1. Name of finished pharmaceutical product:

NEUROCARE 25 (Methylcobalamin, Pregabalin, Folic acid, Pyridoxine hydrochloride & Alpha Lipoic acid Capsules)

S.1 Strength (composition):

Each soft gelatin capsule contains:

Methylcobalamin		750mcg
Pregabalin		25mg
Folic acid	BP	1.5mg
Pyridoxine hydrochloride	BP	3mg
Alpha Lipoic acid	USP	100mg
Excipients		q.s

1.2. Pharmaceutical dosage form:

Soft gelatin capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

2.1 Qualitative Declaration:

S.No	Ingredients	Specification	Function
Fill materials			
1	Methylcobalamin	IHS	Neuropathic disorder
2	Pregabalin	IHS	Anticonvulsants
3	Folic acid	BP	Vitamin
4	Pyridoxine Hydrochloride	BP	Vitamin
5	Alpha Lipoic acid	USP	Antioxidants
6	Anhydrous Calcium Hydrogen Phosphate	BP	Minerals
7	Butylated hydroxy anisole	BP	Antioxidant
8	Butylated hydroxy toluene	BP	Antioxidant
9	Hydrogenated vegetable oil	BP	Suspending agent
10	Yellow Bees wax	BP	Suspending agent
11	Lecithin	USP	Emollient
12	Refined soya oil	BP	Diluent
Shell materials			
13	Gelatin	BP	Gelling agent
14	Glycerol	BP	Plasticizer
15	Liquid Sorbitol (Non-crystallising)	BP	Plasticizer
16	Methylhydroxy benzoate	BP	Preservative
17	Titanium dioxide	BP	Opacifier
18	Allura Red	IHS	Colouring agent
19	Sunset Yellow FCF	IHS	Colouring agent
20	Brilliant Blue FCF	IHS	Colouring agent
21	Purified water	BP	Solvent

2.2 Quantitative declaration:

Each soft gelatin capsule contains:

Methylcobalamin		750mcg
Pregabalin		25mg
Folic acid	BP	1.5mg
Pyridoxine hydrochloride	BP	3mg
Alpha Lipoic acid	USP	100mg
Excipients		q.s

Batch Size: 160000 Capsules

S. No	Ingredients	Label claim mg/cap	Overages	Specification[1]	Added mg/cap	Added kg/batch	Reason for Inclusion
Fill Material							
1.	Methylcobalamin	750mcg	50	IHS	1.125	0.180	Neuropathic disorder
2.	Pregabalin	25mg	10	IHS	27.500	4.400	Anticonvulsants
3.	Folic acid	1.5mg	50	BP	2.250	0.360	Vitamin
4.	Pyridoxine Hydrochloride	3mg	10	BP	3.300	0.528	Vitamin
5.	Alpha Lipoic acid	100mg	10	USP	110.000	17.600	Antioxidants
6.	Anhydrous Calcium Hydrogen Phosphate	---	---	BP	110.000	17.600	Minerals
7.	Butylated hydroxy anisole	---	---	BP	0.100	0.016	Antioxidant
8.	Butylated hydroxy toluene	---	---	BP	0.100	0.016	Antioxidant
9.	Hydrogenated vegetable oil	---	---	BP	25.000	4.000	Suspending agent
10.	Yellow Bees wax	---	---	BP	15.000	2.400	Suspending agent
11.	Lecithin	---	---	USP	20.000	3.200	Emollient
12.	Refined soya oil*	---	---	BP	385.625	61.700	Diluent
Shell Material[2]							
13.	Gelatin[3]	---	---	BP	234.710	37.554	Gelling agent
14.	Glycerol	---	---	BP	62.608	10.017	Plasticizer
15.	Liquid Sorbitol (Non-crystallising)	---	---	BP	41.724	6.676	Plasticizer
16.	Methylhydroxy benzoate	---	---	BP	1.408	0.225	Preservative
17.	Titanium dioxide	---	---	BP	1.255	0.201	Opacifier
18.	Allura Red	---	---	IHS	0.083	0.013	Colouring agent
19.	Sunset Yellow FCF	---	---	IHS	0.193	0.031	Colouring agent
20.	Brilliant Blue FCF	---	---	IHS	0.020	0.003	Colouring agent
21.	Purified water	---	---	BP	38.000	6.080	Solvent

*- Adjust the quantity to obtain desired medicament weight of 700.00mg/cap with respect to potency calculation using Refined soya oil.

[1] Current pharmacopoeial monographs are implied.

[2] In the batch formula excess material is added to compensate process loss. Process loss due to Cooking tank wastages, Placebo wastage, Service tank/spreader box retention & Net Wastage.

[3] Gelatin is derived from Bovine bones free from skills, spinal cord and vertebrae. Country of origin – India.

Abbreviation:

USP : United State Pharmacopoeia

BP : British Pharmacopoeia

IHS : In-House Specification

3. PHARMACEUTICAL FORM

Light brown coloured oblong shaped opaque soft gelatin capsules contains reddish yellow colour oily mass.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEUROCARE - 25 is indicated for Peripheral Neuropathy, Diabetic Neuropathy, Drug induced Neuropathy, Fibromyalgia, Adjunctive therapy for adult patients with partial onset seizures.

4.2 Posology and method of administration

Dosage:

As directed by the Physician

Method of administration:

Oral

4.3 Contraindications

It should not be used in patients on Levodopa therapy and hypersensitivity to any of the above ingredients.

