FLUOXETINE
MOTIVEST®
20 mg Capsule
ANTIDEPRESSANT / SELECTIVE SEROTONIN-REUPTAKE INHIBITOR

FORMULATION
Each capsule contains:
Fluoxetine HCl equivalent to Fluoxetine, USP............................ 20 mg

PRODUCT DESCRIPTION
Fluoxetine (Motivest) is a hard gelatin capsule filled with white or gray-white powder. The capsule cap is green while the body is light yellow in color.

PHARMACOLOGY
The exact mechanism of fluoxetine's psychotropic actions (antidepressant, anti-obsessive-compulsive and anti-bulimic) remains unclear but is presumed to be linked to its selective inhibition of the central nervous system (CNS) neuronal uptake of serotonin. Fluoxetine-induced inhibition of the CNS neuronal uptake of serotonin causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Clinical studies have shown that at clinically relevant doses, fluoxetine blocks the uptake of serotonin into human platelets. Preclinical studies also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Fluoxetine has practically no affinity to other receptors such as α_1-, α_2-, and ß-adrenergic; serotonergic; dopaminergic; histaminergic; muscarinic; and GABA receptors.

PHARMACOKINETICS
Fluoxetine is well absorbed from the gastrointestinal tract after oral administration. The oral bioavailability of fluoxetine is estimated to be about 60 to 80%. Food may delay absorption by approximately 1 to 2 hours but generally does not affect the amount of drug that reaches the circulation. Peak fluoxetine plasma concentrations of 15 to 55 ng/mL are achieved within 6 to 8 hours after oral administration of a 40 mg dose.

Fluoxetine has high affinity for plasma proteins which is independent of plasma concentration and is approximately 94.5% protein-bound at plasma concentrations of 200 to 1000 ng/mL. The apparent volume of distribution of fluoxetine and norfluoxetine (active metabolite) in healthy adults is an average of 20 to 45 L/kg.

Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is the predominant enantiomer present in plasma at steady state. Fluoxetine is extensively metabolized in the liver to norfluoxetine, the only identified active metabolite formed by demethylation of fluoxetine, and a number of other unidentified metabolites. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. Fluoxetine and norfluoxetine are slowly cleared from the circulation. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

A subset (about 7%) of the population, referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs), has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). A study involving labeled and unlabeled enantiomers given as a racemate showed that these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. The total sum at steady state of the plasma concentrations of the four active enantiomers was not significantly greater among poor metabolizers compared with normal metabolizers. Therefore, the net pharmacodynamic activities were essentially the same. In addition, nonsaturable pathways (non-2D6) contribute to the metabolism of fluoxetine. This is the reason why fluoxetine achieves a steady-state concentration rather than increasing without limit.

Like other SSRIs, the metabolism of fluoxetine involves the CYP2D6 system. Thus, concomitant administration with drugs also metabolized by this enzyme system (such as TCAs) may lead to drug interactions.

Even when a fixed dose is used, the relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration) results to significant accumulation of these active species with chronic use and delayed attainment of steady state concentration. Plasma concentrations were in the range of 91 to 302 ng/mL for fluoxetine and 72 to 258 ng/mL for norfluoxetine after 30 days of dosing at 40 mg per day. Fluoxetine's plasma concentrations were higher than those predicted by single dose-studies since metabolism of fluoxetine is not proportional to dose. Norfluoxetine, on the other hand, appears to have linear pharmacokinetics with a mean terminal half-life of 8.6 days after a single dose and 9.3 days after multiple dosing. Steady-state levels after prolonged dosing are similar to levels at 4 to 5 weeks.

Even after discontinuation of fluoxetine therapy, the parent drug and its metabolites will remain in the circulation for several weeks, depending on individual patient characteristics, previous dosage regimen and length of previous therapy at discontinuation, due to the long elimination half-lives of fluoxetine and norfluoxetine. This may be clinically significant particularly when drug discontinuation is required or when new drugs are to be prescribed that might interact with fluoxetine and norfluoxetine after recent fluoxetine withdrawal.

