PROFESSIONAL INFORMATION FOR

NUZAK CAPSULES

SCHEDULING STATUS:

S5

PROPRIETARY NAME (AND DOSAGE FORM):

NUZAK (Capsules).

COMPOSITION:

NUZAK capsules: each capsule contains fluoxetine hydrochloride equivalent to 20mg Fluoxetine. Fluoxetine hydrochloride is an antidepressant for oral administration. Chemically it is unrelated to tricyclic or tetracyclic antidepressants. Chemically it is (±)-N-methyl-3-phenyl-3-[(α, α, α-trifluoro-p-tolyl)oxy]propylamine hydrochloride, $C_{17}H_{18}F_3NOHCl$. Its molecular mass is 345.79.

The other ingredients are colloidal silicon dioxide, magnesium stearate, maize starch and purified talc.

Capsule cap: bronidiol, gelatin, indigo carmine, polyvinyl pyrrolidone K-30, quinoline yellow W.S, sodium lauryl sulphate, sunset yellow supra, titanium dioxide.

Capsule body: bronidiol, gelatin, polyvinyl pyrrolidone K-30, quinoline yellow W.S, sodium lauryl sulphate, titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A. 1.2 Psychoanaleptics (antidepressants).

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Fluoxetine is an inhibitor of the neuronal inactivation of serotonin (5-HT) by blocking active reuptake.

By inhibiting removal of serotonin from the synaptic cleft, fluoxetine enhances serotonergic function.

Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the serotonin uptake into human platelets.

Pharmacokinetics:

Fluoxetine has a long half-life: - fluoxetine 2-3 days

- Nor-fluoxetine 7-9 days.

Changes in dosage would therefore not be fully reflected in the plasma for several weeks. This is to be taken into consideration during adjustments and the cessation of treatment.

INDICATIONS:

Major depressive episodes: A single episode and recurrent depression with associated anxiety.

Obsessive-compulsive disorders: This must be experienced as intrusive, markedly distressing and interfering significantly with the person's occupational and social functioning. Fluoxetine is indicated for the treatment of obsessive-compulsive disorder.

Bulimia nervosa: Fluoxetine significantly reduces binge-eating and purging.

CONTRAINDICATIONS:

Hypersensitivity to fluoxetine.

Fluoxetine is not considered a suitable form of therapy for the depressive component of bipolar (manic depressive) illness as mania may be precipitated.

Severe renal failure (glomerular filtration rate of less than 10 ml per minute).

The acute phase of myocardial infarction.

Unstable epilepsy.

Monoamine oxidase (MAO) inhibitors:

A potentially lethal hyperserotonergic state known as serotonin syndrome may occur in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor. The syndrome may be manifested by a change in mental status (confusion, hypomania, including extreme agitation that may progress to delirium

and coma), also myoclonus, rigidity, autonomic instability with possible rapid fluctuation of vital sign, hyperreflexia, restlessness, diaphoresis, tremor, incoordination, shivering. Some cases presented with features resembling neuroleptic malignant syndrome.

Concurrent use of fluoxetine with MAO inhibitors may result in gastrointestinal symptoms, hyperpyretic episodes, severe convulsions, confusion, agitation, restlessness and hypertensive crises. At least 5 weeks should elapse between the initiation of therapy with a MAO inhibitor and the discontinuation of fluoxetine. Death has been reported following the initiation of a MAO inhibitor shortly after fluoxetine administration was stopped.

Fluoxetine and nor-fluoxetine are excreted in breast milk and should not be prescribed to nursing mothers.

The safety in pregnancy has not been established.

Pediatric safety and efficacy have not been established.

WARNINGS:

Fluoxetine should be discontinued in patients who develop a rash, since systemic effects, possibly related to vasculitis, have occurred in such patients.

Selective-serotonin reuptake inhibitors (SSRIs)/serotonin- norepinephrine reuptake inhibitors (SNRIs) may increase the risk of postpartum haemorrhage (see "**PREGNANCY AND LACTATION**" and "**SIDE EFFECTS**").

Special warning:

This medicine should at all times be kept out of the reach of children. Even small doses may be fatal to them.

