Product Summary

1. **Name of the medicinal product**
   Injection of Pyridoxine (Vit. B6), Mecobalamin (Vit. B12) and Nicotinamide (Vit. B3)

2. **Qualitative and quantitative composition**
   Each 2 ml contains:
   Pyridoxine Hydrochloride I.P. 100 mg.
   Mecobalamin I.P. 1000 mcg.
   Nicotinamide I.P. 100 mg.

3. **Pharmaceutical form**
   Injection for IV/IM use

4. **Clinical particulars**

4.1 **Therapeutic indications**
   I. Peripheral Neuropathy of Various etiology
   II. Compression Neuropathy
   III. Diabetic Neuropathy
   IV. Other Neurological Disorders
      a. Parkinson’s Disease
      b. Alzheimer’s Disease
      c. Epilepsy
      d. Facial Palsy
   V. a. Disturbed Cognitive functions and memory.
      b. Sleep wake disorders.
   VI. In trauma, Megaloblastic Anaemia caused by Vitamin B12 deficiency, Cancer, Hyperhomocysteinemia.
4.2 Posology and method of administration
As directed by the Physician.

4.3 Contraindications
Known hypersensitivity to any of the active constituents or excipients.

4.4 Special warnings and precautions for use
Not to be used in newly born or premature infants.
Additional precautions that need to be considered are as follows
(1) Administration
Mecobalamin is susceptible to photolysis. It should be used promptly after the package is opened, and caution should be taken so as not to expose the ampules to direct light.
(2) Intramuscular administration
In intramuscular administration, caution should be exercised by following the instructions mentioned below to avoid adverse effects on tissues or nerves.
   a) Avoid repeated injection at the same site.
   b) Do not inject in densely innervated site.
   c) If insertion of the injection needle causes intense pain or if blood flows back into the syringe, withdraw the needle immediately and inject at a different site.

4.5 Interaction with other medicinal products and other forms of interaction
The content of pyridoxine may interfere with the effects of concurrent levodopa therapy.

4.6 Pregnancy and lactation
The usual precautions should be observed when administering drugs during pregnancy, especially in the first trimester.
However animal studies are insufficient with respect to effects on pregnancy/ and-or/ embryonal/foetal development/ and-or/ parturition/ and-or/ postnatal development (see section 5.3). The potential risk for humans is unknown (see section 4.8).

4.7 Effects on ability to drive and use machines
None known.
4.8 Undesirable effects

Adverse reactions reported as possibly associated to Renerve Plus® are not reported. Hence all events appearing after administration of Renerve Plus® should be considered as due to the combination of the three vitamins. However, the following are the undesirable effects known when the individual vitamins are given as stand alone treatments.

Niacinamide

Vasodilatory effects (flushing)

Vasodilation is commonly seen in patients given high doses of nicotinic acid for the treatment of hyperlipidaemias. Very large single doses cause hypotension, although tolerance develops to this effect after several days of continued high dose intake. In general, flushing is a mild and transient effect although in many clinical trials it has resulted in patients withdrawing from treatment. The flushing activity appears to be related to the presence of a carboxyl group on the pyridine nucleus since compounds lacking this function, including nicotinamide, are not associated with facial flushing (Bean and Spies, 1940). Flushing is associated with periods of rapid rises in blood concentrations, and sustained-release formulations were developed for the use of nicotinic acid in the treatment of hypercholesterolaemia, in order to minimise this side-effect. Flushing is produced via prostaglandin D2 release (Morrow et al., 1989 and 1992) and a “niacin flush-test” has been used as a method of investigating essential fatty acid metabolism (Glen et al., 1996). Tolerance develops due to decreased formation of prostaglandin D2 on repeated dosage (Stern et al., 1991). Although flushing is not a clearly adverse effect and single oral doses of 100 mg do not alter heart rate or blood pressure, some patients in the study of Spies et al. (1938) reported dizziness after oral nicotinic acid (doses not defined). Theoretically if flushing occurred in the elderly, it could exacerbate mild postural hypotension, and could increase the risk of falls, which are a common cause of morbidity in the elderly. This risk relates to taking supplements containing nicotinic acid (not nicotinamide), especially if taken on an empty stomach.

Gastrointestinal effects

Gastrointestinal effects such as dyspepsia, diarrhoea and constipation are common in patients with hypercholesterolaemia given high doses of nicotinic acid (3 g/day -
especially as the sustained-release formulation; Knopp et al., 1985).

