



New Zealand Data Sheet

Apo-Fluoxetine

Fluoxetine hydrochloride equivalent to Fluoxetine 10mg & 20mg capsules

Presentation

APO-FLUOXETINE 10mg capsules are grey and green (size #4 capsules) imprinted "APO 10". Each capsule contains fluoxetine hydrochloride equivalent to 10mg of fluoxetine and typically weighs 134.5mg.

APO-FLUOXETINE 20mg capsules are ivory and light green (size #3 capsules) imprinted "APO 20". Each capsule contains fluoxetine hydrochloride equivalent to 20mg of fluoxetine and typically weighs 242mg.

This product is not currently marketed in New Zealand.

Uses

Actions

Fluoxetine is an antidepressant for oral administration. The antidepressant, antiobsessional and antibulimic actions of fluoxetine are presumed to be linked to its ability to inhibit the neuronal reuptake of serotonin.

Fluoxetine inhibits the reuptake of serotonin into human platelets. Antagonism of muscarinic, Histaminergic, and α_1 -adrenergic receptors has been hypothesised to be associated with various anticholinergic, sedative and cardiovascular effects of classical tricyclic antidepressant drugs. In vitro receptor binding studies have demonstrated that fluoxetine binds to these and other membrane receptors (opioid, serotonergic (5-HT₁, 5-HT₂), adrenergic (α_1 , α_2 , α_3) and dopaminergic) less potently than do the tricyclic drugs.

Pharmacokinetics

Fluoxetine is readily absorbed from the gastrointestinal tract after oral administration with peak plasma concentrations 6 to 8 hours after administration. Food may delay the rate but not affect the extent of absorption. Fluoxetine may therefore be taken with or without food.

Over the concentration range from 200-1000ng/mL approximately 94% of fluoxetine is bound in vitro to human serum proteins including albumin and α_1 -glycoprotein. The interaction between fluoxetine and other highly protein bound drugs has not been fully evaluated but may be important.

Fluoxetine is extensively metabolised in the liver by demethylation to its primary active metabolite, norfluoxetine. Norfluoxetine has a pharmacological activity similar to that of fluoxetine and contributes to the long duration of action of fluoxetine. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Fluoxetine is a racemic mixture (50:50) of R-fluoxetine and S-fluoxetine. From animal models it has been shown that both enantiomers are active but S-fluoxetine is eliminated more slowly and is therefore the predominant enantiomer in plasma at steady state. Metabolism leads to R and S enantiomers of norfluoxetine with the S enantiomer being considered as active as the parent drug and the R enantiomer being considered much less active. This metabolism is subject to genetic polymorphism. While the small proportion of the population known as slow metabolisers do show a different spectrum of parent drug and metabolite the overall activity does not appear to be altered.

The relatively slow elimination of fluoxetine (elimination half life of 1-3 days after acute administration and 4-6 days after chronic administration) and norfluoxetine (elimination half life of 4-16 days) leads to significant accumulation of these active species in chronic use. After 30 days of dosing at 40mg/day, plasma concentrations of fluoxetine were higher than those predicted by single dose studies presumably because its metabolism is not proportional

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to dose. Norfluoxetine appears to have linear pharmacokinetics. Steady state plasma levels are attained after 4 to 5 weeks of continuous drug administration. Patients receiving fluoxetine at doses of 40 to 80 mg/day over periods as long as 3 years exhibited, on average, plasma concentrations similar to those seen among patients treated for 4 to 5 weeks. Similarly because of the long half-lives of fluoxetine and norfluoxetine, it may take up to 1 to 2 months for the active drug substance to disappear from the body. This is of potential consequence in the withdrawal of fluoxetine.

Liver impairment can affect the elimination of fluoxetine. In patients with cirrhosis, the elimination half-life of fluoxetine was prolonged (a mean of 7.6 days) while the norfluoxetine elimination half-life was also prolonged (mean of 12 days). Fluoxetine should be used with caution in patients with liver disease and a lower dose is advised.

After a single dose of fluoxetine, the pharmacokinetics of fluoxetine and norfluoxetine among subjects with different levels of impaired renal function, including anephric patients on chronic haemodialysis, showed similar results. But with chronic administration, the accumulation of fluoxetine or its metabolites (possibly including some not yet identified) may occur in patients with severely impaired renal function and use of a lower or less frequent dose is advised.

