DAEWON Oxeflu Cap. 20mg

(Fluoxetine hydrochloride 22.4mg)

■ **COMPOSITION** : Each capsule contains

Fluoxetine hydrochloride ..... 22.4mg(20.0mg as fluoxetine)

■ **INDICATIONS**

1. Depression

Fluoxetine HCl is indicated for the treatment of depression. The efficacy of fluoxetine HCl was established in 5- and 6-week trials with depressed outpatients (≥18 years of age) whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation. The antidepressant action of fluoxetine HCl in hospitalized depressed patients has not been adequately studied. The effectiveness of fluoxetine HCl in long-term use (i.e., for more than 5~6 weeks) has not been systematically evaluated in placebo-controlled trials. So the usefulness of the drug in patients receiving fluoxetine HCl for extended periods should be reevaluated periodically.

2. Bulimia Nervosa

Fluoxetine HCl is indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa. The effectiveness of fluoxetine HCl in long-term use (i.e., for more than 16 weeks) has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use fluoxetine HCl for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient .

3. Obsessive-Compulsive Disorder

Fluoxetine HCl reduces effectively the symptoms of Obsessive-Compulsive Disorder in double blind, placebo-controlled trials. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning. The effectiveness of fluoxetine HCl in long-term use (i.e., for more than 13 weeks) has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use fluoxetine HCl for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

4. Premenstrual syndrome (=PMS)

PMS has the obvious symptoms of anxiety, depression, irritability.

These symptoms show periodically(the last of luteal phase in menstrual cycle) and disappear at the onset of the menopause . These symptoms decreased work or social performance and are accompanied with mammalgia, headache, arthralgia, abdominal distention and weight gain. But except for General Discomfort sense before menstruation.

The effectiveness of this medicine in long-term use(more than 6 months) has not been systematically evaluated , so the physician who elects to use fluoxetine HCl for extended period should periodically reevaluate the long-term usefulness of the drug for the individual patient.

■ **DOSAGE & ADMINISTRATION**

<Adults>

1. Depression

1) Initial Treatment

A dose of 20mg/day, administered in the morning, is recommended as the initial dose. In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20mg to 80mg/day. A dose increase may be considered after several weeks if no clinical improvement is observed. Doses above 20mg/day may be administered on a once a day (morning) or b.i.d. schedule (i.e., morning and noon) and should not exceed a maximum dose of 80mg/day. the full antidepressant effect may be delayed until 4 weeks of treatment or longer.

2) Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

2. Bulimia Nervosa

The recommended dose is 60mg/day, and should not exceed a maximum dose of 80mg/day. Measure the electrolyte concentration of patients before treatment.

3. Obsessive-Compulsive Disorder

The recommended dose is 20~60mg/day, and should not exceed a maximum dose of 80mg/day.

4. Premenstrual syndrome (=PMS)

The recommended dose is 20mg/day. Revaluate the need of continuous administration to the patient after treatment for 6months.

A lower or less dosage should be used for the elderly, the patient with renal and/or hepatic impairment, concurrent disease or on multiple concomitant medications. Add or reduct the doses of this medicine according to age or symptoms.

■ **PRECAUTIONS**

1. Contraindication

1) Patients with a history of hypersensitivity to this medicine

2) Patients with a severe renal disorder (glomerular filtration rate<10ml/min)

3) Patients receiving a monoamine oxidase inhibitor (MAOI)

2. Precaution

1) Patients with a history of epileptic seizures (patients with unstable seizures should not be allowed administration, patients who can adjust their seizure should be monitored during therapy. If they become worse, should stop this medicine)

2) Patients with the possibility of a suicide attempt (The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for fluoxetine HCl should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.)

3) Patients with Concomitant Illness

① Patients with concomitant systemic illness (Caution is advisable in using fluoxetine HCl in patients with diseases or conditions that could affect metabolism or hemodynamic responses.)