DOSAGE AND DIRECTIONS FOR USE:

To be taken orally by adults only.

Major depression: 20 mg daily, taken as a single morning dose. Doses of up to 80 mg daily in divided doses may be employed if necessary. Doses more than 20 mg should be divided into two doses taken in the morning and at noon.

Obsessive-compulsive disorders: recommended doses of 20 to 60 mg daily.

Bulimia nervosa: 60 mg daily.

Fluoxetine may be taken with or without food.

A recommended maximum dose for elderly patients is 60 mg. Caution should be used if the elderly patient suffers from systemic illnesses or receives multiple medications for concomitant diseases.

Missed dose: Skip the missed dose and continue on the schedule with the next dose.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

Asthenia, fever, palpitations and vision disturbances may occur.

Peripheral anticholinergic side-effects: notable dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation. When these effects are severe the medicine should be discontinued or reduced. Drowsiness or excessive sedation in certain patients. Disorientation and agitation, insomnia and restlessness may also occur with normal doses. The risks of central nervous system depression are greater when administered together with other nervous system depressants e.g. alcohol, barbiturates. The elderly are more prone to these effects and therapy should be initiated at lower than standard doses.

Gastro-intestinal disturbances: vomiting, nausea, dry mouth, diarrhoea, dyspepsia. Anorexia and weight loss may also occur.

Neurological side-effects: anxiety, insomnia, drowsiness, fatigue, nervousness, headache, tremor, dizziness, convulsions (see "**Special precautions**") and decreased libido, abnormal dreams and sexual dysfunction.

Respiratory system: Dyspnoea may be the only preceding symptom to pulmonary events (including fibrosis and/or inflammatory processes of varying histopathology).

Skin and appendages: A rash or urticaria may develop in a small percentage of patients (see "**WARNINGS**"). Serious systemic events have developed in patients with a rash and less frequently death has occurred. This is possibly related to vasculitis. Anaphylactoid reactions have been reported. Also serum sickness and excessive sweating.

Endocrine system: Hypothyroidism has been reported.

Hyponatremia has been reported especially in geriatric or volume-depleted patients. This appeared to be reversible when fluoxetine was discontinued.

Elevated serum transaminase values have occurred.

The following have been reported in association with fluoxetine, but no causal relationship has been established: confusion, cerebral vascular accident, ecchymoses, eosinophilic pneumonia, aplastic anaemia, dyskinesia (for example, buccal-lingual-masticatory syndrome, which resolved following the discontinuation of the medicine), gastro-intestinal haemorrhage, hyperprolactinaemia, movement disorders in high-risk factor patients (this includes the medicines associated with such events). Pre-existing movement disorders may worsen, suicidal ideation, immune related haemolytic anaemia, pancreatitis, pancytopenia, thrombocytopenia, thrombocytopenic purpura, violent behaviour and vaginal bleeding after the withdrawal of the medicine.

Frequency not known: Postpartum haemorrhage*

This event has been reported for the therapeutical class of SSRIs/SNRIs (see "WARNINGS**" and "**PREGNANCY AND LACTATION**").*

Special precautions:

At the time of initiation of the therapy patients should be advised not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery, for at least several days as psychoactive medicines may impair judgement or skills. Impaired decision making could lead to accidents.

Withdraw the medicine if allergic skin reactions appear.

Because of renal excretion and hepatic metabolism of fluoxetine, lower doses, e.g. alternate day dosing is recommended in patients with impaired renal and hepatic function.

Fluoxetine may alter glycaemic control. Hypoglycaemia has occurred during therapy and hyperglycaemia following the discontinuation of the medicine. Insulin and oral hypoglycaemic dosage may need to be adjusted. Caution should therefore be used in diabetic patients.

Depressed patients with suicidal tendencies should be carefully supervised during treatment. Caution should be observed with patients suffering from a depressive phase of manic depressive psychosis, as occasional hypomania or mania can be precipitated in such patients. Withdraw the medicine if the depression turns into a manic phase.

Cardiac disease: Occasional problems of tachycardia, dysrrhythmias, orthostatic hypotension and other unwanted effects on blood pressure, aggravation of conduction disturbances, and electro-cardiographic abnormalities may occur. Regular cardiological and electro-cardiographic examination is advised.