Special Population:

Hepatic disease: Fluoxetine's elimination half-life was prolonged in cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. Exercise caution when giving fluoxetine to patients with liver disease; a lower or less frequent dose should be used.
Renal disease: Fluoxetine 20 mg given once a day for two months in depressed patients on dialysis produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose may not be necessary in these patients.
Elderly: The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years old) did not differ significantly from that in younger normal subjects. A study involving healthy depressed elderly patients (≥60 years old) who received fluoxetine 20 mg for six weeks was done to determine the effects of age on the metabolism of fluoxetine. It showed that combined fluoxetine plus norfluoxetine plasma concentrations was 209.3±85.7 ng/mL at the end of six weeks.
Children and adolescents: A pharmacokinetic study involving pediatric patients (children: ages 6 to <13; adolescents: 13 to <18) with major depressive disorder or obsessive disorder who received fluoxetine 20 mg per day for 62 days showed that the average steady-state concentrations of fluoxetine in children were 2-fold higher than in adolescents (171 and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in children were 1.5 fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences may be due to differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Higher average steady-state fluoxetine and norfluoxetine concentrations were shown in children relative to adults; however, these concentrations were within the range of concentrations seen in the adult population. Similar in adults, fluoxetine and norfluoxetine accumulated extensively after multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

INDICATIONS
- For the treatment of:
  - Major Depressive Disorder (MDD)
  - Obsessive-Compulsive Disorder
  - Bulimia Nervosa
  - Panic Disorder
  - Premenstrual Dysphoric Disorder (a severe form of PMS)
- In combination with olanzapine:
  - Acute treatment of depressive episodes associated with bipolar I disorder in adult patients
    Fluoxetine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.
  - Acute treatment of Treatment Resistant Depression in adults (defined as MDD in adult patients who do not respond to two separate trials of different antidepressants of adequate dose and duration in the current episode)
    Fluoxetine monotherapy is not indicated for the treatment of treatment resistant depression.

DOSAGE AND ADMINISTRATION
General Dosing Recommendations:
Patients with MDD who are shifted to TCAs should receive lower doses of the TCA during concomitant use or after recent fluoxetine discontinuation.
Shifting from a monoamine oxidase inhibitor (MAOI) to fluoxetine requires a 14-day wash-out period before initiating fluoxetine therapy. Likewise, when switching from fluoxetine to a MAOI, a minimum of 5 weeks should lapse before initiating the MAOI.

Therapy with drugs that are predominantly metabolized by the CYP2D6 system and have a relatively narrow therapeutic index (e.g., flecainide, propafenone, vinblastine, and TCAs) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous five weeks. Thus, the patient's dosing requirements resemble those of poor metabolizers. (see also **Drug Interactions**)

Fluoxetine should be administered orally, with or without food.

Fluoxetine in combination with olanzapine should be administered once a day in the evening, without regard to meals.

Recommended Oral Fluoxetine Dose:

MAJOR DEPRESSIVE DISORDER (MDD)		
INITIAL TREATMENT		**MAINTENANCE / CONTINUATION / EXTENDED TREATMENT**
ADULTS (≥ 18 YEARS OLD)	**CHILDREN AND ADOLESCENTS (8 TO < 18 YEARS OLD)**	**ADULTS (≥18 YEARS OLD)**
Initial dose: 20 mg once a day, in the morning. A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg per day may be given once a day, in the morning, or divided into two doses given in the morning and at noon. **Maximum Dose:** 80 mg per day	**Initial dose:** 10 or 20 mg once a day, in the morning. For patients receiving 10 mg once a day, dose may be increased to 20 mg once a day after one week. However, due to higher plasma levels in **lower weight children, the starting and target dose** in this group may be **10 mg once a day.** A dose increase to 20 mg once a day may be considered after several weeks if insufficient clinical improvement is observed.	It is generally agreed that acute episodes of MDD require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and or sustain euthymia is unknown.
Full antidepressant effect may be delayed until four weeks of treatment or longer.		
Or, as prescribed by a physician.		