② Patients with a recent history of myocardial infarction or unstable heart disease. (Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received fluoxetine HCl in double-blind trials were retrospectively evaluated ; no abnorminal electrocardiogram that resulted in atriovetricular separation were observed. The mean heart rate was reduced by approximately 3 beats/min.)

③ Patients with cirrhosis (In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used.)

④ Patients with a severe renal disorder (It's rare that this medicine is metabolized fully and is excreted through urine. But the treatment in renal impared patients for long time should be careful.)

⑤ Patients with diabetes (fluoxetine HCl may alter glycemic control. Hypoglycemia has occurred during therapy with fluoxetine HCl, and hypoglycemia has changed for better following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with fluoxetine HCl is instituted or discontinued.)

3. Adverse effects

1) Generally : nervous disorder(anxiety, nervousness, insomnia, etc.), drowsiness, fatigue, adynamia, tremor, sweating, Gastrointestinal disorder(anorexia, vomiting, diarrhea, etc.), dizziness, head convulsion

2) Adverse effects related with stopping this medicine

In clinical trials, 15% of 4,000 patients discontinued because of nervousness, anxiety, insomnia, etc. of central nervous system (5.3%) vomiting, etc. of Gastrointestinal system (3.0%), adynamia, headache, etc. of whole body system (1.5%), rash, itch, etc. of Skin(1.4%).

3) Rash and Possibly Allergic Events In clinical trials, 4% of 5,600 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphoma, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely. In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1of patients was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness. Since the introduction of fluoxetine HCl, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events. Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone or in combination, have been reported. Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom. Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, fluoxetine HCl should be discontinued.

4) Anxiety and Insomnia

In clinical trials, 10% to 15% of patients treated with fluoxetine HCl was reported anxiety, nervousness and insomnia.

5) Altered Appetite and Weight

Significant weight loss, especially in underweight depressed patients may be an undesirable result of treatment with fluoxetine HCl. In placebo-controlled clinical trials for depression, 9% of patients treated with fluoxetine HCl was reported anorexia (decreased appetite). Weight loss was reported in 13% of patients treated with fluoxetine HCl. However, only rarely have patients discontinued treatment with fluoxetine HCl because of anorexia or weight loss.

6) Activation of Mania/Hypomania In clinical trials for depression, mania/hypomania was reported in 1% of patients treated with fluoxetine HCl and Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

7) Seizures

In clinical trials for depression, convulsions (or events described as possibly having been seizures) were reported in 12 of 6,000 patients(0.2%) treated with fluoxetine HCl. The percentage appears to be similar to that associated with other marketed antidepressants.

8) Hyponatremia

Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when fluoxetine HCl was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

9) Platelet Function

There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

10) Incidence in Placebo-Controlled Clinical Studies

TABLE enumerate the most common treatment-emergent adverse events associated with the use of fluoxetine HCl (incidence of at least 1% for fluoxetine HCl). For estimating the occurrence rates of adverse events in the other treatment, "this clinical trial, the characteristics of patients and the others" should not be used. The quoted frequency should not be compared with the data from the other treatment or clinical trials by the other investigators.

11) The other adverse effects

During clinical trial, this medicine was administered to about 5,600 patients at multi dosages. Below percentages are the rates of adverse effect appeared over 1 case in 5,600 patients.(except for adverse effects in former table) * 1 group(>1%), 2 group(1~0.1%), 3 group(<0.1%)

(1) Whole body

-1 group : feeling cold

-2 group : feeling cold, fever, cyst, swelling of face, hangover, pain of jaw, discomfort, pain of neck, rigidity of neck, backache

-3 group : expansion of abdomen, cellulites, chickenpox, cold symptom, erythematous lupus, Monilia, serologic disease

(2) Circulatory system

-1 group : angina pectoris, arrhythmia, bleeding, hypertension, migraine, postural hypotension, faint, frequent pulse

