating vitamin B12- deficient megaloblastic anemia could result in progressive and irreversible neurologic damage.
- Anaphylactic shock and death have been reported after parenteral vitamin B12 administration.
- Blunted or impeded therapeutic response to vitamin B12 may be due to such conditions as infection, uremia and drugs having bone marrow suppressant properties such as chloramphenicol, and concurrent iron or folic acid deficiency.

<u>Precautions</u>

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

- Vitamin B12 is not a substitute for folic acid and since it might improve folic acid deficient megaloblastic anemia, indiscriminate use of vitamin B12 could 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.
- Hypokalemia and thrombocytosis could occur upon conversion of severe megaloblastic to normal erythropoiesis with vitamin B12 therapy. Therefore, serum potassium levels and the platelet count should be monitored carefully during therapy.
- Vitamin B12 deficiency may suppress the signs of polycythemia vera. Treatment with vitamin B12 may unmask this condition.
- If a patient is not properly maintained with COBASWIFT NS, intramuscular vitamin B12 is necessary for adequate treatment of the patient. No single regimen fits all cases, and the status of the patient observed in follow-up is the final criterion for adequacy of therapy.
- The effectiveness of COBASWIFT NS in patients with nasal congestion, allergic rhinitis and upper respiratory infections has not been determined. COBASWIFT NS should be deferred until symptoms have subsided.

Laboratory Tests

- Vitamin B12, folate and iron levels should be obtained prior to treatment. If folate levels are low, folic acid should also be administered. All hematologic parameters should be normal when beginning treatment with COBASWIFT NS.
- Vitamin B12 blood levels must be monitored initially at one month after the start of treatment with COBASWIFT NS.
- A decline in the serum levels of vitamin B12 after one month of treatment with vitamin B12 nasal spray may indicate that either the spray is not being administered properly as indicated, alternatively, the dose may need to be adjusted upward. Patients should be seen one month after each dose adjustment; continued low levels of serum vitamin B12 may indicate that the patient is not a candidate for this mode of administration.
- Patients with pernicious anemia 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.

4.5 Drug-Interaction:

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

4.6 Use in special populations

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.

Nursing Mothers

Vitamin B12 appears in the milk of nursing mothers in concentrations which approximate the mother's vitamin B12 blood levels.

4.7 Undesirable effects:

Summary of safety profile

In a phase III study comparing efficacy and safety of COBASWIFT NS and comparator vitamin B12 nasal spray, no incidences of deaths or SAE were observed with the use of COBASWIFT NS. A total of 9 Adverse Events (AEs) were reported in 8 subjects (3.38%). All the AEs were considered as TEAEs (Treatment Emergent Adverse Events) and majority of TEAE's were mild in severity.

System Organ Class Preferred Term	**COBASWIFT NS (N = 157) n (%)**	**Comparator (N = 80) n (%)**	**Overall (N = 237) n (%)**
Subjects with at least one TEAE in each group	4 (2.55)	4 (5.00)	8 (3.38)
Blood and lymphatic system disorders	1 (0.64)	0 (0)	1 (0.42)
Leukopenia	1 (0.64)	0 (0)	1 (0.42)
Gastrointestinal disorders	0 (0)	1 (1.25)	1 (0.42)
Dyspepsia	0 (0)	1 (1.25)	1 (0.42)
General disorders and administration site conditions	2 (1.27)	1 (1.25)	3 (1.27)
Fatigue	1 (0.64)	0 (0)	1 (0.42)
Pyrexia	1 (0.64)	1 (1.25)	2 (0.84)
Infections and infestations	0 (0)	1 (1.25)	1 (0.42)
Upper respiratory tract infection	0 (0)	1 (1.25)	1 (0.42)
Nervous system disorders	1 (0.64)	0 (0)	1 (0.42)
Headache	1 (0.64)	0 (0) [0]	1 (0.42)
Respiratory, thoracic and mediastinal disorders	0 (0)	2 (2.50)	2 (0.84)
Cough	0 (0)	1 (1.25)	1 (0.42)
Nasal pruritus	0 (0)	1 (1.25)	1 (0.42)

Abbreviation(s): AE= adverse event; n = number of subjects in the specified treatment category; N = number of subjects in the specified treatment; SOC = system organ class; PT = preferred term.
Note 1: SOC and PT are coded using the MedDRA Version 22.1.
Note 2: Subjects reporting a particular adverse event for SOC/PT more than once were counted only once for that adverse event under SOC/PT.