OBSESSIVE-COMPULSIVE DISORDER (OCD)		
INITIAL TREATMENT		**MAINTENANCE / CONTINUATION / EXTENDED TREATMENT**
ADULTS (≥ 18 YEARS OLD)	**CHILDREN AND ADOLESCENTS (7 TO < 18 YEARS OLD)**	**ADULTS (≥ 18 YEARS OLD)**
Initial dose: 20 mg once a day, in the morning. A dose increase may be considered after several weeks if insufficient clinical improvement is observed. **Recommended Dose Range:** 20 to 60 mg per day. Doses above 20 mg per day may be given once a day, in the morning, or divided into 2 doses given in the morning and at noon. **Maximum Dose:** 80 mg per day	**In adolescents and higher weight children:** 10 mg once a day, in the morning. After two weeks, the dose should be increased to 20 mg once a day. Additional dose increase may be considered after several weeks if insufficient clinical improvement is observed. **Dose Range:** 20 to 60 mg per day **Initial dose in lower weight children:** 10 mg once a day, in the morning Additional dose increase may be considered after several weeks if insufficient clinical improvement is observed. **Dose Range:** 20 to 30 mg per day Experience with daily doses greater than 20 mg is very minimal; there is no experience with doses greater than 60 mg.	While there are no systematic studies that answer the question of how long to continue fluoxetine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of fluoxetine after 13 weeks has not been documented in controlled trials, adult patients have been continued in therapy under double-blind conditions for up to an additional six months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.
The full therapeutic effect may be delayed until five weeks of treatment or longer.		
Or, as prescribed by a physician.		

BULIMIA NERVOSA	
INITIAL TREATMENT	**MAINTENANCE/ CONTINUATION/ EXTENDED TREATMENT**
ADULTS (≥ 18 YEARS OLD)	**ADULTS (≥ 18 YEARS OLD)**
Recommended dose: 60 mg once a day, in the morning. For some patients, it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg per day have not been systematically studied in patients with bulimia.	Fluoxetine at 60 mg/day for up to 52 weeks has been shown to be effective as maintenance therapy. Patients should be reassessed periodically to determine the need for maintenance therapy.
Or, as prescribed by a physician.	

PANIC DISORDER	
INITIAL TREATMENT	**MAINTENANCE/ CONTINUATION/ EXTENDED TREATMENT**
ADULTS (≥ 18 YEARS OLD)	**ADULTS (≥ 18 YEARS OLD)**
Initial dose: 10 mg once a day; Increase to 20 mg once a day after one week. A dose increase may be considered after several weeks if no clinical improvement is observed. **Maximum Dose:** 60 mg per day	There is no clinical evidence to establish how long patients with panic disorder should be maintained on fluoxetine. Patients should be reassessed periodically to determine the need for maintenance therapy.
Or, as prescribed by a physician.	

PREMENSTRUAL DYSPHORIC DISORDER (PMDD) IN ADULTS (≥ 18 YEARS OLD)
Recommended dose: 20 mg once a day given continuously throughout the menstrual cycle. Initial treatment should be limited to six months, after which patients should be reassessed regarding the benefit of continued therapy.
Or, as prescribed by a physician.

Fluoxetine in Combination with Oral Olanzapine:

DEPRESSIVE EPISODES ASSOCIATED WITH BIPOLAR I DISORDER	
INITIAL TREATMENT	**MAINTENANCE/ CONTINUATION/ EXTENDED TREATMENT**
ADULTS (≥ 18 YEARS OLD)	**ADULTS (≥ 18 YEARS OLD)**
Initial dose: Fluoxetine 20 mg and olanzapine 5 mg once a day in the evening, without regard to meals; Dosage adjustments, if indicated, can be made based on efficacy and tolerability within the dose ranges of fluoxetine 20 to 50 mg and olanzapine 5 to 12.5 mg. Antidepressant efficacy was shown with fluoxetine and olanzapine in combination with a dose range of fluoxetine 25 to 50 mg and olanzapine 6 to 12 mg. Safety of coadministration of doses above fluoxetine 75 mg with olanzapine 18 mg has not been evaluated in clinical studies.	While there is no body of evidence to answer the question of how long a patient treated with fluoxetine and olanzapine in combination should remain on it, it is generally accepted that bipolar I disorder, including 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.
Or, as prescribed by a physician.	

