1. NAME OF THE MEDICINAL PRODUCT:

Co-Depricap Capsule 3/25mg or 6/25mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION: Co-Depricap Capsule 3/25mg

Each capsule contains:
Olanzapine USP …….. 3mg
Fluoxetine (as HCl) …. 25mg

Co-Depricap Capsule 6/25mg
Each capsule contains:
Olanzapine USP …….. 6mg
Fluoxetine (as HCl) …. 25mg

Excipients: Pregelatinized Starch, Sodium Lauryl Sulphate

Description:
Co-Depricap Capsule 3/25mg
Hard gelatin capsule size No. "02" dark amethyst opaque cap and dark amethyst opaque body both imprinted with white NQ logo, containing yellow dry powder.

Co-Depricap Capsule 6/25mg
Hard gelatin capsule No. "02" with yellowish green opaque cap and body both imprinted with black NQ logo containing yellow dry granular powder.

3. PHARMACEUTICAL FORM:

Capsule

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications (Leaflet)

Depressive Episodes Associated with Bipolar I Disorder: Co-Depricap (Olanzapine and Fluoxetine HCl) Capsule is indicated for the acute treatment of depressive episodes associated with Bipolar I Disorder in adults.

Treatment Resistant Depression: Co-Depricap (Olanzapine and Fluoxetine HCl) Capsuleis indicated for the acute treatment of Treatment Resistant Depression (Major Depressive Disorder in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode).

4.2 Posology and method of administration (Leaflet)

Depressive Episodes Associated with Bipolar I Disorder: Co-Depricap (Olanzapine and Fluoxetine HCl) Capsule should be administered once daily in the evening, generally beginning with the 6mg/25mg capsule. While food has no appreciable effect on the absorption of Olanzapine and Fluoxetine HCl Capsule given individually, the effect of food on the absorption of Olanzapine and Fluoxetine HCl Capsule has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with **Co-Depricap** (Olanzapine and Fluoxetine HCl) Capsule in a dose range of Olanzapine 6mg to 12mg and Fluoxetine 25mg to 50mg. The safety of doses above 18mg/75mg has not been evaluated in clinical studies. It is generally accepted that Bipolar I Disorder, including the depressive episodes associated with Bipolar I Disorder, is a chronic illness requiring chronic treatment. The physician should periodically re-examine the need for continued pharmacotherapy.

Treatment Resistant Depression:

Co-Depricap (Olanzapine and Fluoxetine HCl) Capsule should be administered once daily in the evening, generally beginning with the 6mg/25mg capsule. While food has no appreciable effect on the absorption of Olanzapine and Fluoxetine given individually, the effect of food on the absorption of **Co-Depricap** (Olanzapine and Fluoxetine HCl) Capsule

has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with **Co-Depricap** (Olanzapine and FluoxetineHCl) Capsule in a dose range of Olanzapine 6mg to 18mg and Fluoxetine 25mg to 50mg. The safety of doses above 18mg/75mg has not been evaluated in clinical studies. It is generally accepted that Treatment Resistant Depression (Major Depressive Disorder in adult patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) is a chronic illness requiring chronic treatment. The physician should periodically re-examine the need for continued pharmacotherapy.

4.3 Contraindications: (Leaflet)

Olanzapine and Fluoxetine HCl Capsule is contra-indicated, if patient is hypersensitive to active substances and any of its excipients.

4.4 Special warnings and precautions for use:

Clinical Worsening and Suicide Risk: Patients with Major Depressive Disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking medications and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders; and these disorders themselves are the strongest predictors of suicide.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of drugs, including
Olanzapine.

4.5 Interaction with other medicinal products and other forms of interaction: (Leaflet)

Mono Amine Oxidase Inhibitors (MAOI): Olanzapine and Fluoxetine HCl should not be used in combination with MAOI or within a minimum of 14 days of discontinuing therapy with MAOI. There have been reports of serious, sometimes fatal reactions (including rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma) in patients receiving Fluoxetine in combination with an MAOI, and in patients who have recently discontinued Fluoxetine and are then started on MAOI. **CNS Acting Drugs:** Caution is advised if the concomitant administration of Olanzapine and Fluoxetine HCl and other CNS active drugs is required. In evaluating individual cases, consideration should be given to use lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status.

4.6. Fertility, Pregnancy and Lactation

Olanzapine

Pregnancy:

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion.

