APPROVED PROFESSIONAL INFORMATION (Clean)

SCHEDULING STATUS

S5

PROPRIETARY NAME (and dosage form)

KIZOFRIN 25 mg (Tablet)

KIZOFRIN 100 mg (Tablet)

KIZOFRIN 200 mg (Tablet)

KIZOFRIN 300 mg (Tablet)

COMPOSITION

KIZOFRIN 25 mg:

Each film-coated tablet contains quetiapine fumarate equivalent to quetiapine 25 mg.

Contains lactose.

KIZOFRIN 100 mg:

Each film-coated tablet contains quetiapine fumarate equivalent to quetiapine 100 mg.

Contains lactose.

KIZOFRIN 200 mg:

Each film-coated tablet contains quetiapine fumarate equivalent to quetiapine 200 mg.

Contains lactose.

KIZOFRIN 300 mg:

Each film-coated tablet contains quetiapine fumarate equivalent to quetiapine 300 mg.

Contains lactose.

The other ingredients of **KIZOFRIN** are calcium hydrogen phosphate; cellulose microcrystalline; lactose; magnesium stearate; povidone; silica colloidal anhydrous; sodium starch glycolate and talc.

The coating material of **KIZOFRIN 25 mg** contains hypromellose; iron oxide red (C.I. No: 77491); iron oxide yellow (C.I. No: 77492); macrogol / PEG 400 and titanium dioxide (C.I. No: 77891).

The coating material of **KIZOFRIN 100 mg** contains hypromellose; iron oxide yellow (C.I. No: 77492); macrogol / PEG 400 and titanium dioxide (C.I. No: 77891).

The coating material of **KIZOFRIN 200 mg** contains hypromellose; macrogol 400 and titanium dioxide (C.I. No: 77891).

The coating material of **KIZOFRIN 300 mg** contains hypromellose; macrogol 400 and titanium dioxide (C.I. No: 77891).

The imprinting ingredients used on **KIZOFRIN 100 mg**, **KIZOFRIN 200 mg** and **KIZOFRIN 300 mg** contains ammonium hydroxide; iron oxide black (C.I. No: 77499); isopropyl alcohol; N-butylalcohol; propylene glycol and shellac glaze in ethanol.

PHARMACOLOGICAL CLASSIFICATION

A 2.6.5 Central nervous system depressants: Miscellaneous structures

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Quetiapine is an atypical antipsychotic agent which interacts with a broad range of neurotransmitter receptors. Quetiapine exhibits a higher affinity for serotonin ($5HT_2$) receptors in the brain than it does for dopamine D_1 and D_2 receptors in the brain. Quetiapine also has high affinity at histaminergic and adrenergic alpha-1 receptors, with a lower affinity at adrenergic alpha-2 receptors, but no appreciable affinity at benzodiazepine or cholinergic muscarinic receptors. Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance, in animal models.

In man, quetiapine does not produce sustained elevations in prolactin. Quetiapine, when given twice a day, maintains $5HT_2$ and D_2 receptor occupancy for up to 12 hours after dosing.

Pharmacokinetic properties:

Following oral administration, quetiapine is absorbed and extensively metabolised. The principal human plasma metabolites do not have significant pharmacological activity. Administration with food does not significantly affect the bioavailability of quetiapine.

The elimination half-life of quetiapine is approximately 7 hours. Quetiapine is approximately 65 % - 83 % bound to plasma proteins.

The pharmacokinetics of quetiapine are variable but do not differ significantly between women and men.

In the elderly, the mean clearance of quetiapine is approximately 30 % - 50 % lower than that seen in adults aged 18 - 65 years.

The mean plasma clearance of quetiapine was reduced by approximately 25 % in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1,73 m^2) and in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects.

Quetiapine is extensively metabolised with the parent compound accounting for less than 5 % of unchanged medicine-related material in the urine or faeces, following the administration of radio-labelled quetiapine.

Approximately 73 % of the radioactivity is excreted in the urine and 21 % in the faeces.

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine.

Quetiapine and several of its metabolites were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities, but only at concentrations at least 10-50 fold higher than those observed in the usual effective dose range of 300 to 450 mg/day in humans.

