APPROVED PACKAGE INSERT FOR ZYDUS-FLUOXETINE 20 mg

SCHEDULING STATUS:

S5

PROPRIETARY NAME (and dosage form):

ZYDUS-FLUOXETINE 20 mg (capsules)

COMPOSITION:

Each capsule contains fluoxetine hydrochloride equivalent to 20 mg fluoxetine.

PHARMACOLOGICAL CLASSIFICATION:

A.1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION:

Fluoxetine is a selective serotonin (5 – HT) uptake inhibitor in the central nervous system. The antidepressant and anti-obsessive-compulsive effects of fluoxetine are thought to be related to its effect on serotonergic neurotransmission.

Pharmacokinetics:

Fluoxetine is well absorbed after oral administration and metabolised by demethylation in the liver to the active metabolite, norfluoxetine, and other unidentified metabolites. The involvement of cytochrome P450 2D6(CYP2D6) has been identified in fluoxetine metabolism.

The elimination half – life of fluoxetine is 4 to 6 days, whereas that of the active metabolite, norfluoxetine, is 4 to 16 days.

Excretion is about 80% renal and approximately 15% in the faeces.

INDICATIONS:

ZYDUS-FLUOXETINE is indicated for the treatment of:

- **Major depressive disorders**
- **Obsessive-compulsive disorder**
- **Bulimia nervosa**

CONTRA-INDICATIONS:

- Hypersensitivity to fluoxetine or to any of the ingredients.
- **Concomitant use of a monoamine oxidase inhibitor (MAOI)**.

  At least 14 days should elapse between discontinuing a MAOI and initiating therapy with **ZYDUS-FLUOXETINE**. In view of the long half-life of **ZYDUS-FLUOXETINE** at least 5 weeks should elapse after stopping therapy with **ZYDUS-FLUOXETINE** before starting a MAOI. If **ZYDUS-FLUOXETINE** has been prescribed chronically and/or at a high dose, a longer interval should be considered.

  There have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, the serotonin syndrome, 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 **ZYDUS-FLUOXETINE** with a MAOI

and in patients who have recently discontinued **ZYDUS-FLUOXETINE** and are then started on a MAOI. Serious and fatal cases of the serotonin syndrome, some with features resembling neuroleptic malignant syndrome, have been reported in patients treated with **ZYDUS-FLUOXETINE** and an MAOI in temporal proximity (See **WARNINGS**).

- Severe renal function impairment (GFR < 10 ml/min), as accumulation may occur during chronic treatment.

WARNINGS:

The serotonin syndrome – characterised by the clustering of clinical features of changes of mental state (agitation, confusion, disorientation) and neuromuscular activity (myoclonus, hyper-reflexia, tremor, rigidity, incoordination), in combination with auto-immune dysfunction (especially fever, sweating, diarrhoea) – may occur in patients who receive **ZYDUS-FLUOXETINE** either alone or in temporal association with the use of a MAOI and other selective serotonin re-uptake inhibitors (SSRIs) or serotonergic agents. Since death and serious morbidity may follow the serotonin syndrome, **ZYDUS-FLUOXETINE** should be stopped.

ZYDUS-FLUOXETINE should be discontinued in patients who develop a **rash or other allergic reactions**. Anaphylactoid reactions and serious systemic events involving the skin, kidney, liver or lung have been reported in patients receiving **ZYDUS-FLUOXETINE**.

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and or the emergence of suicidal ideation and behaviour, whether or not

they are taking antidepressant medicines this risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with **ZYDUS-FLUOXETINE** should, nevertheless be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy, or at any time of dose changes either increases or decreases.

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.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania and mania). 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, consideration should be given to changing the therapeutic regimen, including possibly discontinuing **ZYDUS-FLUOXETINE**, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, **ZYDUS-FLUOXETINE** should be tapered (See PRECAUTIONS and DOSAGE AND DIRECTIONS FOR USE).

INTERACTIONS:

Due to the long elimination half-life of **ZYDUS-FLUOXETINE** and norfluoxetine, the potential for interactions exist not only with concomitantly administered medicines but also with medicines administered several weeks after discontinuation of **ZYDUS-FLUOXETINE** therapy.

- **Monoamine oxidase inhibitors** (See **CONTRA-INDICATIONS**)
- **Medicines metabolised by cytochrome P450 CYP2D6 – ZYDUS-FLUOXETINE** is an inhibitor of cytochrome P450 CYP2D6. There is potential for interaction with other medicines that are metabolised by this enzyme, therefore a reduction in the dosage of such medicines, with initiation of therapy at the low dose range for medicines having a relatively narrow therapeutic index, may be needed when used concurrently with **ZYDUS-FLUOXETINE** or within 5 weeks of discontinuing **ZYDUS-FLUOXETINE**.
- **CNS active medicines**
    - **Lithium** – both increased and decreased concentrations of lithium have been reported when used concurrently with **ZYDUS-FLUOXETINE**. Close monitoring of lithium levels is recommended.
    - **Phenytoin, carbamazepine, haloperidol, clozapine, diazepam, alprazolam, imipramine and desipramine** – changes in blood levels, sometimes with clinical manifestations of toxicity, have been reported when these medicines are used concomitantly with **ZYDUS-FLUOXETINE**. The use of conservative titration schedules of these medicines and monitoring of clinical status should be considered. The half-life of concurrently administered diazepam may be prolonged.

- **Tryptophan** – Adverse reactions, including agitation, restlessness and gastro-intestinal distress have been reported when **ZYDUS-FLUOXETINE** has been used in combination with tryptophan.
- **Protein bound medicines** – As **ZYDUS-FLUOXETINE** is bound to plasma protein its plasma concentration or that of other protein bound medicines such as warfarin and digoxin could be altered when used concomitantly. Altered anti-coagulant effects (laboratory values and/or clinical signs and symptoms) and increased bleeding has been reported when warfarin and fluoxetine are given concurrently. Careful coagulation monitoring is recommended in this case and when **ZYDUS-FLUOXETINE** is discontinued.