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.8 Overdose:

No data is available for the overdose of Methylcobalamin.

5. Pharmacological properties:

5.1 Mechanism of Action:

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 B 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.

5.2 Pharmacodynamic properties:

Vitamin B12 is crucial for neurologic function, red blood cell production, and DNA synthesis, and is a cofactor for three major reactions: the conversion of methylmalonic acid to succinyl coenzyme A; the conversion of homocysteine to methionine; and the conversion of 5-methyltetrahydrofolate to tetrahydrofolate.

Clinical study summary:

A multi-centric, open-label, multiple-dose, two-arm, parallel-group study was conducted in 237 subjects (220 completed) with subclinical serum vitamin B12 level <200 pg/mL.

The proportion of subjects achieving serum vitamin B12 level >200 pg/mL at Day 14 with COBASWIFT NS was similar to the comparator treatment. No statistically significant difference was observed between the two treatment groups with regards to subjects achieving serum vitamin B12 level >200 pg/mL at Days 14, 21 and 28 ($p>0.05$). During the study, 5 doses of COBASWIFT NS were administered over period of 21 days in comparison to 9 doses of comparator treatment over the same duration.

Based on nasal sensory evaluation questionnaire score assessed immediately after IP administration at Day 14, COBASWIFT NS treatment was well accepted by subjects with regards to overall comfort during and after nasal instillation.

5.3 Pharmacokinetic properties:

Absorption

A mono-centric, open-label, multiple-dose single-arm, clinical study was conducted in 12 healthy subjects. Each subject received 3 doses (6 sprays, i.e. two sprays per dose, one spray in each nostril) of COBASWIFT NS on Day 0, 2 and 7. The time to reach maximum serum vitamin B12 level was ~1 hr. 85% of patients achieved vitamin B12 levels >200pg/ml.

Distribution

In the blood, vitamin B12 is bound to transcobalamin II, a specific B-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 GI tract daily via the bile; in normal subjects with sufficient intrinsic factor, all but about one mcg is reabsorbed. When vitamin B12 is administered in doses which saturate the binding capacity of plasma proteins and the liver, the unbound B12 is rapidly eliminated in the urine. Retention of B12 in the body is dose-dependent.

6. Nonclinical properties:

6.1 Animal Toxicology or Pharmacology

The toxicological studies performed on the rats and rabbits demonstrated methylcobalamin intra nasal formulation was well tolerated up to the highest tested concentration of 5000 µg/mL, which delivered 91.5 µg/kg (250 µg/day) and 189.4 µg/kg (50 µg/day) dose to rabbit and rat, respectively. A dose of 91.5 µg/kg for rabbit and 189.4 µg/kg to rats was equivalent to 3.5 times and 3.7 time the human dose of nasal spray, which was also established as NOAEL (No-Observed-Adverse-Effect-Level) for these species. At the end of study, microscopic evaluations of nasal cavity did not reveal any changes up to the highest dose of methylcobalamin tested in both species.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential have not been performed.

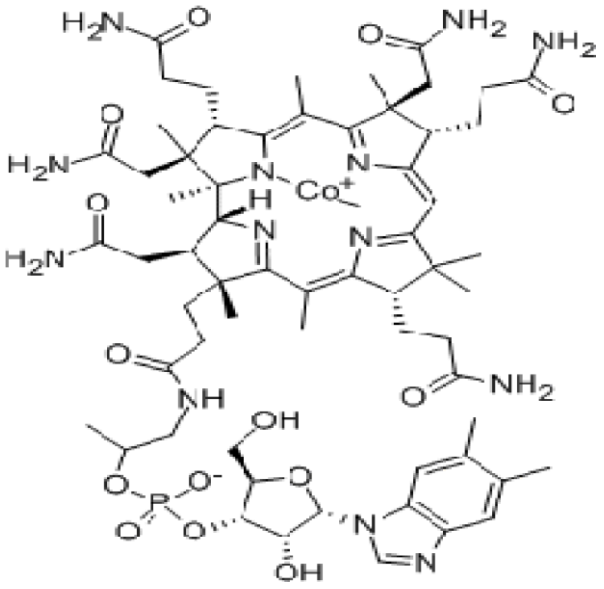
7. Description:

General Information

The molecular and structural information for methylcobalamin is provided below.