TREATMENT RESISTANT DEPRESSION	
INITIAL TREATMENT	**MAINTENANCE/ CONTINUATION EXTENDED TREATMENT**
ADULTS (≥ 18 YEARS OLD)	**ADULTS (≥ 18 YEARS OLD)**
Initial dose: Fluoxetine 20 mg and olanzapine 5 mg once a day in the evening, without regard to meals; Dosage adjustments, if indicated, can be made based on efficacy and tolerability within the dose ranges of fluoxetine 20 to 50 mg and olanzapine 5 to 20 mg. Antidepressant efficacy was shown with fluoxetine and olanzapine in combination with a dose range of fluoxetine 25 to 50 mg and olanzapine 6 to 18 mg. Safety of coadministration of doses above fluoxetine 75 mg with olanzapine 18 mg has not been evaluated in clinical studies.	While there is no body of evidence to answer the question of how long a patient treated with fluoxetine and olanzapine in combination should remain on it, it is generally accepted that treatment resistant depression is a chronic illness requiring chronic treatment. The physician should periodically re-examine the need for continued pharmacotherapy.
Or, as prescribed by a physician.	

Fluoxetine in Combination with Olanzapine Dosing in Special Population:
Patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of fluoxetine or olanzapine in combination (female gender, geriatric age, non-smoking status), or those patients who may be pharmacodynamically sensitive to olanzapine:

Recommended starting dose: Fluoxetine 20 mg and olanzapine 2.5 to 5 mg;
Dose modifications may be necessary in patients who exhibit a combination of factors that may slow metabolism.
When indicated, dose escalation should be done with caution in these patients.
Fluoxetine and olanzapine in combination have not been systematically studied in patients 65 years and older or in patients below 18 years old.

Discontinuation of Fluoxetine:
There have been spontaneous reports of adverse reactions occurring upon discontinuation of fluoxetine, selective norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs), particularly when abrupt, such as dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these reactions are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but with a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy which may minimize the risk of discontinuation symptoms with this drug.

CONTRAINDICATIONS
- Hypersensitivity to fluoxetine or to any ingredient in the product
- Monoamine oxidase inhibitors (see **Drug Interactions** and **Dosage and Administration**)
- Thioridazine (see **Drug Interactions**)
- Pimozide (see **Drug Interactions**)

WARNINGS AND PRECAUTIONS
Suicidality and Antidepressant Drugs: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of fluoxetine or any other antidepressant in a child, adolescent or a young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond 24 years old; there was a reduction in risk with antidepressants compared to placebo in adults 65 years and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Fluoxetine is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD).

Clinical Worsening and Suicide Risk
Patients with 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 antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorder, and these disorders themselves are the strongest predictors of suicide. There has been long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Prescriptions of fluoxetine should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder and Monitoring for Mania/Hypomania
Bipolar disorder may present initially as a major depressive episode. It is thought that treating such an episode with an antidepressant alone may precipitate a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described for clinical worsening and suicide risk represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. Careful screening entails accurate recording of the patient's psychiatric history, particularly family history of suicide, bipolar disorder and depression. It should be noted that fluoxetine and olanzapine combination is approved for the acute treatment of depressive episodes associated with bipolar **I** disorder. Fluoxetine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar **I** disorder.

Rash and Allergic Events
Fluoxetine has been reported to cause rash and/or urticaria, which may be associated with fever, leukocytosis, arthralgia, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. These symptoms usually resolve upon discontinuation of the drug and/or adjunctive treatment with antihistamines or steroids. There are also rare reports of patients who developed serious cutaneous systemic illnesses, identified to be leukocytoclastic vasculitis, vasculitis, erythema multiforme, and serum sickness. Since fluoxetine's introduction, predisposed patients with rash have developed lupus-like syndrome. Such untoward effects are rare but may be life-threatening as these severely affect the lung, kidney or liver. Anaphylactoid events (either alone or in combination) including bronchospasm, angioedema, laryngospasm, and urticaria have been reported. There have been rare reports of pulmonary events including inflammatory processes of varying histopathology and/or fibrosis. Fluoxetine should be discontinued in cases where a patient develops rash that appears to have no other probable cause.