The efficacy shown by fluoxetine in elderly patients is similar to its effects in younger patients. It is typically well tolerated by elderly patients. The effects of concomitant illness and/or concomitant drugs have not been evaluated.

Indications

- Treatment of depression and its associated anxiety.
- Treatment of Bulimia Nervosa.
- Treatment of obsessive-compulsive disorder.
- Treatment of Premenstrual dysphoric disorder (a severe form of PMS).

Dosage and Administration

Since it may take up to four or five weeks to reach steady-state plasma levels of fluoxetine sufficient time should be allowed to elapse before dosage is gradually increased. Higher dosages are usually associated with an increased incidence of adverse reactions.

Depression:

The recommended adult initial dosage is 20 mg administered once daily in the morning. A gradual dose increase should be considered only if clinical improvement is not observed after several weeks. Doses in excess of 20mg daily should be administered as a divided dose twice daily (morning and noon). Dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited. Full antidepressant effect may be delayed until four weeks of treatment or longer.

Bulimia Nervosa:

The recommended adult dosage is 60 mg per day, although studies show that lower doses may also be efficacious. Electrolyte levels should be assessed prior to initiation of treatment.

Obsessive-Compulsive Disorder:

The recommended adult initial dosage is 20 mg administered once daily in the morning. A gradual dose increase should be considered only if clinical improvement is not observed after several weeks. Doses in excess of 20mg daily should be administered as a divided dose

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twice daily (morning and noon). A dose range of 20 mg per day to 60 mg per day is recommended.

Premenstrual Dysphoric Disorder:

20mg per day is recommended continuously throughout the menstrual cycle. Initial treatment should be limited to 6 months, after which patients should be reassessed regarding the benefit of continued therapy.

For any indication, the total fluoxetine dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited.

During maintenance therapy, the dosage should be kept at the lowest effective level.

A lower or less frequent dosage should be used patients with renal and/or hepatic impairment and in those on multiple medications.

Use in the Elderly:

A lower or less frequent dosage is also recommended in the elderly.

Use in Children and Adolescents (under 18 years of age):

The safety and effectiveness of fluoxetine in patients below the age of 18 years has not been established. (see "Warnings and Precautions")

Contraindications

Fluoxetine is contraindicated in patients with known hypersensitivity to the drug.

Monoamine Oxidase Inhibitors:

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 a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, fluoxetine should not be used in combination with a MAOI, or within 14 days of discontinuing therapy with a 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 a MAOI. Limited reports suggest that orally administered cyproheptadine or intravenously administered dantrolene may benefit patients experiencing such reactions.

Warnings and Precautions

Children and Adolescents (under 18 years of age):

In clinical trials, adverse events related to suicidality (suicidal thoughts and suicidal behaviours) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in children and adolescents treated with SSRIs (and venlafaxine) compared to those treated with placebo.

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Clinical Worsening and Suicide Risk:

Patients of any age with Major Depressive Disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressive medications, and this risk may persist until significant remission occurs. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patients presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Mania and Bipolar Disorder:

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that fluoxetine is not approved for use in treating bipolar depression.

Rash and possible allergic events

Testing of more than 5,600 patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Approximately a third of cases were withdrawn from the study because of the rash and/or systematic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leucocytosis, arthralgias, oedema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved quickly when treatment with fluoxetine was discontinued and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In clinical trials, two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to

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have a leucocytoclastic vasculitis, and the other a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic manifestations suggestive of serum sickness.

Systemic events, possibly related to vasculitis, have developed in patients with rash. Even though these events are rare, they can 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 in combination and alone, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. The only preceding symptom to these events has been dyspnoea.

It is not known if these systemic events and rash have a common cause or if they are due to different aetiologies or pathogenic processes. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative aetiology cannot be identified, fluoxetine should be discontinued.

Particular caution should be exercised in patients with a history of allergic reactions.

Implications of the Long Elimination half-life of Fluoxetine:

Because of the long elimination half-lives of fluoxetine and its major active metabolite norfluoxetine, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies of titration to final dose and withdrawal from treatment. Even when dosing is stopped, active drug substance will persist in the body for weeks due to the long elimination half-lives of fluoxetine and nor fluoxetine. This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following discontinuation of fluoxetine.