**Hepatotoxicity**
Severe and potentially life-threatening hepatotoxicity has been associated with treatment of patients with 3-9 g nicotinic acid per day for periods of months or years for the treatment of hypercholesterolaemia. Severe cases show liver dysfunction and fulminant hepatitis and may even proceed to encephalopathy requiring liver transplantation. Many of the patients showing hepatotoxicity were taking the slow release formulation of the compound, so that in contrast to the flushing discussed above, the development of hepatic toxicity is a function of long-term chronic exposure to relatively constant levels rather than the fluctuating levels and rapid rises which produce flushing.

**Glucose intolerance**
Nicotinic acid (3 g/day) has been reported to impair glucose tolerance in otherwise healthy individuals treated for hypercholesterolaemia.

**Other effects**
There have been rare reported cases of a range of effects including blurred vision, macular oedema and increased plasma homocysteine concentrations in patients given high doses of nicotinic acid. These effects were reported at doses similar to those producing hepatic dysfunction, and were reversible upon cessation of high dose treatment. There has been a single report of a possible association with congenital malformation in women taking nicotinamide during early pregnancy (Nelson and Forfar, 1971). On the basis of their retrospective survey of drug and vitamin prescriptions during pregnancy in 1369 mothers, the authors reported that a significantly (P<0.05) higher proportion of women with infants showing abnormalities took nicotinamide in the first 56 days (5/458), compared with mothers of normal babies (1/911). In contrast no such relationship was found during later phases of pregnancy or over the whole of the pregnancy. The paper did not report the doses of nicotinamide taken. This finding is in contrast to the results of the large multicentre study on vitamins and the prevention of neural tube defect (MRC Vitamin Study Research Group,1991). In that study 1817 women with high risk for producing a
baby with neural tube defect were randomised into 4 groups; one group received folic acid, one group a multivitamin preparation (that did not include folate but contained 15 mg/day of nicotinamide), one group was given both preparations and one group received neither preparation. Although the study focused on neural tube defects, any foetal malformation was recorded together with other pregnancy outcomes, and there was no difference in incidence between the multivitamin preparation and placebo.

**Pyridoxine**

Paresthesia, somnolence, and low serum folic acid levels have been reported.

**Mecobalamin**

Adverse reactions were reported in 13 of 2,872 patients (0.45 %). (At the end of the reexamination period)

1. Clinically significant adverse reactions (incidence unknown)

   **Anaphylactoid reaction**

   Anaphylactoid reaction such as decrease in blood pressure or dyspnea, may occur. Patients should be carefully observed. In the event of such symptoms, treatment should be discontinued immediately and appropriate measures taken.

2. Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Rash</td>
</tr>
<tr>
<td>Others</td>
<td>Headache and hot sensation</td>
</tr>
</tbody>
</table>

   *Note: In the event of such symptoms, treatment should be discontinued.*

**CLINICAL STUDIES**

**Clinical efficacy**

Mecobalamin was administered intramuscularly to patients with peripheral neuropathies at single doses of 500 μg and 100 μg (low-dose group) daily 3 times a week for 4 consecutive weeks in a double-blind clinical trial. In the chronic stage and fixed stage of peripheral neuropathies in the 500 μg group aggravation of symptoms was significantly suppressed compared to the low-dose group and this dose was
thus demonstrated to be useful.
In a placebo-controlled double-blind clinical trial, mecobalamin was administered intravenously or intramuscularly to patients with peripheral neuropathies at a single dose of 500 μg daily 3 times a week for 4 consecutive weeks. The improvement rate for intravenous administration was 38.7% (24/62) for moderately to remarkably improved and 74.2% (46/62) for fairly to remarkably improved. The improvement rate for intramuscular administration was 46.3% (25/54) for moderately to remarkably improved and 81.5% (44/54) for fairly to remarkably improved. The equivalence of mecobalamin efficacy for both administration routes was thus demonstrated. The diseases of subjects in the trial were diabetic neuropathy, polyneuritis, cervical spondylosis, sciatica, alcoholic neuropathy, facial paralysis and mononeuritis, etc.
When mecobalamin was administered to patients with megaloblastic anemia due to vitamin B12 deficiency, their hemograms and symptoms improved in 3 weeks to 2 months after starting administration.

4.9 Overdose
In the unlikely event of over dosage, treatment is symptomatic and supportive.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Pyridoxine Hydrochloride:
Perhaps the most important of Vitamin Bs for a healthy body. Vitamin B6 is a master vitamin in the processing of amino acid - the building blocks of all proteins and some hormones. It plays a role in the multiplication of all cells and the production of red blood cells and the immune system. It also acts as co-enzymes for substances that regulate and stimulate brain and central nervous system responses.
- Boost immunity
- Protects against cancer and cell abnormalities
- Helps control diabetes.