Serotonin Syndrome
SSRIs such as fluoxetine, and serotonin and SNRIs can cause potentially fatal serotonin syndrome, particularly when taken together with other serotonergic drugs (such as triptans) and agents which inhibit the degradation of serotonin (MAOIs). Characteristic symptoms of serotonin syndrome include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia) neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). In cases where concurrent administration of a triptan and fluoxetine is needed, close therapeutic monitoring is important particularly during initial treatment and dosing shifts (increase or decrease). The coadministration of fluoxetine and serotonin precursors (such as tryptophan) is strongly discouraged.

Abnormal bleeding
SSRIs and SNRIs, including fluoxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anti-coagulants may add to this risk. Bleeding events associated with use of SSRIs and SNRIs include ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Anxiety and Insomnia
Clinical trials have reported that fluoxetine can cause anxiety, nervousness or insomnia. These adverse events have been associated with the highest incidence of fluoxetine therapy discontinuation.

Altered Appetite and Weight
Significant weight loss, particularly in underweight depressed or bulimic patients, may be an undesirable result of treatment with fluoxetine.

Activation of Mania/Hypomania
Clinical trials have documented that a small portion of patients manifested symptoms of mania/hypomania.

Hyponatremia
Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including fluoxetine. This appears to be the result of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. There have been reports of serum sodium lower than 110 mmol/L and appeared to be reversible upon fluoxetine discontinuation. Elderly patients are at greater risk of developing hyponatremia with SSRIs and SNRIs including patients taking diuretics or who are volume-depleted. Discontinue fluoxetine use in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

Seizures
Fluoxetine should be used with caution in patients with a history of convulsive disorder. Treatment should be 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 and patients with controlled epilepsy should be carefully monitored.

Akathisia
The use of fluoxetine has been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. Increasing the dose may be detrimental in patients who develop these symptoms.

Long Elimination Half-Lives of Fluoxetine and its Metabolites
The full effect of dose titration and drug withdrawal will not be immediately apparent because of the relatively slow elimination of fluoxetine and its metabolites.

Use in Patients with Concomitant Illness
Caution should be exercised when prescribing fluoxetine to patients with diseases or conditions that affect metabolism or hemodynamic responses. Fluoxetine may alter glycemic control. Hypoglycemia has occurred during therapy with fluoxetine, and hyperglycemia has developed after discontinuation of the drug. As is true with many other types of drugs when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic, dosage may need to be adjusted when therapy with fluoxetine is instituted or discontinued.

Interference with Cognitive and Motor Performance
Patients should be warned that psychoactive drugs may impair judgment, thinking or motor skills. They should be advised to avoid tasks which require complete mental alertness such as operating hazardous machinery and driving vehicles until they are sure that their treatment does not significantly impede their ability to perform such activities.

DRUG INTERACTIONS
- **Monoamine Oxidase Inhibitors (MAOIs)** (e.g., tranylcypromine, isocarboxazid, phenelzine and selegeline): Concomitant use of fluoxetine and MAO inhibitors is contraindicated.
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 leading to delirium and coma) in patients receiving fluoxetine in combination with a MAOI, and in patients who have recently discontinued fluoxetine and are then started on a MAOI. There have also been reports that this may lead to a condition resembling neuroleptic malignant syndrome. Thus, fluoxetine should not be used in combination with a MAOI, or within a minimum of 14 days of discontinuing therapy with a MAOI. A wash-out period should be observed when switching to or from MAOIs (see also **Dosage and Administration**).

- **Thioridazine:** Fluoxetine inhibits the CYP2D6 enzyme system thereby increasing plasma levels of thioridazine. This interaction is clinically significant particularly for poor metabolizers because they are at greater risk of experiencing dose-related adverse effects associated with thioridazine. Thioridazine has been known to cause prolongation of the QTc interval, which is linked to serious ventricular arrhythmias (such as *torsades de pointes*-type arrhythmias) and sudden death. This risk is increased with fluoxetine-induced inhibition of thioridazine metabolism.
Thioridazine should not be administered with fluoxetine or within a minimum of five weeks after fluoxetine has been discontinued because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine.