Anxiety and Insomnia:

Anxiety, nervousness and insomnia were reported by 10 to 15% of patients treated with fluoxetine. In 5% of these patients treatment with fluoxetine was discontinued due to these symptoms.

Weight Change:

Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with fluoxetine. Discontinuation of treatment with fluoxetine is rarely required.

Mania/Hypomania:

During clinical trials hypomania or mania occurred in approximately 1% of fluoxetine treated patients. The incidence in a general patient population which might also include bipolar depressives is unknown. The likelihood of hypomanic or manic episodes may be increased at the higher dosage levels. Such reactions require a reduction in dosage or discontinuation of the drug.

Seizures:

Fluoxetine should be used with caution in patients with a history of convulsive disorders. Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

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Hypokalaemia:

Self-induced vomiting often leads to hypokalemia which may lower seizure threshold and/or may lead to cardiac conduction abnormalities. Electrolyte levels of bulimic patients should be assessed prior to initiation of treatment.

Mydriasis:

Mydriasis has been reported in association with fluoxetine; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Concomitant Illness:

Clinical experience with fluoxetine in patients with concomitant systemic illness is limited and it should be used cautiously in such patients, especially those with diseases or conditions that could affect metabolism or haemodynamic responses.

Fluoxetine hydrochloride has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infraction or unstable heart disease.

Fluoxetine hydrochloride should be given with caution to patients suffering from anorexia nervosa and only if the expected benefits (e.g. co-morbid depression) markedly outweigh the potential weight reducing effect of the drug.

In patients with diabetes, fluoxetine can change glycaemic control. Hypoglycaemia has occurred during therapy with fluoxetine, and hyperglycaemia has developed following discontinuation of the drug. When taken concurrently by patients with diabetes, insulin and/or oral hypoglycaemic dosage may need to be adjusted when therapy with fluoxetine is instituted or discontinued.

Since fluoxetine is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination. However, until an adequate number of patients with severe renal impairment have been evaluated in the course of chronic treatment, fluoxetine should be used with caution in such patients.

Since clearances of fluoxetine and norfluoxetine may be decreased in patients with impaired liver function including cirrhosis, a lower or less frequent dose should be used in such patients.

Hyponatraemia:

Several cases of hyponatraemia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatraemia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible aetiologies, 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. It may be advisable to monitor electrolytes in such patients during the first weeks of therapy.

Haemorrhage:

Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, haematoma, epistaxis, vaginal bleeding and gastrointestinal bleeding). This risk may be potentiated by concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin or other medicines that affect coagulation. Apo-Fluoxetine should

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therefore be used with caution in patients concomitantly treated with medicines that increase the risk of bleeding or in patients with a past history of abnormal bleeding or in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

General Anaesthetics:

Since little is known about the interaction between fluoxetine and general anaesthetics, fluoxetine should be discontinued for as long as clinically possible prior to elective surgery.

Dependence Liability:

Fluoxetine has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. 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.

Cognitive and Motor Performance:

Because fluoxetine may impair judgement, thinking or motor skills patients should be cautioned against driving an automobile or operating hazardous machinery until they are reasonably certain that treatment with fluoxetine does not affect them adversely.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with fluoxetine hydrochloride.

Information for Patients and Families:

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to this medicine's efficacy and safety when used in the treatment regimen proposed.

Use in Pregnancy and Lactation:

Category C

Fluoxetine use should be considered during pregnancy only if the potential benefit justifies the potential risk to the foetus, taking into account the risks of untreated depression.

Experimental animal studies do not indicate direct or indirect harmful effect, with respect to the development of the embryo or foetus or the course of gestation. Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

This drug crosses the placenta.

Results of a number of epidemiological studies assessing the risk of fluoxetine exposure in early pregnancy have been inconsistent and have not provided conclusive evidence of an increased risk of congenital malformations. However, one meta-analysis suggests a potential

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risk of cardiovascular defects in infants of women exposed to fluoxetine during the first trimester or pregnancy compared to infants or women who were not exposed to fluoxetine.

At the end of pregnancy, caution should be exercised, as transitory withdrawal symptoms (eg. Transient jitteriness, difficulty feeding, tachypnea and irritability) have been reported rarely in the neonate after maternal use near term.