-3 group : 1 level atrioventricular node, bradycardia, bundle branch block, cerebral ischemia, myocardial infarction, thrombotic phlebitis, vascular headache, ventricular arrhythmia

(3)Digestive system

-1 group : increase of appetite

-2 group : aphthous stomatitis, distress of swallowing, belching, esophagitis , gastritis, gingivitis, glossitis, abnormality of liver function test, melena, stomatitis, thirst

-3 group : bloody stool, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, liver tumor, hyperacidity, hypersalivation, jaundice, hepatomalacia, oral ulcer, expansion of salivary gland, gastric ulcer, decoloration of tongue, swelling of tongue, hepatitic idiosyncrasy

(4) Endocrinal system

-2 group : hypothyroidism

-3 group : goiter, hyperthyroidism

(5) Blood and lymph system

-2 group : anemia, tumor of lymphatic gland

-3 group : increase of bleeding time, disease of blood, decreasing leukocyte, increasing lymphocyte, dotted bleeding, palate patch, increasing sedimentation speed, thrombocythemia

(6) Metabolism and Nutrition

-1 group : weight loss

-2 group : swelling of whole body, hypoglycemia, peripheral edema, weight gain

-3 group : dehydration, gout, hypercholesterolemia, hyperglycemia, hyperlipemia, hypoglycemia action, hypokalemia, hypernatremia, iron deficiency anemia

(7) Musculoskeletal system

-2 group : arthritis, bone pain, bursitis, tendosynovitis and spasm

-3 group : necrosis of bone, osteochondrodystrophy, muscle bleeding, myositis, osteoporosis, morbid fracture, rheumarthritis

(8) Nervous system

-1 group : abnormal dream and passion

-2 group : abnormal gait, acute brain symptom, akathisia for long time, amnesia, dull feeling, kinesioneurosis, constriction of tongue, irritation about central nervous system, convulsion, delusion, depersonalization, emotional anxiety, euphoria, hallucination, hostility, hyperkinesis, hypoesthesia, impossible coordination, increasing sexual desire, manic action, neuralgia, neuritis, paranoid action, psychosis, dizziness

-3 group : abnormal electroencephalogram, antisocial action, chronic brain symptom, abnormal sense around mouth, inhibition of central nervous system, coma, abnormal stomatolalia, dystonia, extrapyramidal symptom, activation of tension, hysteria, myoclonus, nystagmus, paralysis, hyporeflexia, stupor, torticollis

(9) Respiratory system

-1 group : bronchitis, rhinitis, oscitation

-2 group : asthma, epistaxis, hiccup, hyperventilation, pneumonia

-3 group : apnea, hemoptysis, hypoxia, swelling of larynx, swelling of lung, fibroid lung, fluid of pleura

(10) Skin
-2 group : acne, alopecia areata, contact dermatitis, dry skin, herpetiformis, spotted papule, hives
-3 group : eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsuitism, psoriasis, purple eruption, pustular eruption, seborrhea, depigmented skin, macronutrient skin, subcutaneous knot, vesicatory eruption

(11) Sensory system
-2 group : amblyopia, conjunctivitis, pain of ear, pain of eye, pupillary dilatation, photosensitivity reaction, ear noise
-3 group : inflammation of eye muscle, cataract, damage of cornea, deafness, double vision, hemophthalmos, glaucoma, iritis, ptosis of palpebra, squint

(12)Urogenital system
-2 group : abnormal ejaculation, amenorrhea, mastalgia, cystitis, dysuria, fibrous and cystic breast, impotence, leucorrhea, menopause, menorrhagia, abnormal ovary, uracratia, ischuria, micturition desire, dysuria, colpitis
-3 group : ectrosis, proteinuria, mammary distention, abnormal sexual sense, epididymitis, epiphora, bleeding urine, hypomenorrhea, calculus of kidney, metrorrhagia, orchitis, polyuria, pyelitis, pyuria, salpingitis, painful urethra, urethritis, abnormal Urogenital system, urolithiasis, hysterospasm, elytrorrhagia

4. General precaution

1) The Long Elimination Half-Lives of Fluoxetine and Its Metabolites
Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see DOSAGE AND ADMINISTRATION).