Special precaution should be taken in men with prostatic hypertrophy. In the elderly male patient suffering from prostatism, urinary retention may be precipitated.

Because of the epileptogenic effect, fluoxetine should be used with caution in patients with a history of epilepsy. The medicine should be avoided in patients with unstable epilepsy.

This medicine should not usually be given to patients receiving other central nervous system depressants, e.g. barbiturates, and to patients receiving MAO inhibitors, only after a suitable interval. The pressor effects of the direct acting sympathomimetic agents, adrenaline and noradrenaline, are enhanced, and the use of local anaesthetics containing these vasoconstrictors should be avoided as hypertensive reactions may occur. The simultaneous administration of anticholinergic agents may be dangerous. The hypotensive effect of certain antihypertensive agents may be reduced.

Narrow-angle glaucoma may be aggravated.

Avoid electroconvulsive therapy. Prolonged seizures have been reported.

Altered platelet function and/or abnormal results from laboratory studies have been reported. Also abnormal bleeding in several patients taking fluoxetine. It is not clear whether fluoxetine had a causative role.

Undesirable loss of mass may occur in underweight depressed patients.

Do not use during pregnancy and lactation.

Safety and efficacy in children have not been established.

Re-evaluate periodically in long-term use.

The same precautions should be observed when treating patients with obsessive-compulsive disorders because the comorbidity between obsessive-compulsive disorders and depression is well established.

Caution should be used in debilitated patients or those taking multiple central nervous system-active medication.

Use with caution in the elderly.

INTERACTIONS:

Patients receiving **NUZAK** in combination with tryptophan have been reported to experience adverse reactions such as gastro-intestinal distress, agitation and restlessness. There have been reports of both increases and decreases in lithium levels when used concomitantly with fluoxetine. Caution is advised if concomitant administration of **NUZAK** and central nervous system active medicines are prescribed. Lithium levels should be monitored.

NUZAK should not be used concomitantly with monoamine oxidase inhibitors (see "**CONTRAINDICATIONS**").

Fluoxetine is bound to plasma proteins and the concurrent administration may alter the plasma concentrations of other plasma bound medicines, e.g. digoxin and warfarin. Conversely fluoxetine may be changed by other agents. The long elimination half-lives of fluoxetine and nor-fluoxetine should be borne in mind when considering pharmacokinetic and pharmacodynamic interactions. Greater than 2-fold increases in stable plasma levels of other antidepressants have been reported when fluoxetine has been administered in combination with these agents.

The half-life of concurrently administered diazepam may be prolonged.

PREGNANCY AND LACTATION

The safety in pregnancy has not been established

NUZAK is excreted in breast milk and should not be prescribed to nursing mothers.

Observational data indicate an increased risk (less than 2- fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see "**WARNINGS**" and "**SIDE EFFECTS**").

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms: Nausea, vomiting, excitation of the central nervous system. Death has been reported.

Overdose and poisoning may be characterised by central nervous system depression or excitation, severe anticholinergic effects and cardiotoxicity.

Drowsiness, restlessness, ataxia, stupor, coma, pyrexia, palpitations, tachycardia, cardiac arrhythmias, hypotension, and in severe cases, respiratory depression, may occur. Epileptiform seizures may occur. Mixed poisoning with other central nervous system depressants is not uncommon.

Treatment: Essentially symptomatic and supportive. No specific antidotes for fluoxetine are known. Forced diuresis, dialysis, heamoperfusion and exchange transfusion are of unlikely benefit due to **NUZAK's** large volume of distribution.

IDENTIFICATION:

Hard, opaque gelatin capsules of size '2', with cream coloured body and a light green cap, and having 'NZC' printed in black on both halves.

PRESENTATION:

10 capsules packed in a blister strip.

Pack sizes:- 1 x 10, 3 x 10 and 10 x 10 capsules.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light.

Keep the blister strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

32/1.2/0384

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DATE OF PUBLICATION OF THIS PROFESSIONAL INFORMATION:

Date of registration: 25 May 1998

Date of revision of the text: 02 December 2021