Neonates exposed to fluoxetine and other SSRIs or serotonin and noradrenaline reuptakes inhibitors (SNRIs), late in the third trimester have been uncommonly reported to have clinical findings or respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. Such events can arise immediately upon delivery and are usually transient. These features could be consistent with either a direct effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. When treating a pregnant women with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of the treatment.

Epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Recent data suggests the use of SSRIs, including fluoxetine, after the first 20 weeks of pregnancy may be associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The data shows the absolute risk among those who used SSRIs late in pregnancy was reported to be about 6 to 12 per 1000 women, compared to 1 to 2 per 1000 women in the United States general population. These findings should be taken into account by the physician when making decisions whether to continue the use of SSRIs during pregnancy.

Because fluoxetine is excreted in breast milk, breastfeeding while on fluoxetine is not recommended.

Use in Children:

Safety and effectiveness in patients below the age of 18 have not been established.

Use in the Elderly:

Elderly patients should initially receive fluoxetine in low dosage with slow progressive increases only if required and tolerated. Patients who have concomitant systemic illness or who are receiving other drugs concomitantly should be under careful observation at all dosage levels.

Adverse Effects

Adverse reactions are dose dependent and are more common at doses higher than 20mg/day.

In premarketing trials the most commonly observed adverse reactions associated with the use of fluoxetine central nervous system complaints, including headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, and dizziness or light-headedness; gastrointestinal complaints, including nausea, diarrhoea, dry mouth and anorexia; and excessive sweating. 15% of fluoxetine treated patients discontinued treatment because of adverse reactions which included: psychiatric (5.3%), primarily nausea; and insomnia;

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digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness, asthenia and headaches; skin (1.4%), primarily rash and pruritus. In obsessive compulsive disorder studies, 12.1% of fluoxetine-treated patients discontinued treatment early because of adverse events. Anxiety, and rash, at incidences of less than 2%, were the most frequently reported events. In bulimia nervosa studies, 10.2% of fluoxetine-treated patients discontinued treatment early because of adverse events. Insomnia, anxiety and rash, at incidences of less than 2%, were the most frequently reported events.

The following potentially serious adverse reactions have been reported in clinical practise interactions with MAO inhibitors and possibly other drugs, allergic reactions, cardiovascular reactions, syndrome of inappropriate ADH secretion, and grand mal seizure. Death and life-threatening events have been associated with some of these reactions, although causal relationship to fluoxetine has not necessarily been established. Postmarketing experience also confirms the profile of adverse reactions commonly reported during clinical trials with fluoxetine hydrochloride including allergic skin reactions.

The following adverse effects have been reported either during clinical trials or post-marketing. Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring >1%, infrequent 0.1-1.0% and rare < 0.1%.

Allergic or Toxic:

Frequent: rash, pruritus.

Infrequent: Chills and fever, urticaria, maculopapular rash.

Rare: allergic reaction, erythema multiforme, vesicubullous rash, serum sickness, contact dermatitis, erythema nodosum, purpuric rash, leucocytoclastic vasculitis, leucopenia, thrombocytopenia, arthralgia, angioedema, bronchospasm, lung fibrosis, allergic alveolitis, larynx oedema, respiratory distress.

Neurologic:

Frequent: headache, tremor, dizziness or light-headedness, asthenia, abnormal dreams and agitation.

Infrequent: abnormal gait, ataxia, akathisia, buccoglossal syndrome, hyperkinesia, hypertonia, incoordination, neck rigidity, extrapyramidal syndrome, convulsions, vertigo, amnesia, apathy, CNS stimulation, delusions, depersonalisation, emotional lability, euphoria, hallucinations, hostility, libido increased, manic reaction, paranoid reaction, psychosis, migraine, hypoesthesia, neuralgia, neuropathy, acute brain syndrome.

Rare: dysarthria, dystonia, torticollis, decreased reflexes, nystagmus, myoclonus, hypertonia, hysteria, paralysis, paraesthesia, carpal tunnel syndrome, stupor, coma, abnormal electroencephalogram, antisocial reaction, CNS depression, extrapyramidal syndrome, chronic brain syndrome, dyskinesia and other movement disorders (including worsening of pre-existing conditions or appearance in patients with risk factors [e.g. Parkinson's disease, treatment with neuroleptics or other drugs known to be associated with movement disorders]), neuroleptic malignant syndrome-like events.