INDICATIONS

KIZOFRIN are indicated for the treatment of schizophrenia.

KIZOFRIN are also indicated for the treatment of manic episodes associated with a bipolar disorder. Safety and efficacy beyond 12 weeks has not been established.

CONTRA-INDICATIONS

Hypersensitivity to quetiapine or to any of the other ingredients of **[PRODUCT NAME]** .

Pregnancy and lactation, since safety has not been established.

Safety and efficacy in children and adolescents have not been established.

Advanced liver and renal function impairment, since safety has not been established.

WARNINGS AND SPECIAL PRECAUTIONS

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 casual role, however, for

antidepressant medicine in inducing such behaviour has not been established.

Patients being treated with **KIZOFRIN** 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 disorders 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 suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing **[PRODUCT NAME]** , 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, **KIZOFRIN** should be tapered (See **"DOSAGE AND DIRECTIONS FOR USE"**).

Hyperglycaemia and diabetes mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including **[PRODUCT NAME]** .

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics such as **[PRODUCT NAME]** , should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics such as **KIZOFRIN** should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as **[PRODUCT NAME]** , should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as **[PRODUCT NAME]** , was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of

the suspect medicine.

Somnolence may occur, usually during the first 2 weeks of treatment and generally resolves with the continued administration of **[PRODUCT NAME]** .

Resolution of leucopenia and/or neutropenia usually follows cessation of therapy with **[PRODUCT NAME]** .

Possible risk factors for leucopenia and/or neutropenia include pre-existing low white cell count and history of medicine induced leucopenia and/or neutropenia. Agranulocytosis has been reported in patients on treatment with quetiapine. Although a causal relationship could not be established, the possibility that **KIZOFRIN** may be implicated could not be excluded.

Concomitant illness:

KIZOFRIN should be used with caution in patients with mild to moderate hepatic or renal impairment, with known cerebrovascular disease, cardiovascular disease or other conditions predisposing to hypotension, or with a history of seizures. **KIZOFRIN** may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients.

Quetiapine as in **KIZOFRIN** has not been associated with a persistent increase in QTc intervals. However, caution should be exercised when **KIZOFRIN** is prescribed with medicines known to prolong the QTc interval, especially in the elderly.

Seizures:

When treating patients with a history of seizures, caution is recommended.

Tardive dyskinesia:

There is a potential for **KIZOFRIN** to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, discontinuation of **KIZOFRIN** should be considered.

Neuroleptic malignant syndrome:

Neuroleptic malignant syndrome has been associated with **KIZOFRIN** treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, **KIZOFRIN** should be discontinued and appropriate medical treatment given.

KIZOFRIN contains lactose. Patients with rare hereditary problems of galactose intolerance, lapp lactase efficiency, or glucose-galactose malabsorption should not take **[PRODUCT NAME]** .

Effects on ability to drive and use machines:

KIZOFRIN TABLETS may cause somnolence which may interfere with activities requiring mental alertness. Therefore, until individual susceptibility is known, patients should be advised not to drive or operate machinery.

INTERACTIONS

Because of the primary central nervous system effects of **[PRODUCT NAME]** , **KIZOFRIN** should be used with caution in combination with other centrally acting medicines and alcohol.

The pharmacokinetics of lithium are not altered when co-administered with **[PRODUCT NAME]** .

When co-administered, the pharmacokinetics of sodium valproate and **KIZOFRIN** are not altered to a clinically relevant extent.

The pharmacokinetics of **KIZOFRIN** are not significantly altered following co-administration with the antipsychotics risperidone or haloperidol.

However, co-administration of **KIZOFRIN** and thioridazidine may cause increases in clearance of **[PRODUCT NAME]** .

KIZOFRIN does not induce the hepatic enzyme systems involved in the metabolism of antipyrine. Enzyme inducers such as carbamazepine may decrease the plasma concentrations of quetiapine, and higher doses of **KIZOFRIN** may be necessary.

Co-administration of **KIZOFRIN** with another microsomal enzyme inducer, phenytoin, may also cause increases in clearance of **[PRODUCT NAME]** . Increased doses of **KIZOFRIN** may be required to maintain control of psychotic symptoms in patients co-administered **KIZOFRIN** and phenytoin and other hepatic enzyme inducers (e.g. rifampicin, barbiturates, etc.) The dose of **KIZOFRIN** may need to be reduced if phenytoin, carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of **[PRODUCT NAME]** .