- **Drugs metabolized by CYP 2D6** [antidepressants (e.g., TCAs); antipsychotics (e.g., phenothiazines and most atypicals); antiarrhythmics (e.g., propafenone, flecainide and others)]: Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer.
Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants, antipsychotics, and antiarrhythmics should be approached with caution.
If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered.

- **Serotonergic Drugs** (e.g., linezolid, tramadol, or St. John's Wort): Coadministration of other serotonergic drugs and fluoxetine may precipitate serotonin syndrome.

- **Tryptophan:** Coadministration of fluoxetine and tryptophan causes adverse reactions such as agitation, restlessness, and gastrointestinal distress.

- **Triptans:** Coadministration of triptans and fluoxetine may precipitate serotonin syndrome. If concomitant treatment of fluoxetine with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

- **Drugs highly bound to plasma proteins** (e.g., warfarin and digoxin): Since fluoxetine is tightly bound to plasma proteins, administration of fluoxetine to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Also, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs.

- **Drugs that interfere with hemostasis** (e.g., NSAIDs, aspirin, warfarin): There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. Studies of bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SNRIs or SSRIs are coadministered with warfarin. Patients receiving warfarin should be carefully monitored when fluoxetine is initiated or discontinued.

- **Drugs metabolized by CYP3A4** (e.g., ketoconazole, astemizole, midazolam): In an *in vivo* interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine.
In vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor or the metabolism of several substrates for this enzyme, including astemizole, cisapride and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

- **CNS-active drugs:** Caution is advised if the concomitant use of fluoxetine and these drugs is required. Consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status.

- **TCAs** (e.g., imipramine, desipramine): Combining TCAs with fluoxetine may lead to a significant increase in the concentrations of the former. Dose adjustment and temporary plasma level monitoring is necessary when administering these drugs with fluoxetine or when these are to be initiated following recent discontinuation of fluoxetine.

- **Anticonvulsants** (e.g., phenytoin, carbamazepine): Fluoxetine may increase plasma levels of anticonvulsants to an extent that clinical anticonvulsant toxicity may occur.

- **Antipsychotics** (e.g., haloperidol, clozapine, olanzapine, pimozide): Fluoxetine has been shown to increase blood levels of haloperidol and clozapine.
Coadministration of pimozide and fluoxetine may potentially lead to drug interactions and QTc prolongation; concurrent administration of these drugs is contraindicated.
Fluoxetine causes a small increase in the maximum concentration of olanzapine and a small decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and thus dose modification is not routinely recommended.

- **Benzodiazepines** (e.g., diazepam, alprazolam): Fluoxetine may prolong the half-life of diazepam in some patients.
Plasma concentrations of alprazolam have been shown to increase when coadministered with fluoxetine.

- **Lithium:** Fluoxetine may increase lithium levels, which may result in toxicity and serotogenic effects. It is necessary to monitor lithium levels when this drug is to be administered concurrently.

Other Interaction:
Electroconvulsive Therapy (ECT): There have been rare reports that patients receiving ECT together with fluoxetine experienced prolonged seizures.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
PREGNANCY AND LACTATION
Pregnancy
Pregnancy Category C: There are no adequate and well-controlled clinical studies on the use of fluoxetine in pregnant women. Fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Neonates exposed to fluoxetine, SNRIs, or SSRIs late in the third trimester have developed complications which required prolonged hospitalization, respiratory support and tube feeding. The following clinical manifestations have been reported: respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SNRIs and SSRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome.

Exposure of infants to SSRIs during late pregnancy may increase the risk for persistent pulmonary hypertension of the newborn (PPHN). However, this clinical finding has not been firmly established.

Labor and Delivery
Fluoxetine's effect on labor and delivery is unknown. Its use during labor and delivery should be limited to cases where clinical benefits clearly outweigh the potential risk to the fetus.