2) Interference With Cognitive and Motor Performance
Any psychoactive drug may impair judgment, 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.

3) Information for Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe fluoxetine HCl: Because fluoxetine HCl may impair judgment, thinking, or motor 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. Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast feeding an infant. Patients should be advised to notify their physician if they develop a rash or hives.

4) Laboratory Tests : There are no specific laboratory tests recommended.

5) Carcinogenesis, Mutagenesis, and Impairment of Fertility
There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with fluoxetine HCl.
Carcinogenicity : The dietary administration of fluoxetine to rats for 2 years at doses (approximately 7.5~9 times, the maximum recommended human dose of 80mg) produced no evidence of carcinogenicity.
Mutagenicity : Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays : bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.
Impairment of Fertility : The fertility studies conducted in rats at doses(5~9 times, the maximum recommended human dose) indicated that fluoxetine had no adverse effects on fertility.
An immaterial decrease of the existence rate in neonates is associated with the reduction of food-eating in mother and the inhibition of increase in weight.

6) Animal toxicology : Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

7) Physical and Psychological Dependence: Fluoxetine HCl has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with fluoxetine HCl did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of fluoxetine HCl (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

8) The remedial value about PMS with treatment of depression is very different, so the treatment of fluoxetine appears generally an improvement in remedy of first period. In clinical trial, Within usual 1~2 period after discontinuing a treatment, it became known that it was the tendency that the symptom appeared again. Before the administration is started for PMS, benefits and risks of taking medicine should be given to patients. (except for released capsule)

5. Drug interaction : As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility.

1) Monoamine Oxidase Inhibitors
Other Antidepressants : In two studies, previously stable plasma evels of imipramine and desipramine have increased greater than 2 to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of tricyclic antidepressant (TCA) may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued.

2) Tryptophan
Five patients receiving fluoxetine HCl in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

3) The other antidepressants
There have been reports of increase(more than 2 times) in stable plasma concentration of the other antidepressants when fluoxetine is co-administered with the other antidepressants

4) Lithium
There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

5) Clearance rate of diazepam
The half-life of concurrently administered diazepam may be prolonged in some patients.

6) Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins
Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs.

7) CNS Active Drugs
The risk of using fluoxetine HCl in combination with other CNS active drugs has not been systematically evaluated. So, caution is advised if the concomitant administration of fluoxetine HCl and such drugs is required.

8) Electroconvulsive Therapy (ECT)
There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

9) Drugs Metabolized by P450 2D6
Fluoxetine, like other agents that are metabolized by P450 2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the P450 2D6 system and that have a relatively narrow therapeutic index 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 5 weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P450 2D6, the need for decreased dose of the original medication should be considered.

10) Warfarin : Altered anti-coagulant effects, including increased bleeding, have been reported when fluoxetine is co-administered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

6. Pregnant and nursing mother

1) In animal studies in rat at doses(9~11 times of the maximum recommended human dose) there was no evidence of teratogenicity. There was not the clinical trial evaluated properly in pregnant mother, The safety of administration in pregnant mother isn't established. So fluoxetine HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2) The effect of fluoxetine HCl on labor and delivery in humans is unknown.

3) Because fluoxetine HCl is excreted in human milk, nursing while on fluoxetine HCl is not recommended. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4ng/ml. The concentration in the mother's plasma was 295.0ng/ml. But no adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine HCl developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340ng/ml of fluoxetine and 208ng/ml of norfluoxetine on the second day of feeding.

7. Use in children

Safety and effectiveness in pediatric patients(less than 18years old) have not been established.

8. Use in the elder

Greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.