Behavioural:

Frequent: insomnia, anxiety, nervousness, agitation, abnormal dreams, drowsiness and fatigue.

Infrequent: confusion, delusions, hallucinations, manic reaction, paranoid reaction, psychosis, depersonalisation, apathy, emotional lability, euphoria, hostility, amnesia, increased libido.

Rare: antisocial reaction, hysteria, suicidal ideation, violent behaviours.

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Autonomic:

Frequent: excessive sweating.

Infrequent: dry mouth, constipation, urinary retention, vision disturbance, diplopia, mydriasis, hot flushes.

Cardiovascular:

Infrequent: chest pain, hypertension, syncope, hypotension (including postural hypotension), angina pectoris, arrhythmia, tachycardia.

Rare: bradycardia, ventricular arrhythmia, first-degree AV block, bundle branch block, myocardial infarct, cerebral ischemia, cerebral vascular accident, thrombophlebitis.

Gastrointestinal:

Frequent: nausea, disturbances of appetite, diarrhoea.

Infrequent: vomiting, stomatitis, dysphagia, eructation, oesophagitis, gastritis, gingivitis, glossitis, melena, thirst, abnormal liver function tests.

Rare: bloody diarrhoea, haematemesis, gastrointestinal haemorrhage, duodenal ulcer, stomach ulcer, mouth ulceration, hyperchlorhydria, colitis, enteritis, cholecystitis, cholelithiasis, hepatitis, hepatomegaly, liver tenderness, jaundice, increased salivation, salivary gland enlargement, tongue discolouration, faecal incontinence, pancreatitis.

Respiratory:

Frequent: bronchitis, rhinitis, yawn.

Infrequent: asthma, dyspnoea, hyperventilation, pneumonia, hiccups, epistaxis.

Rare: apnoea, lung oedema, larynx oedema, lung fibrosis/alveolitis, hypoxia, pleural effusion, haemoptysis.

Metabolic and Nutritional:

Frequent: weight loss.

Infrequent: generalised oedema, peripheral oedema, face oedema, tongue oedema, hypoglycaemia, hypothyroidism, weight gain.

Rare: dehydration, gout, goitre, hyperthyroidism, hypercholesteremia, hyperglycaemia, hyperlipemia, hyperprolactinemia, hypokalaemia, hyponatraemia, iron deficiency anaemia, syndrome of inappropriate ADH secretion.

Endocrine System:

Infrequent: Hypothyroidism

Rare: Goitre and hyperthyroidism

Haematologic:

Infrequent: anaemia, lymphadenopathy, haemorrhage, abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding.

Rare: bleeding time increased, leucocytosis, lymphocytosis, thrombocytopenia, thrombocytopenic purpura, thrombocytopenia, retinal haemorrhage, petechia, sedimentation rate increased, aplastic anaemia, pancytopenia, immune-related haemolytic anaemia.

Dermatologic:

Infrequent: acne, alopecia, dry skin, herpes simplex, contact dermatitis, maculopapular rash and urticaria.

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Rare: eczema, psoriasis, seborrhoea, erythema multiforme, purpuric rash, pustular rash, subcutaneous nodule, vesiculobullous rash, skin hypertrophy, skin discoloration, herpes zoster, fungal dermatitis, hirsutism, ecchymoses.

Musculoskeletal:

Frequent: muscle pain, back pain, joint pain.

Infrequent: arthritis, bone pain, bursitis, tenosynovitis, twitching.

Rare: bone necrosis, osteoporosis, pathological fracture, chondrodystrophy, myositis, rheumatoid arthritis, muscle haemorrhage.

Special Senses:

Common: abnormal vision, taste perversion

Uncommon: mydriasis

Infrequent: conjunctivitis, ear pain, eye pain, amblyopia, photophobia and tinnitus.

Rare: eye haemorrhage, glaucoma, blepharitis, cataract, corneal lesion, deafness, diplopia, iritis, ptosis, strabismus and taste loss.

Urogenital:

Frequent: painful menstruation, sexual dysfunction, urinary tract infection, frequent micturition.

Infrequent: abnormal ejaculation, impotence, menopause, amenorrhoea, menorrhagia, ovarian disorder, vaginitis, leukorrhoea, fibrocystic breast, breast pain, cystitis, dysuria, urinary retention, urinary urgency, urination impaired, urinary incontinence.