PREGNANCY AND LACTATION:

Safety and efficacy in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Safety and efficacy of **ZYDUS-FLUOXETINE** in children has not been established.

ZYDUS-FLUOXETINE can be administered with or without food. Avoid use of alcohol.

For patients who have concurrent illnesses or hepatic impairment, a lower dose or less frequent dosing should be considered.

Major depressive disorders:

Adults: 20 mg daily, preferably in the morning.

Obsessive-compulsive disorder:

Adults: 20 mg – 60 mg daily.

Bulimia nervosa:

Adults: 60 mg daily.

Due to the pharmacokinetic properties of **ZYDUS-FLUOXETINE**, upward dose titration is advised at intervals of several weeks. Doses above 80 mg daily are not recommended for any of the indications.

Elderly - ZYDUS-FLUOXETINE should be used with caution in the elderly: dosages above 20 mg daily are not recommended.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Cardiovascular system:

Less frequent: Palpitations

Central nervous system:

Frequent: Headache, nervousness, anxiety, drowsiness

Less Frequent: Fatigue, insomnia, tremor, asthenia, *dizziness*, abnormal dreams, agitation, seizures, hypomania, mania, dyskinesias.

Endocrine/Metabolic:

Frequent: Weight loss

Less Frequent: Hyponatraemia, hypothyroidism, fever

Gastrointestinal:

Frequent: Diarrhoea, nausea, dyspepsia, anorexia, vomiting,

Less Frequent: Dry mouth

Kidney/Genitourinary:

Frequent: Decreased libido, sexual dysfunction (delayed or inhibited orgasm).

Liver: Raised transaminase levels

Musculoskeletal system: Arthralgia, myalgia

Ocular: Visual disturbances

Respiratory tract: Dyspnoea, pulmonary inflammation and/or fibrosis

Skin:

Frequent: Rash, urticaria, pruritus, excessive sweating

Less Frequent: Anaphylactoid reactions, serum sickness

Other: The following have been reported in association with **ZYDUS-FLUOXETINE**, but no causal relationship has been established. Aplastic anaemia, cerebral vascular accident, confusion, ecchymoses, eosinophilic pneumonia, gastro intestinal haemorrhage, hyperprolactinaemia, neuroleptic malignant syndrome-like events, pancreatitis, suicidal ideation, pancytopenia, thrombocytopenia, purpura, immune-related haemolytic anaemia, vaginal bleeding (after withdrawal of the medication) and violent behaviour.

Special Precautions:

Close monitoring of patients during the first two or more weeks of treatment with **ZYDUS-FLUOXETINE** is recommended, as improvement may occur during this period. Close supervision of high risk patients, e.g. patients with suicidal tendencies due to major depressive episodes, is recommended.

The same precautions observed when treating patients with depression should be applied when treating patients with obsessive – compulsive disorders, as co-morbidity between these conditions is well established.

ZYDUS-FLUOXETINE should be given with caution in:

- Patients with a history of seizures – There is an increased risk of seizures. **ZYDUS-FLUOXETINE** should be discontinued in any patients who develops a seizure and should be avoided in those with unstable epilepsy. Patients with controlled epilepsy should be carefully monitored. Care is advised in patients receiving electroconvulsive therapy, as prolonged seizures have been reported in patients on **ZYDUS-FLUOXETINE**.
- Hepatic function impairment – Metabolism may be delayed. Lower doses or less frequent dosing is recommended in patients with significant hepatic impairment.
- Renal function impairment – Metabolites may accumulate. Dose adjustment may be necessary in mild to moderate renal failure (GFR 10 – 50 ml/min).
- Under weight individuals - **ZYDUS-FLUOXETINE** may cause weight loss.
- Diabetes mellitus – Glycaemic control may be altered. Insulin and/or oral hypoglycaemic medication dosage may need to be adjusted.
- Patients with a history of bleeding disorders such as altered platelet function – There have been reports of abnormal bleeding.
- Patients with extrapyramidal disorders – **ZYDUS-FLUOXETINE** may cause extrapyramidal symptoms and aggravation of Parkinson’s disease.
- Patients with acute cardiac disease – Clinical experience is limited.

ZYDUS-FLUOXETINE may impair the ability to perform activities requiring mental alertness or physical coordination (e.g. operating machinery, driving a motor vehicle). Patients should be cautioned that their ability to perform potentially hazardous tasks may be impaired.

Withdrawal symptoms – including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, agitation, anxiety and nausea – may occur with discontinuation of **ZYDUS-FLUOXETINE**.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See **SIDE EFFECTS AND SPECIAL PRECAUTIONS**).

Symptoms of overdose:

Symptoms that have been reported include tachycardia, drowsiness, tremor, nausea and vomiting as well as agitation, restlessness, hypomania and seizures.

Treatment of overdose:

Treatment is symptomatic and supportive. There is no specific antidote for **ZYDUS-FLUOXETINE** overdose. Dialysis, haemoperfusion, exchange transfusion and measures to increase urine production are considered unlikely to be of benefit. Activated charcoal may be given by mouth if the amount ingested was large and treatment is within an hour of ingestion.

IDENTIFICATION:

A hard gelatin capsule with an opaque light-green coloured cap and an opaque ivory coloured body containing a white to off-white powder.

PRESENTATION:

Aluminium/PVdC blister strips containing 10 capsules. 3 x10 capsules per outer carton.

STORAGE INSTRUCTIONS:

Store below 25°C. Protect from light. Do not remove the blister from the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

37/1.2/0265

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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