Summary Product Characteristics (SPC)

1. Name of the Finish Pharmaceutical Product:
Brand Name: URUKA PLUS 75
Generic Name: Pregabalin 75 mg & Methylcobalamin 750 mcg
Strength: (75 mg & 750 mcg)
Pharmaceutical Form: Had gelatin capsule Shell

2. Qualitative and quantitative composition
Each hard gelatin capsule contains:
Pregabalin ..... 75 mg
Methylcobalamin ..... 750 mcg
Excipients..... q.s
Approved colour used in capsule shell

3. Pharmaceutical form
Hard gelatin capsules shell,
Brown coloured cap and brown coloured body "size 2" hard gelatin capsules shell filled with light pink coloured powder.

4. Clinical particulars
4.1 Therapeutic indications
It is indicated for management of neuropathic pain associated with diabetic peripheral neuropathy.

Uruka Plus 75 is a combination of Pregabalin and methylcobalamin.

Neuropathic pain

Pregabalin and Methylcobalamin is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy

Pregabalin and Methylcobalamin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

Pregabalin and Methylcobalamin 1s indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

Pregabalin is a structural derivative of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). Pregabalin does not bind directly to GABAA, GABAB, or benzodiazepine receptors, does not augment GABAA responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Methylcobalamin is a kind of endogenous coenzyme vitamin B12. It is well transported to nerve cell organelles and

promotes nucleic acid and protein synthesis, axonal transport, axonal regeneration and myelination.

4.2 Posology and method of administration

The dose range is 75 to 600 mg per day given in either two or three divided doses.

Pregabalin for Neuropathic Pain:

Pregabalin treatment can be started at a dose of 150 mg per day given as two or three divided doses 75 mg b.i.d. based on individual patient response and tolerability the dose may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed to a maximum dose of 600 mg per day after an additional 7 day interval.

Methylcobalamin: Oral administration of Methylcobalamin (500 mcg three times daily for four months) resulted in subjective improvement in burning sensations, numbness loss of sensation and muscle cramp.

Method of administration: the combination is for oral use only, may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Regular consumption of alcohol is an important risk for the development and the progression of neuropathic disease so this combination should be avoided.

Pregabalin:

Diabetic patients

In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medicinal products.

Hypersensitivity reactions

There have been reports in the posmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial perioral, or upper airway swelling occur.

Dizziness, somnolence, loss of consciousness, confusion, and mental impairment

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Renal failure

Cases of renal failure have been reported and in some cased discontinuation of pregabalin did show reversibility of this adverse reaction.

Methylcobalamin: The prolonged use of larger doses of Methylcobalamin is not recommended for patients whose occupation requires the handling of mercury/mercury compound.

4.5 Interaction with other medicinal products and other forms of interaction

Pregabalin: Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, it is unlikely to produce, or be subject to pharmacokinetic interactions.

In vivo studies and population pharmacokinetic analysis:
Accordingly, in vivo studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral Antidiabetic, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.
Oral contraceptives, norethisterone and or ethinyl oestradiol:
Co-administration of pregabalin with the oral contraceptives norethisterone and or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either substance.
Ethanol, Lorazepam, oxycodone:
Pregabalin may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral dosed of pregabalin co administered with oxycodone, lorazepam or ethanol did not result in clinically important effects on respiration. I the posmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medicinal products. Pregabalin appears to additive in the impairment of cognitive and gross motor function caused by oxycodone.
Methylcobalamin: There is no known adverse reactions when taken in conjunction with medications.

4.6 Pregnancy and lactation

Women of childbearing potential /Contraception in males and females
As the potential risk for humans is unknown effective contraception must be used in women of child bearing potential.

Pregnancy
There are no adequate data from the use of pregabalin in pregnant women.
Studied in animals have shown reproductive toxicity. The potential risk for humans is unknown
Uruka should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus)

Breast-feeding:
Pregabalin is excreted into human milk. The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast feeding or to discontinue pregabalin therapy taking into account the benefit of breast feeding for the child san the benefit of therapy for the woman

Fertility
There are no clinical data on the effects of pregabalin on female fertility.
In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were on effects on sperm motility.
A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these finding is unknown.

4.7 Effects on ability to drive and use machines

Uruka plus may have minor or moderate influence on the ability to drive and use machines. Uruka plus a 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

Pregabalin: The most commonly reported adverse reactions were dizziness and somnolence. Adverse reaction were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adcerse reaction was 12% for patients receiving pregabalin and 5% of patients reveiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness. The patient should be informed about this at the start of the treatment. In case of unexpected effects consult your doctor.

Methylcobalamin: Methylcobalamin has excellent to liability and no known toxicity

4.9 Overdose

Pregabalin: In overdoses up to 15 g , no unexpected adverse reactions were reported.

In the post marketing experience , the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confessional state, agitation, and restlessness.

Treatment of pregabalin overdose should include general supportive and may include haemodialysis if necessary. There are no reports of Methylcobalamin Overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pregabalin binds to an auxiliary subunit (a_2-8 protein) of voltage-gated calcium channels in the central nervous system.

Methylcobalamin: the exact mechanism of action is not yet elucidated, it is possible that Methylcobalamin is needed for the synthesis of melatonin, since the biosynthetic formation of melatonin requires the donation of a methyl group.

5.2 Pharmacokinetic properties

Pregabalin

Absorption

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be 2': 90% and is independent of dose. Following repeated administration, steady state is achieved within 25 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in Cmax by approximately 25-30% and a delay in tmax to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution

In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats, in humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 I/Kg. Pregabalin is not bound to plasma proteins.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin approximately 98% of the radioactivity recovered in the urine was unchanged

pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9 % the dose.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug.

Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance.

Methylcobalamin: Absorption of Methylcobalamin following oral administration. The quantity of cobalmin detected following a small oral dose of Methylcobalamin but significantly more cobalmin accumulates in liver tissue following administration of Methylcobalamin. Human urinary excretion of Methylcobalamin is about one third, indicating substantially grater tissue retention

5.3 Preclinical safety data

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose, Lactose, Purified Talc, Magnesium Stearate, Croscarmellose Sodium, Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C. Protected from light & moisture

6.5 Nature and contents of container

10 Capsules in Alu-Alu blister, 3 of such packed in carton along with package insert.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Theon Pharmaceuticals Limited
Plot No. 400 Industrial Area Phase -1
Panchkula -134113
Haryana
India

8 MARKETING AUTHORISATION NUMBER(S)

xxxx

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

xxxx

10 DATE OF REVISION OF THE TEXT

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