Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Depricap Liquid

2. Qualitative and quantitative composition

Each 5ml (teaspoon) contains:
Fluoxetine (As HCl) …….20mg

For full list of excipients, see section 6.1

3. Pharmaceutical form

Oral Solution
Clear transparent, colorless to slightly yellow colored liquid with pleasant odour and sweet taste.

4. Clinical particulars

4.1 Therapeutic indications

Adults: DEPRICAP (Fluoxetine) is approved for the treatment of major depression (including pediatric depression), obsessive-compulsive disorder (in both adult and pediatric populations), bulimia nervosa, panic disorder and Premenstrual Dysphoric Disorder (PMDD). In addition, Fluoxetine is used to treat trichotillomania. DEPRICAP (Fluoxetine) is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity. Children and Adolescents Aged 8 Years and Above: Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

4.2 Posology and method of administration

For oral administration. Major Depressive Episodes: Adults and the elderly: The recommended dose is 20mg daily. Dosage should be reviewed and adjusted, if necessary, within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, in some patients, with insufficient response to 20mg, the dose may be increased gradually up to a maximum of 60mg. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose. Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.
Obsessive-compulsive Disorder (OCD): Adults and the elderly: The recommended dose is 20mg daily. Although there may be an increased potential for undesirable effects at higher doses, in some patients, if after two weeks there is insufficient response to 20mg, the dose may be increased gradually up to a maximum of 60mg. If no improvement is observed within 10 weeks, treatment with Fluoxetine should be reconsidered. If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis. Dosage adjustments should be

made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. The need for treatment should be reassessed periodically.

Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.

Bulimia Nervosa: Adults and the elderly: A dose of 60mg/day is recommended. Long-term efficacy (more than 3 months) has not been in bulimia nervosa.

DOSAGE IN AGE GROUPS: Adults: The recommended dose may be increased or decreased. Doses above 80mg/day have not been systematically evaluated. Fluoxetine may be administered as a single or divided dose, during or between meals. When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment. The capsule and liquid dosage forms are bioequivalent. Children and adolescents aged 8 years and above (moderate to severe major depressive episode): Treatment should be initiated and monitored under specialist supervision. The starting dose is 10mg/day given as 2.5ml of the Fluoxetine liquid formulation. Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose. After one to two weeks, the dose may be increased to 20mg/day. Lower-weight children: Due to higher plasma levels in lower-weight children, the therapeutic effect may be achieved with lower doses. For pediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within 9 weeks, treatment should be reconsidered.

Elderly: Caution is recommended when increasing the dose, and the daily dose should generally not exceed 40mg. Maximum recommended dose is 60mg/day. A lower or less frequent dose (e.g., 20mg every second day) should be considered in patients with hepatic impairment, or in patients where concomitant medication has the potential for interaction with Fluoxetine.

4.3 Contraindications

Hypersensitivity to Fluoxetine or to any of its excipients. Fluoxetine is contra-indicated in combination with a non-selective Monoamino Oxidase Inhibitor (MAOI). Similarly, at least 5 weeks should elapse after discontinuing Fluoxetine treatment before starting a MAOI. If Fluoxetine has been prescribed chronically and/or at a high dose, a longer interval should be considered. The combination of Fluoxetine with a reversible MAOI (e.g., moclobemide) is not recommended. Treatment with Fluoxetine can be initiated the following day after discontinuation of a reversible MAOI.

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age: Fluoxetine should only be used in children and adolescents aged 8 to 18 years for the treatment of moderate to severe major depressive episodes and it should not be used in other indications. Fluoxetine should be discontinued in any patient entering amanic phase. It is important that the prescriber discusses carefully the risks and benefits of treatment with the child/young person and/or their parents.