Mecobalamin:
- Mecobalamin is a Neurotropic and acts as a growth promoter for nerve cells, a property which helps to regenerate Central and Peripheral nervous tissue damaged in disorder such as diabetic peripheral neuropathy.
- Mecobalamin acts as a methyl donor for the synthesis of Lecithin, a major
component of the Myelin sheath.

- Mecobalamin facilitates methylation of t-RNA which play a fundamental role in protein synthesis and stimulates methionine synthesis and helps to restore normal levels of RNA in nerve cells.
- Mecobalamin acts as a co-factor in the enzyme methionine synthase which regenerates methionine thus generating an increased supply of S-Adenosyl Methionine (SAMe) and SAMe protects from Neurotoxicity.
- Mecobalamin normalizes Nerve cell conduction by healing the damaged nerve cells and restores delayed synaptic transmission and diminished neurotransmitters to normal.
- Mecobalamin improves the excitability of the nerve fibres and thus improves the neurotransmission.

**Niacinamide:**
Vitamin B3 is required for cell respiration, helps in the release of energy and metabolism of carbohydrates, fats, and proteins, proper circulation and healthy skin, functioning of the nervous system, and normal secretion of bile and stomach fluids. It is used in treating schizophrenia and other mental illnesses and a memory-enhancer. Nicotinic acid given in drug dosage improves the blood cholesterol profile. Reports confirm that with sufficient supply of Niacinamide, there is improvement in mental alertness.

A deficiency may cause pellagra and is characterized by bilateral dermatitis, diarrhea and dementia. A shortage of niacin may be indicated with symptoms such as depression, diarrhea, dizziness, fatigue, halitosis, headaches, indigestion, insomnia, limb pains, loss of appetite, low blood sugar, muscular weakness, skin eruptions, and inflammation.

5.2 Pharmacokinetic properties

**Single-dose administration**
Mecobalamin was administered intramuscularly or intravenously to 12 healthy adult male volunteers at a single dose of 500 μg. The time to reach peak serum total vitamin B12 (abbreviated to B12) concentration ($t_{\text{max}}$) was 0.9 hr after intramuscular administration and immediately to 3 min after intravenous administration, and the increment (except endogenous serum total B12) in peak serum total vitamin B12
concentration ($\Delta C_{\text{max}}$) was 22.4 ng/mL after intramuscular administration and 85.0 ng/mL after intravenous administration. The area under the serum total B12 concentration-time curve ($\Delta \text{AUC}$) calculated by increment of the actual values at 144 hr after administration was 204.1 ng.hr/mL after intramuscular administration and 358.6 ng.hr/mL after intravenous administration.

On the other hand, the rate of binding saturation showed a similar increase in both groups of subjects for 144 hr after administration.

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### Serum total vitamin B12 concentration after single administration of METHYCOBAL Injection 500 µg

<table>
<thead>
<tr>
<th></th>
<th>$t_{\text{max}}$(hr)</th>
<th>$\Delta C_{\text{max}}$(ng/mL)</th>
<th>$\Delta \text{AUC}_{0-144}$(ng.hr/mL)</th>
<th>$t_{1/2}$(hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.V.</td>
<td>0- 3 min</td>
<td>85.0±8.9</td>
<td>358.6±34.4</td>
<td>27.1</td>
</tr>
<tr>
<td>I.M.</td>
<td>0.9±0.1</td>
<td>22.4±1.1</td>
<td>204.1±12.9</td>
<td>29.0</td>
</tr>
</tbody>
</table>

Mean ± S.E., n=12

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**Repeated-dose administration**

Mecobalamin was administered intravenously to 6 healthy adult male volunteers at a single dose of 500 µg daily for 10 consecutive days. Serum total B12 concentration determined before each administration increased from day today. After 2 days of
administration, the serum total B12 concentration was 5.3±1.8 ng/mL, about 1.4 times the 24 hr value (3.9±1.2 ng/mL) after administration. At 3 days of administration it had increased to 6.8±1.5 ng/mL, about 1.7 times the 24 hr value, and this concentration was maintained until the last dosing.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. Pharmaceutical particulars
6.1 List of excipients
Benzyl Alcohol I.P. 85 1% W/V
Water For Injection I.P Q.S

6.2 Incompatibilities
None known.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store in a cool place. Protect from light.

Administrative data
7. Marketing authorisation holder
Strides Shasun Limited
Strides House, Bilekahalli,
Bannerghatta Road,
Bengaluru – 560 076, India

8. Toll free number for reporting
1800 4190601

9. Date of text
16th May 2016