Chemical name: Methyl-5,6-dimethylbenzimidazolylcobalamin

Structural formula:



Structure of Methylcobalamin
Molecular formula: $C_{63}H_{91}CoN_{13}O_{14}P$

Description, Strength and Packaging:

COBASWIFT NS is a pink to red colored translucent solution filled into 10 ml black coated vial snap fitted with 100 µl pump with actuator and protective cap.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

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

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

COBASWIFT NS is packed in 10 ml black coated USP Type I vial fitted with 100 µl pump with actuator and protective cap.

8.4 Storage and handing instructions:

- Store upright at temperature not exceeding 30°C.
- For intranasal use only.
- Shake well before use. Priming required before initiation off first dose.

9. Keep out of reach of children.

Patient Counselling Information

Package leaflet: Information for the user

COBASWIFT NS
Methylcobalamin Nasal Spray

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1. What COBASWIFT NS is and what it is used for?

COBASWIFT NS contains methylcobalamin, which is the biologically active form of vitamin B12.

It is used for the treatment and maintenance therapy of vitamin B12 deficiency.

9.2. What you need to know before you take COBASWIFT NS?

Do not take COBASWIFT NS if:

- You are sensitive to cobalt or vitamin B12

Warnings and precautions

Warnings

- Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with vitamin B12 suffered severe and swift optic atrophy.
- Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B12. Folic acid is not a substitute for vitamin B12 although it may improve vitamin B12-deficient megaloblastic anemia. Exclusive use of folic acid in treating vitamin B12- deficient megaloblastic anemia could result in progressive and irreversible neurologic damage.
- Anaphylactic shock and death have been reported after parenteral vitamin B12 administration.
- Blunted or impeded therapeutic response to vitamin B12 may be due to such conditions as infection, uremia and drugs having bone marrow suppressant properties such as chloramphenicol, and concurrent iron or folic acid deficiency.

Precautions

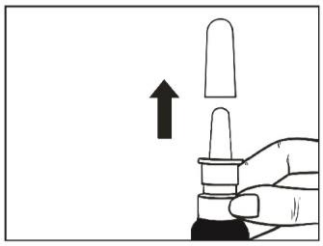
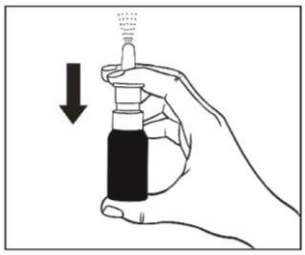
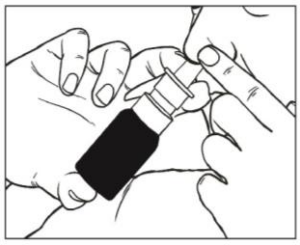
- Doses of vitamin B12 exceeding 10 mcg daily may produce hematologic response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.
- The validity of diagnostic vitamin B12 or folic acid blood assays could be compromised by medications, and this should be considered before relying on such tests for therapy.
- Vitamin B12 is not a substitute for folic acid and since it might improve folic acid deficient megaloblastic anemia, indiscriminate use of vitamin B12 could mask the true diagnosis.
- Hypokalemia and thrombocytosis could occur upon conversion of severe megaloblastic to normal erythropoiesis with vitamin B12 therapy. Therefore, serum potassium levels and the platelet count should be monitored carefully during therapy.
- Vitamin B12 deficiency may suppress the signs of polycythemia vera. Treatment with vitamin B12 may unmask this condition.
- If a patient is not properly maintained with COBASWIFT NS, intramuscular vitamin B12 is necessary for adequate treatment of the patient. No single regimen fits all cases, and the status of the patient observed in follow-up is the final criterion for adequacy of therapy.
- The effectiveness of COBASWIFT NS in patients with nasal congestion, allergic rhinitis and upper respiratory infections has not been determined. Therefore, treatment with COBASWIFT NS should be deferred until symptoms have subsided.