9. Management in overdosage

1) Human Experience
As of December 1987, there were 2 deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57mg/L and 4.18mg/L, respectively. A second death involved 3 drugs yielding plasma concentrations as follows: fluoxetine, 1.93mg/L ; norfluoxetine, 1.10mg/L ; codeine, 1.80mg/L ; temazepam, 3.80mg/L. One other patient who reportedly took 3,000mg of fluoxetine experienced 2 grand mal seizures that remitted spontaneously without specific anticonvulsant treatment. The actual amount of drug absorbed may have been less due to vomiting. Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the 2 deaths noted above, all other overdose cases recovered without residua. Since introduction, reports of death attributed to overdosage of fluoxetine alone have been extremely rare.

2) Animal Experience
Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies. The oral median lethal dose in rats and mice was found to be 452 and 248mg/kg respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.
Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80mg/day, chronically. In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed.
Consequently, the value of theECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose.

3) Management in overdosage
Ensure an adequate airway, oxygenation and ventilation. Activated charcoal or using it with sorbitol is more effective than vomiting or washing stomach. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended.
Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam. In managing overdosages, consider the possibility of multiple drug involvement.
Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

* Adverse Events : Incidence In Placebo-Controlled Clinical Trials

BodySystem/ Adverse events	Adverse events	Percentage of Patients Reporting Event	BodySystem/ Adverse events	Adverse events	Percentage of Patients Reporting Event
	Fluoxetine HCl (N=1730)	Placebo (N=799)		Fluoxetine HCl (N=1730)	Placebo (N=799)
Nervous System			**Body as a Whole**		
			Anergia	4.4	1.9
Headache	20.3	15.5	Flu syndrome	3.4	3.1
Nervousness	14.9	8.5	Melagra	1.6	1.1
Insomnia	13.8	7.1	Fever	1.4	-
Somnolence	11.6	6.3	Cardiagra	1.3	1.1
Anxiety	9.4	5.5	Allergy	1.2	1.1
Tremor	7.9	2.4	Influenza	1.2	1.5
Dizziness	5.7	3.3			
Fatigue	4.2	1.1	**Respiratory System**		
Sedation	1.9	1.3	URI	7.6	6.0
Paresthesia	1.7	2.0	Symptom like Cold	2.8	1.9
Hyposexuality	1.6	-	Pharyngitis	2.7	1.3
Light feeling of head	1.6	-	Epistaxis	2.6	2.3
			Headache	2.3	1.8
Concentration decreased	1.5	-	Sinusitis	2.1	2.0
			Cough	1.6	1.6
			Dyspnea	1.4	-
Digestive System			**Cardiovascular System**		
Nausea	21.1	10.1			
Diarrhea	12.3	7.0	Flush	1.8	1.0
Dry mouth	9.5	6.0	Palpitation	1.3	1.4
Anorexia	8.7	1.5			
Dyspepsia	6.4	4.3	**Musculoskeletals system**		
Constipation	4.5	3.3			
Bellyache	3.4	2.9	Back pain	2.0	2.4
Vomiting	2.4	1.3	Arthralgia	1.2	1.1
Hypogeusia	1.8	-	Muscle pain	1.2	1.0
Flatulence	1.6	1.1			
Gastrointestinal tumor	1.0	1.4	**Urogenital System**		
			Menstrual pain		
			Abnormal	1.9	1.4
Skin and Appendages			Ejaculation	1.9	-
			Frequent		
Sweating	8.4	3.8	Urination	1.6	-
Rash	2.7	1.8	Urinary infection	1.2	-
Pruritus	2.4	1.4			
			Particular sensitivity		
			Visual disorder	2.8	1.8

■ **STORAGE** : Tight container, room temperature (1-30℃)

■ **USE TERM** : 3 years from the manufacturing date

■ **PACKS** : 20, 100 capsules

※ Medicine : Keep out of reach of children.

This drug is manufactured in accordance with Korea Good Manufacturing Practice (KGMP) as recommended by WHO.