ANZACK TABLETS 20MG

NAME AND STRENGTH OF ACTIVE INGREDIENT(S):

Each tablet contains:
Fluoxetine Hydrochloride equivalent to Fluoxetine ……20mg

PRODUCT DESCRIPTION:

A round, light green, scored, flat of diameter 7mm tablets with 'MPI' logo.

PHARMACODYNAMICS :

Fluoxetine is a selective inhibitor of serotonin reuptake and has practically no affinity to other receptors such as α_{1-}, α_{2-}, and β-adrenergic; serotonergic; dopaminergic; histaminergic; muscarinic; and GABA receptors.

PHARMACOKINETICS:

Fluoxetine is well absorbed from the gastrointestinal tract following oral administration. At least 60 – 80% of an oral dose appears to be absorbed. The bioavailability is not affected by food intake.
Fluoxetine is approximately 94.5% bound to plasma protein and it is widely distributed with volume of distribution of 20-45 l/kg. Steady-state plasma concentrations are achieved after dosing for several weeks. The steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks.
Fluoxetine had a non-linear pharmacokinetic profile with first pass liver effect. Maximum plasma concentration is generally achieved 6 to 8 hours after administration. Fluoxetine is extensively metabolized by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolized by the liver to the active metabolite norfluoxetine (desmethylfluoxetine) by desmethylation.
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 of about 60% is mainly via the kidney. Fluoxetine is secreted into breast milk.
At-risk populations:
The kinetic parameters are not altered in healthy elderly patients. In case of hepatic insufficiency, fluoxetine and norfluoxetine half-lives are increased to 7 and 12 days, respectively. A lower or less frequent dose should be considered. The kinetic parameters have not been altered in patients with mild, moderate or complete (anuria) renal insufficiency after single-dose administration of fluoxetine. However, after repeated administration, an increase in steady-state plateau of plasma concentrations may be observed.

INDICATION:

Depression: Anzack is indicated for the treatment of symptoms of depressive illness, with or without associated anxiety symptoms.
Obsessive-compulsive disorder.
Pre-menstrual Dysphoric Disorder (PMDD): Anzack is indicated for the treatment of pre-menstrual dysphoric disorder. Diagnosis of PMDD: The essential diagnostic features of PMDD are clear and established cyclicity (occuring during the 1st week of the luteal phase in most menstrual cycles) of symptoms such as depressed mood, anxiety, affective lability, accompanied by impairment in social and/or occupational function and physical symptoms (such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, weight gain) – all of which must be severe. This syndrome should be distinguished from the commoner 'pre-menstrual tension (distinguished from PMDD by milder symptoms and less impact on normal activities)' and from any co-existing psychiatric disorder.

RECOMMENDED DOSAGE:

For oral administration to adults only.
Depression, with or without associated anxiety symptoms:
Adults and the elderly: A dose of 20mg/day is recommended.
Obsessive-compulsive disorder:
Adults and the elderly: 20mg/day to 60mg/day. A dose of 20mg/day is recommended as the initial dose. Although there may be an increased potential for side-effects at higher doses, a dose increase may be considered after several weeks if there is no response.
Pre-menstrual Dysphoric Disorder (PMDD):
A dose of 20mg/day is recommended. Initial treatment should be limited to 6 months, after which patients should be reassessed regarding the benefit of continued therapy.
All indications:
The recommended dose may be increased or decreased. Doses above 80mg/day have not been systemically evaluated. Fluoxetine may be administered with or without food. When dosing is stopped, active drug substances will persist in body for weeks. This should be borne in mind when starting or stopping treatment. Dosage tapering is unnecessary in most patients.
Children:
The use of Anzack in children is not recommended, as safety and efficacy have not been established.
A lower or less frequent dose should be considered in patients with hepatic impairment, concurrent diseases, or who are taking multiple medications (See 'Interactions').

ROUTE OF ADMINISTRATION:
Oral

CONTRAINDICATIONS:
Hypersensitivity to fluoxetine or to any of its excipients.
Fluoxetine is contra-indicated in combination with monoamine oxidase inhibitors (MAOIs). There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, fluoxetine should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping fluoxetine before starting an MAOI.

WARNINGS AND PRECAUTIONS:
1. *Rash and allergic reactions*: Rash, anaphylactoid events, and progressive systemic events, sometimes serious (involving skin, kidney, liver or lung) have been reported. Upon the appearance of rash or other allergic phenomena for which an alternative aetiology cannot be identified, fluoxetine should be discontinued.
2. *Suicidality in Children and Adolescents*:
   - Antidepressants increase the risk of suicidal thinking and behaviour (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.
   - Anyone considering the use of antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
   - Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behaviour.
   - Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.