Rash and allergic reactions: Rash, anaphylactoid events and progressive

systemic events, sometimes become serious (involving skin, kidney, liver or lung) have been reported.
Seizures: Treatment should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency.
Hepatic/Renal function: Fluoxetine is extensively metabolized by the liver and excreted by the kidneys. A lower dose, e.g., alternate day dosing, is recommended in patients with significant hepatic dysfunction. Pregnancy: Fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing Mothers: Breast feeding is not recommended. Tamoxifen: Fluoxetine should whenever possible be avoided during tamoxifen treatment. Cardiac disease: Caution is advisable. Weight loss: Weight loss may occur in patients taking Fluoxetine, but it is usually proportional to baseline body weight. Diabetes: In patients with diabetes, treatment with an SSRI may alter glycemic control.
Hypoglycemia has occurred during therapy with Fluoxetine and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic dosage may need to be adjusted. Suicide/suicidal thoughts or clinical worsening: It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Withdrawal symptoms seen on discontinuation of SSRIs treatment: Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor, and headache are the most commonly reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that Fluoxetine should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's needs. Fluoxetine oral liquid contains sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Using an NSAID with Fluoxetine e.g. Aspirin, Ibuprofen, Naproxen, Celecoxib, Diclofenac, Indomethacin, Meloxicam and others, may cause you to bruise or bleed easily. Tell your doctor about all other medications you are using, especially any other antidepressants such as Amitriptyline, Escitalopram, Imipramine, Sertraline and others e.g., Alprazolam; Clopidogrel; Clozapine; Flecainide; Haloperidol; Vinblastine; a blood thinner such as Warfarin; Migraine headache medicine such as Almotriptan, Frovatriptan, Sumatriptan, Naratriptan, Rizatriptan or Zolmitriptan; or seizure medication such as Phenytoin or Carbamazepine.

4.6 Pregnancy and Lactation

Pregnancy
Fluoxetine should not be used during pregnancy unless the clinical condition of the woman requires treatment with fluoxetine and justifies the potential risk to the foetus. Abrupt discontinuation of therapy should be avoided during pregnancy. If fluoxetine is used during pregnancy, but caution should be exercised, especially during late pregnancy or just prior to the onset of labour since the following effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, and difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

Lactation:
Fluoxetine and its metabolite, norfluoxetine, are known to be excreted in human breast milk. Adverse events have been reported in breast-feeding infants. If treatment with fluoxetine is considered necessary, discontinuation of breast-feeding should be considered; however, if breast-feeding is continued, the lowest effective dose of fluoxetine should be prescribed.

Fertility:
Animal data have shown that fluoxetine may affect sperm quality. Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines
Fluoxetine has no or negligible influence on the ability to drive and use machines. Although fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive drug may impair judgement or skills. Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

4.8 Undesirable effects
The incidence of adverse effects with Fluoxetine is less than 1% of treated cases commonly observed. The commonly observed adverse effects associated with Fluoxetine were nervous system complaints; including anxiety, nervousness and insomnia, drowsiness and fatigue / asthenia, tremor, sweating, gastrointestinal complaints; including anorexia, nausea and diarrhoea, dizziness/light headedness, body as whole; primarily asthenia, headache and skin; primarily rash and pruritus.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the Pharmacy and Poisons Board (PPB) through the Pharmacovigilance Electronic Reporting System (PvERS)

at https://pv.pharmacyboardkenya.org/ or by using the approved PPB ADR reporting forms.

4.9 Overdose

Symptoms

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias (including nodal rhythm and ventricular arrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest(including very rare cases of Torsade de Pointes), pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdosage of fluoxetine alone has been extremely rare.

Rarely features of the "serotonin syndrome" may occur. This includes alteration of mental status, neuromuscular hyperactivity and autonomic instability. There may be hyperpyrexia and elevation of serum creatine kinase. Rhabdomyolysis is rare.

Management

Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. No specific antidote is known.

Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of any benefit. Activated charcoal, which may be used with sorbitol, may be as or more effective, than emesis or lavage. In managing overdosage, consider the possibility of multiple drug involvement. An extended time for close medical observation may be needed in patients who have taken excessive quantities of a tricyclic antidepressant if they are also taking, or have recently taken, fluoxetine.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI) and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as alpha1-, alpha2- and beta -adrenergic; serotonergic; dopaminergic; histaminergic 1; muscarinic; and GABA receptors.

Major depressive episodes: Fluoxetine has been shown to be significantly more effective than placebo, as measured by the Hamilton Depression Rating Scale (HAM-D). In these studies, Fluoxetine produced a significantly higher rate of response (defined by a 50% decrease in the HAM-D score) and remission compared to placebo. Obsessive-compulsive disorder: In short-term trials (under 24 weeks), Fluoxetine was shown to be significantly more effective than placebo. There was a therapeutic effect at 20mg/day, but higher doses (40 or 60mg/day) showed a higher response rate. In long-term studies (three short-term studies extension phase and a relapse prevention study), efficacy has not been shown.