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. All hematologic parameters should be normal when beginning treatment with vitamin B12.
- Vitamin B12 blood levels and peripheral blood counts must be monitored initially at one month after the start of treatment with vitamin B12.
- A decline in the serum levels of B12 after one month of treatment with B12 nasal spray may indicate that the spray is not being administered as directed or the dose may need to be adjusted upward. Patients should be seen one month after each dose adjustment; continued

low levels of serum B12 may indicate that the patient is not a candidate for this mode of administration.

- Patients with pernicious anemia 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

- **Pregnancy and breast-feeding**

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.

Nursing Mothers

- Vitamin B12 appears in the milk of nursing mothers in concentrations which approximate the mother's vitamin B12 blood level.

9.3. How to use COBASWIFT NS

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

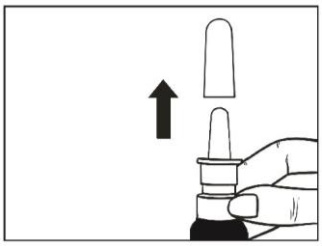
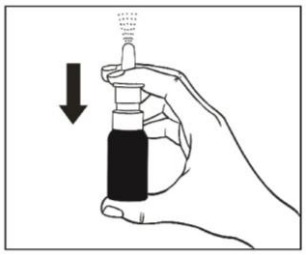
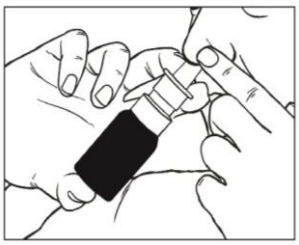




Fig. 1 **Fig. 2** **Fig. 3**

- **Instruction for Handling and Storage:**
  - COBASWIFT NS should be stored below 30ºC. Shake well before use.
- **Instructions for using COBASWIFT NS:**
  - Remove the plastic cap (see figure 1).
  - Before you use COBASWIFT NS for the first time, prime the pump by pressing downward on the shoulders of the white nasal applicator using your index finger and middle finger while holding the base of the bottle with your thumb 5 times (see figure 2).

- Gently blow your nose to clear the nostrils. Close one nostril. Carefully insert the nasal applicator/tip (about 1 cm) into the other open nostril tilting the bottle slightly in a straight line with the nasal cavity (see figure 3). Press down and release the pump once.
- Repeat above step for the other nostril.

Do not breathe deeply after administration.

- **After use of COBASWIFT NS:**
- Your nose may feel wet inside, some amount may trickle out of the nostril and into the mouth and you may notice a slight taste in the throat, this is normal and will soon pass.

Cobaswift NS solution is pink to red color translucent solution and may give pink to red colouration to the secretion temporarily.

- **If you forget a dose:**
- Use the spray as soon as you remember, then take the next dose at the usual time. Do not take a double dose to make up for a missed dose.

9.4. Possible side effects

- COBASWIFT NS is quite safe, as all the side effects observed during clinical study were less than 1%.

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

How to store COBASWIFT NS

- Store upright at temperature not exceeding 30°C.
- For intranasal use only.
- Shake well before use. Priming required before initiation of first dose.
- Keep out of reach of children.

9.5. Contents of the pack and other information

What COBASWIFT NS contains

- COBASWIFT NS contains methylcobalamin, which is an active form of vitamin B12.
- COBASWIFT NS is packed in 10 ml black coated USP Type I vial fitted with 100 µl pump with actuator and protective cap.

10. Details of manufacturer

M/s. Biodeal Pharmaceuticals Pvt Ltd.,

Village Sainimajara, Nalagarh-Ropar Road,

Nalagarh, Distt. Solan,

Himachal Pradesh (India)-174101

11. Details of permission or licence number with date

MF/SND/21/000195 dated 09-June-2021

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/COBASWIFT NS 250mcg/Oct-21/01/PI