Lactation
Prescribing fluoxetine to breastfeeding mothers is strongly discouraged because a considerable amount of fluoxetine and its metabolites are excreted in breastmilk.

INFANTS AND CHILDREN
Clinical trials have demonstrated fluoxetine's efficacy in treating MDD among pediatric patients 8 to ≤18 years old. It has also been shown to be effective in the treatment of OCD in pediatric patients 7 to <18 years old.

Fluoxetine has not been proven to be safe and effective for use in pediatric patients <8 years old with MDD and <7 years old with OCD. It is not approved for use in pediatric patients with bulimia nervosa, panic disorder and PMDD.

ELDERLY
Fluoxetine's safety and efficacy in geriatric patients have been established. There is no significant difference in the drug's pharmacologic profile between the elderly and younger patient groups, but some older individuals may exhibit greater sensitivity. Hyponatremia caused by fluoxetine may be clinically significant for this population and monitoring is necessary.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS
Body as a Whole: Chills, chills and fever, face edema, intentional injury, fever, flu syndrome, asthenia, malaise, hypothermia
Cardiovascular System: Vasodilation, hemorrhage, hypertension, palpitation, angina pectoris, arrhythmia, congestive heart failure, hypotension, myocardial infarction, chest pain, postural hypotension, syncope, tachycardia, vascular headache, atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation
Digestive System: Constipation, diarrhea, dry mouth, dyspepsia, flatulence, nausea, vomiting, aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, abnormal liver function tests, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst, biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, colon hemorrhage, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema, acute abdominal syndrome
Hemic and Lymphatic System: Anemia, ecchymosis, blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia
Metabolic/Endocrine and Nutritional Disorders: Anorexia, weight loss, weight gain, increased appetite, dehydration, generalized edema, gout, hypercholesterolemia, hyperlipemia, hypokalemia, peripheral edema, alcohol intolerance, increased alkaline phosphatase, increased BUN, increased creatine phosphokinase, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, increased ALT, hyponatremia, hypothyroidism, diabetic acidosis, diabetes mellitus, decreased/increased libido, impotence, sexual dysfunction, priapism, galactorrhea
Musculoskeletal System: Arthritis, bone pain, bone fractures, bursitis, leg cramps, tenosynovitis, arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis, arthralgia, myalgia, pelvic pain
Nervous System: Abnormal dreams, abnormal thinking, anxiety, dizziness, nervousness, somnolence, tremor, insomnia, agitation, amnesia, confusion, emotional lability, sleep disorder, abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypoesthesia, incoordination, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder, psychosis, vertigo, abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, decreased/increased reflexes, stupor, headache, migraine, neuroleptic malignant syndrome-like events, suicidal ideation
Respiratory System: Pharyngitis, sinusitis, yawn, asthma, epistaxis, hiccups, hyperventilation, apnea, atelectasis, decreased cough, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor, dyspnea
Skin and Appendages: Sweating, pruritus, rash, urticaria, anaphylactoid reaction, vasculitis, angioedema, serum sickness-like reaction, acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash, furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, photosensitivity reaction
Special Senses: Abnormal vision, conjunctivitis, dry eyes, mydriasis, photophobia, blepharitis, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, visual field defect, ear pain, tinnitus, taste perversion, taste loss
Urogenital System: Abnormal ejaculation, urinary frequency, abortion, albuminuria, amenorrhea, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation, fibrocystic breast, hematuria, leukorrhea, menorrhagia, metrorrhagia, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, breast engorgement, glycosuria, hypomenorrhea, kidney pain, oliguria, uterine hemorrhage, uterine fibroids enlargement

OVERDOSAGE AND MANAGEMENT
Symptoms of fluoxetine overdosage include nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias to cardiac arrest, pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. No specific antidote is known. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage. Due to the large volume of distribution of fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdosage, consider the possibility of multiple drug involvement. Close medical attention may be required in patients who have taken excessive quantities of a TCA if they are also taking, or have recently taken, fluoxetine.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.
Keep the product out of reach and sight of children.

AVAILABILITY: Alu / PVC Blister pack X 10's (Box of 30's) - DR-XY34198

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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