Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ziprasidone Pfizer 40mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ziprasidone hydrochloride monohydrate equivalent to 40 mg of ziprasidone

Excipient(s):
Each 40 mg capsule contains 87.83 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (Capsule)
No 4, blue capsules, marked “Pfizer” and ZDX 40

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ziprasidone is indicated for the treatment of schizophrenia in adults.

Ziprasidone is indicated for the treatment of manic or mixed episodes of moderate severity in bipolar disorder in adults and children and adolescents aged 10-17 years (prevention of episodes of bipolar disorder has not been established - see section 5.1).

4.2 Posology and method of administration

Adults
The recommended dose, in acute treatment of schizophrenia and bipolar mania, is 40 mg twice daily taken with food. Daily dosage may subsequently be adjusted on the basis of individual clinical status up to a maximum of 80 mg twice daily. If indicated, the maximum recommended dose may be reached as early as day 3 of treatment.

It is of particular importance not to exceed the maximum dose as the safety profile above 160 mg/day has not been confirmed and ziprasidone is associated with dose-related prolongation of the QT interval (see sections 4.3 and 4.4).

In maintenance treatment of schizophrenia patients, ziprasidone should be administered at the lowest effective dose; in many cases, a dose of 20 mg twice daily may be sufficient.

Elderly
A lower starting dose is not routinely indicated but should be considered for those 65 and over when clinical factors warrant.

Use in renal impairment
No dose adjustment is required in patients with impaired renal function (see section 5.2).

Use in hepatic impairment
In patients with hepatic insufficiency, lower doses should be considered. (See sections 4.4 and 5.2).

Children and Adolescents

Bipolar Mania:

The recommended dose, in acute treatment of bipolar mania, in paediatric patients (age 10 to 17 years) is a single dose of 20 mg on day 1, with food. Ziprasidone should subsequently be administered with food in two daily divided doses, and should be titrated over 1-2 weeks to a target range of 120-160 mg/day for patients weighing ≥45 kg, or to a target range of 60-80 mg/day for patients weighing <45 kg. Subsequent dosing should be adjusted on the basis of individual clinical status within the range of 80-160 mg/day for patients weighing ≥45 kg, or 40-80 mg/day for patients weighing <45 kg. Asymmetric dosing, with morning doses 20 mg or 40 mg less than evening doses, was permitted in the clinical trial. (See Sections 4.4 ,5.1 and 5.2).

It is of particular importance not to exceed the weight-based maximum dose as the safety profile above the maximum dose (160 mg/day for children ≥45 kg and 80 mg/day for children <45 kg) has not been confirmed and ziprasidone is associated with dose-related prolongation of the QT interval (see sections 4.3 and 4.4).

Schizophrenia:

The safety and efficacy of ziprasidone in paediatric patients with schizophrenia have not been established (see sections 4.4).

4.3 Contraindications

Known hypersensitivity to ziprasidone or any of the excipients. Known QT-interval prolongation. Congenital long QT syndrome. Recent acute myocardial infarction. Uncompensated heart failure. Arrhythmias treated with class IA and III antiarrhythmic medicinal products.

Concomitant treatment with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, dolasetron mesilate, mefloquine, sertindole or cisapride.

(See sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

A medical history, including assessment of family history, and physical examination should be undertaken to identify patients for whom ziprasidone treatment is not recommended (see section 4.3).

QT interval
Ziprasidone causes a mild to moderate dose-related prolongation of the QT-interval (see section 4.8 and 5.1).

Ziprasidone should not be given together with medicinal products that are known to prolong the QT-interval (see sections 4.3 and 4.5). Caution is advised in patients with significant bradycardia. Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with ziprasidone is started. If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If cardiac symptoms, such as palpitations, vertigo, syncope or seizures occur, then the possibility of a malignant cardiac arrhythmia should be considered and a cardiac evaluation including an ECG should be performed. If the QTc interval is > 500 msec, then it is recommended that the treatment should be stopped (see section 4.3).

There have been rare post-marketing reports of torsade de pointes in patients with multiple confounding risk factors taking ziprasidone.