Lactation

In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

Fluoxetine (as HCl)

Pregnancy:

There are no adequate and well-controlled clinical studies on the use of fluoxetine in pregnant women. Results of a number of published epidemiological studies assessing the risk of fluoxetine exposure during the first trimester of pregnancy have demonstrated inconsistent results.

Breast-feeding:

Fluoxetine is excreted in human breast milk. In 1 breast milk sample, the concentration of

fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208/mL of norfluoxetine on the 2nd day of feeding.

4.7. Effects on ability to drive and use machines:

No effect on the ability to drive and use machines.

4.8. Undesirable effects: (Leaflet)

Commonly Observed Adverse Reactions in Short-Term Controlled Studies Including Depressive Episodes Associated with Bipolar I Disorder and Treatment Resistant Depression: **Sexual Dysfunction:** In the pool of controlled Olanzapine and Fluoxetine HCl studies in patients with Bipolar depression, there were higher rates of the treatment-emergent adverse reactions decreased and abnormal in the Olanzapine and Fluoxetine HCl group than in the placebo group. Sexual dysfunction, including priapism has been reported with all SSRIs.

Body as a Whole: Frequent: chills, neck rigidity, photosensitivity reaction; Rare: death.

Cardiovascular System: Frequent: vasodilatation; Infrequent: QT-interval prolonged.

Digestive System: Frequent: diarrhea; Infrequent: nausea and vomiting; Rare: gastrointestinal hemorrhage, liver fatty deposits.

Nervous System: Infrequent: buccoglossal syndrome, coma, depersonalization, emotional hypokinesia, movement disorder; Rare: hyperkinesia, libido increased, withdrawal syndrome.

4.9. Overdose: (Leaflet)

No specific antidote for either Fluoxetine or Olanzapine overdose is known. Treatment should be supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES: (Leaflet)

5.1 Pharmacodynamics properties and Pharmacokinetic properties:

Pharmacodynamics:

Olanzapine binds with high affinity to the following receptors: serotonin 5HT2 and 5HT6, dopamine D1-4, histamine H 1 receptor and adrenergic a1 receptors. Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT3 and muscarinic M1-5. Olanzapine binds weakly to GABA, BZD, and b-adrenergic receptors.

Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Pharmacokinetics:

Absorption and bioavailability: Olanzapine: It is well absorbed and reaches peak concentration approximately in 6 hours following an oral dose. Food does not affect the rate or extent of Olanzapine absorption. It is metabolized extensively by first pass effect with approximately 40% of the dose metabolized before reaching the systemic circulation. Fluoxetine: Following a single oral 40mg dose, peak plasma concentrations of Fluoxetine from 15 to 55ng/ml are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of Fluoxetine, although it may delay its absorption by 1 to 2 hours; which is probably not clinically significant. **Distribution:** The in-vitro binding to human plasma proteins of Olanzapine and Fluoxetine in combination is similar to the binding of the individual components. Olanzapine: It is extensively distributed throughout the body with a volume of distribution of approximately 1000L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100ng/ml, binding primarily to albumin and a1-acid glycoprotein. Fluoxetine: Over the concentration range from 200 to 1000ng/ml, approximately 94.5% of Fluoxetine is bound in vitro to human serum proteins, including albumin and a-glycoprotein. **Metabolism and Elimination:** Olanzapine and Fluoxetine HCl therapy yielded steady state concentrations of nor-fluoxetine similar to those seen with Fluoxetine in the therapeutic dose range. Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours.

5.2 Preclinical safety data:

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients

Excipients:

Pregelatinized Starch, Sodium Lauryl Sulphate

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

24 months

6.4 Special precautions for storage: (Leaflet)

Store below 30□C.

Protect from light and moisture.

Keep out of the reach of children.

6.5 Nature and contents of container:

Co-Depricap 3mg/25mg Capsules are available in Alu-Alu pack size of 14's.
Co-Depricap 6mg/25mg Capsules are available in Alu-Alu pack size of 14's.

6.6 Special precautions for disposal and other handling (Leaflet)

No special requirements.

7. MARKETING AUTHORISATION HOLDER:

Nabiqasim Industries (Pvt.) Ltd.
17/24, Korangi Industrial Area, Karachi – Pakistan.

8. MARKETING AUTHORISATION NUMBER:

Co-Depricap Capsule 3/25 mg - 076135

Co-Depricap Capsule 6/25 mg - 076136

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORISATION:

First Authorization: 29 October, 2013

10. DATE OF REVISION OF THE TEXT:

January-2018

11. DOSIMETRY

Not applicable