4.4 Special Warning & Precaution for use

Should not be prescribed to individuals who are allergic to any of the active or inactive compounds in the product

Pediatric Use:

It is not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

General use:

Protect from light. Prolonged daily dose administration over 25,000 Units vitamin A should be under close supervision. Blood level assays are not a direct measure of liver storage. Liver storage should be adequate before discontinuing therapy. Single vitamin A deficiency is rare. Multiple vitamin deficiency is expected in any dietary deficiency.

4.5 Interaction with other medicinal products and other forms of Interactions:

Absorption of methylcobalamin from the gastro-intestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H2-receptor antagonists and colchicine.

Concurrent use of pregabalin with oxycodone, lorazepam and ethanol may increase the central nervous system effects e.g. depression.

4.6 Pregnancy and lactation

May be or may not be harmful to an unborn baby. Consult a healthcare provider if you are in gestation or plan to have a baby during treatment.

It is not known whether it can pass through the breast milk or not. Nursing mothers should avoid breastfeeding while taking the capsule.

4.7 Effects on ability to drive and use machines

NEUROCARE - 25 may have minor or moderate influence on the ability to drive and use machines. NEUROCARE - 25 may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Adverse effects reported are: nausea, headache, dizziness, somnolence, dry mouth, edema etc.

4.9 OVERDOSE

In case of overdose, treatment should include general supportive measures and may include haemodialysis.

5- PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Methylcobalamin is one of the coenzyme forms of Vitamin B12, which is water-soluble vitamin in the body. Its deficiency leads to damage the nervous system. This causes a wide range of neurological disorders.

Methylcobalamin is required for the conversion of homocysteine to methionine and its derivative S-adenosyl methionine.

Pregabalin (S)-3-(aminomethyl)-5-methylhexanoic acid) is a structural derivative of the inhibitory neurotransmitter alpha-aminobutyric acid(GABA). It has anticonvulsant, analgesic and anxiolytic activity. Pregabalin is used in the management of neuropathic pain, peripheral neuropathy, fibromyalgia and used as an adjuvant therapy for adult patients with partial onset seizures.

Methylcobalamin, folic acid and Vitamin B6 help to decrease the homocysteine levels and improve the neuropathic symptoms.

Alpha lipoic acid acts as a potent antioxidant and improves symptoms of neuropathy.

5.2 Pharmacokinetic Properties

Pregabalin:

After oral administration, Pregabalin is rapidly absorbed in GIT. The Cmax can be achieved within one hour after administration. The oral bioavailability is about 90%. The rate of absorption is influenced by food intake. Pregabalin is not bound to plasma proteins. The Vss of Pregabalin is 0.56L/kg. About 98% of the administered Pregabalin is excreted via the urine as unchanged drug.

Methylcobalamin:

After oral administration, the peak plasma concentration can be achieved after three hours. The vitamin is eliminated in the urine as unchanged drug.

Folic Acid:

Folic acid is absorbed mainly from the proximal part of the small intestine. Folate polyglutamates are considered to be deconjugated to monoglutamates during absorption. Folic acid rapidly appears in the blood where it is extensively bound to plasma proteins. Some folic acid is distributed in body tissues, some is excreted as folate in the urine and some is stored in the liver as folate.

Pyridoxine Hydrochloride:

Pyridoxine is absorbed from the gastro-intestinal tract and converted to the active pyridoxal phosphate which is bound to plasma proteins. It is excreted in the urine as 4-pyridoxic acid.

5.3 Preclinical safety data

In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long term exposure to pregabalin at exposures ≥ 5 times the mean human exposure at the maximum recommended clinical dose.

Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures >2 times the maximum recommended human exposure.

Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.

Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests.

Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long term clinical data. There is no evidence to suggest an associated risk to humans.

In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients

S. No	Ingredients	Specification	Reason for Inclusion
1.	Anhydrous Calcium Hydrogen Phosphate	BP	Diluents
2.	Butylated hydroxy anisole	BP	Antioxidant
3.	Butylated hydroxy toluene	BP	Antioxidant
4.	Hydrogenated vegetable oil	BP	Suspending agent
5.	Yellow Bees wax	BP	Suspending agent
6.	Lecithin	USP	Emollient
7.	Refined soya oil	BP	Diluent
8.	Gelatin	BP	Gelling agent
9.	Glycerol	BP	Plasticizer
10.	Liquid Sorbitol (Non-crystallising)	BP	Plasticizer
11.	Methylhydroxy benzoate	BP	Preservative
12.	Titanium dioxide	BP	Opacifier
13.	Allura Red	IHS	Colouring agent
14.	Sunset Yellow FCF	IHS	Colouring agent
15.	Brilliant Blue FCF	IHS	Colouring agent
16.	Purified water	BP	Solvent

6.2 Incompabilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from direct sunlight.

Keep medicines out of reach of children.

6.5 Nature and contents of container

a) Type of package Blister pack

b) Nature and packaging material - 3X 10's Blister pack

7. Manufacturing site address

Old Survey No. 20/1, new survey No. 9/810

Vandalur – Kelambakkam Road,

Pudupakkam Village, Kancheepuram District – 603 103, Tamilnadu, India

8. Marketing authorization holder

9. Date of first registration/ renewal of the registration

10. Date of revision of the text –Nil