Rare: breast enlargement, galactorrhoea, abortion, dyspareunia, female lactation, hypomenorrhoea, uterine spasm, urinary tract disorder, uterine haemorrhage, vaginal haemorrhage, metrorrhagia, haematuria, albuminuria, polyuria, pyuria, epididymitis, orchitis, pyelonephritis, salpingitis, urethritis, kidney calculus, urethral pain, urolithiasis.

Miscellaneous:

Frequent: chills.

Infrequent: amblyopia, conjunctivitis, cyst, ear pain, eye pain, jaw pain, neck pain, pelvic pain, hangover effect, malaise.

Rare: abdomen enlarged, blepharitis, cataract, corneal lesion, glaucoma, iritis, ptosis, strabismus, deafness, taste loss, moniliasis, hydrocephalus, LE syndrome.

Interactions

The effects of alcohol may be enhanced.

MAI Inhibitors:

Combined use of fluoxetine and MAO inhibitors is contraindicated.

Drugs metabolised by cytochrome P450 2D6:

3-10% of the population has a genetic defect that leads to reduced levels of activity of cytochrome P450 2D6 (such individuals are known as slow metabolisers). Fluoxetine is metabolised by this isoenzyme with the pharmacokinetic properties and relative proportion of metabolites being altered in poor metabolisers. Fluoxetine inhibits the activity of this isoenzyme and may cause normal metabolisers to resemble slow metabolisers. Therapy with medications that are predominantly metabolised by cytochrome P450 2D6 and have a relatively narrow therapeutic index e.g. flecainide, vinblastine, carbamazepine and tricyclic antidepressants should be initiated at the low end of the dose range if a patient is taking fluoxetine concurrently or has taken it in the last 5 weeks. If fluoxetine is added to the

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treatment regimen of a patients already receiving a drug metabolised by P450 2D6 the need for a reduced dosage of the original medication should be considered.

Tryptophan:

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

Potential Effects of coadministration of Medicines Highly Bound to Plasma Proteins:

Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another medicine which is tightly bound to protein (e.g. warfarin, digoxin) 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 medicines.

Medicines that interfere with haemostasis (NSAIDs, aspirin, warfarin, etc):

Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such a medicines concurrently with Apo-Fluoxetine

CNS Active Medicines:

The risk of using fluoxetine hydrochloride in combination with other CNS active medicines has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of fluoxetine hydrochloride and such medicines is required. Consideration should be given to using lower doses of the concomitantly administered drugs, using conservative titration schedules and monitoring of clinical status.

Other Antidepressants:

Previously stable plasma levels 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 has been discontinued. The dose of tricyclic antidepressants may need to be reduced and plasma tricyclic antidepressant concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued.

Anticonvulsants:

Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Antipsychotics:

There is a possible pharmacodynamic and/or pharmacokinetic interaction between some SSRIs and some antipsychotics, including possible elevation of blood levels of haloperidol and clozapine. A single report has suggested possible of additive effects of pimozide and fluoxetine leading to bradycardia.

Benzodiazepines:

The half-life of concurrently administered diazepam may be prolonged in some patients. Coadministration of alprazolam may result in increased alprazolam concentrations.

Apo-Fluoxetine

Fluoxetine hydrochloride equivalent to Fluoxetine 10mg & 20mg capsules

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.

Electroconvulsive Therapy:

There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Overdosage

Reports of death attributed to overdosage of fluoxetine alone have been rare.

Symptoms:

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, including seizures.

Treatment:

Establish and maintain an airway; insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose.

Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures which fail to remit spontaneously may respond to diazepam.

There are no specific antidotes for fluoxetine.

Due to the large volume of distribution of fluoxetine, forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison information centre on the treatment of any overdosage.

Pharmaceutical Precautions

Store below 25°C. Protect from heat, light and moisture.

Medicine Classification

Prescription-Only Medicine.

Package Quantities

For 10mg and 20mg capsules packaging will be:
Blister packs of 30, 60 and 90 capsules.



Apo-Fluoxetine

Fluoxetine hydrochloride equivalent to Fluoxetine 10mg & 20mg capsules

Further Information

Capsules contain lactose and corn starch.

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