3. **Suicide**: Patients should be closely monitored during the first few weeks of treatment.
4. **Seizures**: Seizures are a potential risk with antidepressant drugs. Fluoxetine should be introduced cautiously in patients who have a history of seizures, and discontinued in any patient who develops seizures or where there is an increase in seizure frequency. Fluoxetine should be avoided in patients with unstable seizure disorders/epilepsy.
5. **Mania**: Should be used with caution in patients with a history of mania/hypomania. Fluoxetine should be discontinued in any patient entering a manic phase.
6. **Hepatic function**: A lower dose is recommended in patients with significant hepatic dysfunction.
7. **Cardiac disease**: Caution is advisable.
8. **Weight loss**: May occur in patients
9. **Diabetes**: Hypoglycaemia has occurred during therapy and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.
10. **Haemorrhage**: There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura. Caution is advised in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g atypical antipsychotics such as clozapine, phenothiazines, aspirin, NSAIDs), drugs that may increase risk of bleeding, as well as in patients with a history of bleeding disorders.
11. **St John's Wort**: An increase in serotonergic effects, such as serotonin syndrome, may occur when used together.
12. **Interference with cognitive and motor performance**: Any psychoactive drug may impair judgement, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.
13. **Others**: On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluoxetine, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with fluoxetine should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

INTERACTIONS WITH OTHER MEDICAMENTS:
1. *Monoamine oxidase inhibitors* – refer to section 'Contraindications'
2. *Tricyclic and other antidepressant*: Concurrent administration of fluoxetine and a tricyclic antidepressant (eg. nortriptyline, desipramine, imipramine) reportedly has resulted in adverse effects associated with tricyclic toxicity (including sedation, decreased energy, lightheadedness, psychomotor retardation, dry mouth, constipation, memory impairment)
3. *Benzodiazepines*: Increase in the elimination half-life and plasma concentration of diazepam, decrease in diazepam clearance and the rate of formation of desmethyldiazepam during concomitant use with fluoxetine.
4. *Phenytoin*: Changes in blood elvels have been observed. In some cases, manifestations of toxicity have occurred.

5. *Serotonergic drugs*: Co-administration with serotonergic drugs (eg tramadol, triptans) increase the risk of serotonin syndrome. Use with triptans carries the additional risk of coronary vasoconstriction and hypertension.
6. *Lithium and tryptophan*: There have been reports of serotonin syndrome. A closer and more frequent clinical monitoring is required when used with lithium.
7. *CYP2D6 isoenzyme metabolised drugs*: Fluoxetine metabolism involves the hepatic cytochrome CYP2D6 isoenzyme system. Concomitant therapy with drugs predominantly metabolized by this isoenzyme and which have a narrow therapeutic index (such as flecainide, encainide, carbamazepine and tricyclic antidepressants) should be initiated at or adjusted to the low end of their dose range.
8. *Oral anticoagulants*: Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but including increased bleeding, have been reported. Patient receiving warfarin therapy should be carefully monitored when fluoxetine is initiated or stopped (refer to section '*Warning and Precautions – Haemorrhage*')
9. *Electroconvulsive Therapy (ECT):* There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment, therefore caution is advisable.
10. *Alcohol*: Intake is not advisable
11. *St John's Wort*: interaction may result in an increase of undesirable effects.

PREGNANCY AND LACTATION:

Pregnancy: Fluoxetine can be 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, difficulty in sucking or in sleeping. Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth.

Lactation: Fluoxetine and its metabolite, norfluoxetine are known to be excreted in human breast milk. Adverse effects 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 should be prescribed.

SIDE EFFECTS:

Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Body as a whole: Hypersensitivity (pruritus, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness-like reaction, angioedema), chills, serotonin syndrome, photosensitivity, and very rarely, toxic epidermal necrolysis (Lyell syndrome)

Digestive system: Gastro-intestinal disorders (eg diarrhoea, nausea, vomiting, dyspepsia, dysphagia, taste perversion), dry mouth

Nervous system: Headache, sleep abnormalities (eg. abnormal dreams, insomnia), dizziness, anorexia, fatigue (eg . somnolence, drowsiness), euphoria, transient abnormal movement (eg twitching, ataxia, tremor, myoclonus), seizures and psychomotor restlessness. Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (eg. nervousness), impaired concentration and thought process (eg. depersonalization), panic attacks (these symptoms may be due to underlying disease) and very rarely serotonin syndrome.

Urogenital system: Urinary retention, urinary frequency

Reproductive disorders: Sexual dysfunction (delayed or absent ejaculation, anorgasmia), priapism, galactorrhoea

Hyponatraemia: Hyponatraemia is rare and reversible when fluoxetine is discontinued. Majority associated with older patients, and those taking diuretics or otherwise volume depleted.

Respiratory system: Pharyngitis, dyspnoea. Pulmonary events (including inflammatory processes of varying histopathology and/or fibrosis) have been reported rarely. Dyspnoea may be the only preceeding symptom.

SYMPTOMS AND TREATMENT OF OVERDOSE:

Symptoms : Symptoms of overdose include nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias to cardiac arrest, pulmonary dysfunction and signs of altered central nervous system status ranging from excitation to coma.

Treatment : Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. No specific antidote is known. For diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be 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.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE:

Any psychoactive drug may impair motor skills and patient should be cautioned about operating hazardous machinery, including automobiles.

PRECLINICAL SAFETY DATA:

Not applicable

INSTRUCTION FOR USE:
For oral use only.

DOSAGE FORMS AND PACKAGING AVAILABLE:
Dosage form: Tablets
Pack size: Blisterpack: 10 x 10’s

NAME AND ADDRESS OF MANUFACTURER / PRODUCT REGISTRATION HOLDER:
MALAYSIAN PHARMACEUTICAL INDUSTRIES SDN BHD (101323-U)
Plot 14, Lebuhraya Kampung Jawa,11900 Bayan Lepas,
Pulau Pinang, Malaysia.

DATE OF REVISION:
10/05/2023