Bulimia nervosa: In short-term trials (under 16 weeks), in out-patients fulfilling DSM-III-Rcriteria

for bulimia nervosa, Fluoxetine 60mg/day was shown to be significantly more effective than placebo for the reduction of binging and purging

activities. However, for long-term efficacy no
conclusion can be drawn.
Premenstrual Dysphoric Disorder (PMDD): Selective Serotonin Reuptake Inhibitors (SSRIs) Have emerged as first-line therapy. Several randomized, placebo-controlled trials in women with PMDD (Premenstrual Dysphoric Disorder) have clearly demonstrated that the SSRIs. Have excellent efficacy.

5.2 Pharmacokinetic properties

Absorption: Fluoxetine is well absorbed from the gastro-intestinal tract after oral administration. The bioavailiability is not affected by food intake.
Distribution: Fluoxetine is extensively bound to plasma proteins (about 95%) and it is widely distributed (volume of distribution: 20-40 l/kg). Steady - state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to the concentrations seen at 4 to 5 weeks.
Metabolism: Fluoxetine has a non-linear pharmacokinetic profile with first pass liver effect. Maximum plasma concentration is generally achieved 6-8 hours after administration. Fluoxetine is extensively metabolised by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolised by the liver to the active metabolite norfluoxetine (desmethylfluoxetine), by desmethylation.
Elimination: The elimination half-life of fluoxetine is 4 to 6 days and for norfluoxetine 4 to 16 days. These long half-lives are responsible for persistence of the drug for 5-6 weeks after discontinuation. Excretion is mainly (about 60%) via the kidney. Fluoxetine is excreted into breast milk.

5.3 Preclinical safety data

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies.
In a juvenile toxicology study in CD rats, administration of 30 mg/kg/day of fluoxetine hydrochloride on postnatal days 21 to 90 resulted in irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive tract and decreased fertility. Delays in sexual maturation occurred in males (10 and 30 mg/kg/day) and females (30 mg/kg/day). The significance of these findings in humans is unknown. Rats administered 30 mg/kg also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10 mg/kg/day, plasma levels achieved in animals were approximately 0.8 to 8.8 fold (fluoxetine) and 3.6 to 23.2-fold (norfluoxetine) those usually observed in paediatric patients. At 3 mg/kg/day, plasma levels achieved in animals were approximately 0.04 to 0.5-fold (fluoxetine) and 0.3 to 2.1-fold (norfluoxetine) those usually achieved in paediatric patients.
A study in juvenile mice has indicated that inhibition of the serotonin transporter prevents the accrual of bone formation. This finding would appear to be supported by clinical findings. The reversibility of this effect has not been established.
Another study in juvenile mice (treated on postnatal days 4 to 21) has demonstrated that inhibition of the serotonin transporter had long lasting

effects on the behaviour of the mice. There is no information on whether the effect was reversible. The clinical relevance of this finding has not been established.

Adult animal studies

In a 2-generation rat reproduction study, fluoxetine did not produce adverse effects on the mating or fertility of rats, was not teratogenic, and did not affect growth, development, or reproductive parameters of the offspring.

The concentrations in the diet provided doses approximately equivalent to 1.5, 3.9, and 9.7 mg fluoxetine/kg body weight.

Male mice treated daily for 3 months with fluoxetine in the diet at a dose approximately equivalent to 31 mg/kg showed a decrease in testis weight and hypospermatogenesis. However, this dose level exceeded the maximum-tolerated dose (MTD) as significant signs of toxicity were seen.

6. Pharmaceutical Particulars

6.1 List of Excipients

Excipients:

Methyl Paraben, Propyl Paraben, Benzoic Acid, Sugar Pharma Grade, Neotame, Citric Acid Monohydrate, Liquid Glucose, Mint Flavour, De-ionized Water

6.2 Incompatibilities

Not known

6.3 Shelf-Life

24 Months

6.4 Special Precautions for storage

Store below 30□C.

Protect from light and moisture. Keep out of the reach of children.

6.5 Nature and Content of container

DEPRICAP LIQUID is available in bottle pack of 60ml.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

Nabiqasim Industries (Pvt.) Ltd.

17/24, Korangi Industrial Area, Karachi

8. Marketing Authorization Number

H2022/CTD7073/13507

9. Date of first authorization/renewal of the authorization

2023 March 28

10. Date of revision of the text

2023 March 28