The pharmacokinetics of **KIZOFRIN** is not altered following co-administration with cimetidine a known P450 enzyme inhibitor. The pharmacokinetics of **KIZOFRIN** are not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

CYP3A4 is the main isoenzyme responsible for cytochrome P450 mediated metabolism of quetiapine and caution is advised when **KIZOFRIN** are used with potent inhibitors of CYP3A4 such as macrolide antibiotics (e.g. erythromycin) and azole antifungals (e.g. fluconazole, itraconazole, and ketoconazole); lower doses of **KIZOFRIN** should be used when given with such inhibitors.

KIZOFRIN should be used with caution in patients also receiving antihypertensives or medicines that prolong the QT interval. **KIZOFRIN** may antagonise the actions of dopaminergics such as levodopa.

PREGNANCY AND LACTATION

KIZOFRIN are contra-indicated during pregnancy and lactation, since safety has not been established.

DOSAGE AND DIRECTIONS FOR USE

KIZOFRIN should be administered twice daily, with or without food.

Adults:

For the treatment of schizophrenia the total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the effective dose range of 300 - 450 mg/day. However this may be adjusted, depending on the clinical response and tolerability of the individual patient, within the range 150 - 750 mg/day.

For the treatment of manic episodes associated with bipolar disorder, the total daily dose for the first 4 days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.

The dose may be adjusted depending on the clinical response and tolerability of the individual patient, within the range of 200 - 800 mg/day. The usual effective dose is in the range of 400 - 800 mg/day.

It should be noted that the recommended maximum daily dose of **KIZOFRIN** is 750 mg/day, for the treatment of schizophrenia, and 800 mg/day for the treatment of manic episodes associated with bipolar disorder.

Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit-risk assessment for an individual patient.

Elderly:

KIZOFRIN should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on **KIZOFRIN** 25 mg/day. The dose should be increased daily, in increments of 25-50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Renal and hepatic impairment:

In patients with mild to moderate renal or hepatic impairment, the oral clearance of **KIZOFRIN** is reduced by approximately 25 %. **KIZOFRIN** are extensively metabolised by the liver. Therefore, caution should be exercised when administered to patients with known hepatic impairment.

Patients with renal or hepatic impairment should be started on **KIZOFRIN** 25 mg/day. The dose should be increased daily in increments of 25 - 50 mg, to an effective dose.

SIDE-EFFECTS

The following side-effects have been reported.

Blood and lymphatic system disorders:

Frequent:

Leucopenia

Less frequent:

Eosinophilia, neutropenia

Immune system disorders:

Less frequent

Hypersensitivity (angioedema, anaphylaxis, urticaria/rash)

Endocrine disorders:

Less frequent:

Treatment with quetiapine is associated with dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first 2 to 4 weeks of **KIZOFRIN**

treatment.

Frequency not known:

Rises in prolactin concentrations

Metabolism and nutrition disorders:

Less frequent:

Anorexia

Nervous system disorders:

Frequent:

Dizziness, somnolence, syncope

Less frequent

Seizure, dysarthria, hypertonia, extrapyramidal symptoms (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity and tremor) occur and are not dose related.

Frequency not known:

Anxiety

Eye disorders:

Less frequent:

Asymptomatic changes in the lens of the eye may occur in patients during long-term treatment with **[PRODUCT NAME]** .

Abnormal vision

Frequency not known:

Dry eyes

Ear and labyrinth disorders:

Frequency not known:

Ear pain

Cardiac disorders:

Frequent:

Tachycardia

Less frequent:

Palpitation, prolongation of the QTc interval

Vascular disorders:

Less frequent:

Hypotension, orthostatic hypotension

Frequency not known:

Hypertension

Respiratory, thoracic and mediastinal disorders:

Less frequent:

Dyspnoea, pharyngitis, rhinitis

Gastrointestinal disorders:

Less frequent:

Abdominal pain

Frequency not known:

Diarrhoea, dry mouth; constipation; dyspepsia

Skin and subcutaneous tissue disorders:

Less frequent:

Increased sweating

Musculoskeletal, connective tissue and bone disorders:

Frequency not known:

Myalgia

Renal and urinary disorders:

Frequency not known:

Urinary tract infection

Reproductive system and breast disorders:

Less frequent:

Menstrual changes, galactorrhoea

Rare:

Priapism

General disorders and administrative site conditions:

Frequent:

Asthenia, peripheral oedema

Less frequent:

Headache, flu-like symptoms, fever

Frequency not known:

Back pain, chest pain

Rare:

Neuroleptic malignant syndrome

Investigations:

Frequent:

Weight gain; Elevations in serum transaminases (ALT, AST)

Less frequent:

Elevations in gamma-GT levels; Elevations in non-fasting serum triglyceride

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There have been less frequent reports of overdose of quetiapine alone resulting in death or coma.

In general, reported signs and symptoms were those resulting from an exaggeration of the medicine's known pharmacological effects, i.e. drowsiness, sedation, tachycardia and hypotension.

There is no specific antidote to **[PRODUCT NAME]** . Treatment is symptomatic and supportive.

IDENTIFICATION

KIZOFRIN 25 mg:

Peach, round, biconvex, film-coated tablets debossed with 'E 52' on one side and plain on the other side.

KIZOFRIN 100 mg:

Yellow, round, biconvex, film-coated tablets imprinted with 'E 53' on one side and plain on the other side.

KIZOFRIN 200 mg:

White, round, biconvex, film-coated tablets imprinted with 'E 55' on one side and plain on the other side.

KIZOFRIN 300 mg:

White, capsule shaped, biconvex, film-coated tablets imprinted with 'E 56' on one side and plain on the other side.

PRESENTATION

KIZOFRIN 25 mg:

Blister Pack:

Tablets are packed in white opaque 250 micron PVC film and printed 25 micron aluminium foil with 7 gsm heat seal lacquer. Each blister contains 10 tablets.

Pack sizes: 30's – Each carton contains 3 blisters of 10 tablets each.

90's – Each carton contains 9 blisters of 10 tablets each.

HDPE Container Pack:

Tablets are packed in 40 ml white opaque HDPE container of 33 mm neck finish with 33 mm-400 RS white opaque closure, with TEKNIPLEX HS-123 induction sealing wad.

Pack sizes: 30's - One HDPE container contains 30 tablets.

90's - One HDPE container contains 90 tablets.

KIZOFRIN 100 mg:

Blister Pack:

Tablets are packed in white opaque 250 micron PVC film and printed 25 micron aluminium foil with 7 gsm heat seal lacquer. Each blister contains 10 tablets.

Pack size: 90's – Each carton contains 9 blisters of 10 tablets each.

HDPE Container Pack:

Tablets are packed in 40 ml white opaque HDPE container of 33 mm neck finish with 33 mm-400 RS white opaque closure, with TEKNIPLEX HS-123 induction sealing wad.

Pack size: 90's - One HDPE container contains 90 tablets.

KIZOFRIN 200 mg:

Blister Pack:

Tablets are packed in white opaque 250 micron PVC film and printed 25 micron aluminium foil with 7 gsm heat seal lacquer. Each blister contains 10 tablets.

Pack size: 30's – Each carton contains 3 blisters of 10 tablets each.

HDPE Container Pack:

Tablets are packed in 40 ml white opaque HDPE container of 33 mm neck finish with 33 mm-400 RS white

opaque closure, with TEKNIPLEX HS-123 induction sealing wad.

Pack size: 30's - One HDPE container contains 30 tablets.

KIZOFRIN 300 mg:

Blister Pack:

Tablets are packed in white opaque 250 micron PVC film and printed 25 micron aluminium foil with 7 gsm heat seal lacquer. Each blister contains 10 tablets.

Pack size: 30's – Each carton contains 3 blisters of 10 tablets each.

HDPE Container Pack:

Tablets are packed in 40 ml white opaque HDPE container of 33 mm neck finish with 33 mm-400 RS white opaque closure with TEKNIPLEX HS-123 induction sealing wad.

Pack size: 30's - One HDPE container contains 30 tablets.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Do not remove the blisters from the carton until required. Keep the containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

TBA

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

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