Children and Adolescents
Safety and efficacy of ziprasidone in the treatment of schizophrenia in children and adolescents has not been evaluated.

Neuroleptic malignant syndrome (NMS)
NMS is a rare but potentially fatal complex that has been reported in association with antipsychotic medicinal products, including ziprasidone. The management of NMS should include immediate discontinuation of all antipsychotic medicinal products.

Tardive dyskinesia
There is a potential for ziprasidone to cause tardive dyskinesia and other tardive extrapyramidal syndromes after long-term treatment. Patients with bipolar disorder are known to be particularly vulnerable to this category of symptoms. This is more frequent with increased duration of treatment and increasing age. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of ziprasidone should be considered.

Seizures
Caution is recommended when treating patients with a history of seizures.

Hepatic Impairment
There is a lack of experience in patients with severe hepatic insufficiency and ziprasidone should be used with caution in this group (see sections 4.2 and 5.2).

Medicinal products containing lactose
As the capsule contains the excipient lactose (see section 6.1), patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Increased risk of cerebrovascular accidents in the dementia population
An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Ziprasidon Pfizer should be used with caution in patients with risk factors for stroke.

Increased Mortality in Elderly people with Dementia
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Ziprasidon Pfizer is not licensed for the treatment of dementia-related behavioural disturbances.

Venous Thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ziprasidone and preventive measures undertaken.

Priapism
Cases of priapism have been reported with antipsychotic use, including ziprasidone. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hyperprolactinemia
As with other drugs that antagonize dopamine D2 receptors, ziprasidone may elevate prolactin levels. Disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic and pharmacodynamic studies between ziprasidone and other medicinal products that prolong the QT interval have not been performed. An additive effect of ziprasidone and these medicinal products cannot be excluded, therefore ziprasidone should not be given with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, dolasetron mesilate, mefloquine, sertindole or cisapride. (See section 4.3)

No studies on the interaction of ziprasidone with other medicinal products have been performed in children

CNS medicinal products/alcohol
Given the primary effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting medicinal products and alcohol.

Effect of ziprasidone on other medicinal products
An *in vivo* study with dextromethorphan showed no marked inhibition of CYP2D6 at plasma concentrations 50% lower than those obtained after 40 mg ziprasidone twice daily. *In vitro* data indicated that ziprasidone may be a modest inhibitor of CYP2D6 and CYP3A4. However, it is unlikely that ziprasidone will affect the pharmacokinetics of medicinal products metabolised by these cytochrome P450 isoforms to a clinically relevant extent.

Oral contraceptives – Ziprasidone administration resulted in no significant change to the pharmacokinetics of oestrogen (ethinyl oestradiol, a CYP3A4 substrate) or progesterone components.

Lithium - Co-administration of ziprasidone had no effect on the pharmacokinetics of lithium.

As ziprasidone and lithium are associated with cardiac conduction changes, the combination may pose a risk for pharmacodynamic interactions including arrhythmias, however, in controlled clinical trials, the combination of ziprasidone plus lithium has not demonstrated an increased clinical risk, compared to lithium alone.

There are limited data on co-medication with the mood stabilisers carbamazepine.
A pharmacokinetic interaction of ziprasidone with valproate is unlikely due to the lack of common metabolic pathways for the two drugs. In a study in patients, the co-administration of ziprasidone and valproate showed that the mean concentrations of valproate were within the therapeutic range as compared to valproate administered with placebo.

Effects of other medicinal products on ziprasidone
The CYP3A4 inhibitor ketoconazole (400 mg/day) increased the serum concentrations of ziprasidone by <40%. The serum concentrations of S-methyl-dihydroziprasidone and ziprasidone sulphoxide, at the expected Tmax of ziprasidone, were increased by 55% and 8% respectively. No additional QTc prolongation was observed. Changes in pharmacokinetics due to coadministration of potent CYP3A4 inhibitors are unlikely to be of clinical importance, therefore no dosage adjustment is required. *In vitro* data indicates that ziprasidone is a P-glycoprotein (p-gp) substrate. The *in vivo* relevance is unknown, however co-administration with known p-gp inhibitors such as verapamil, macrolide antibiotics, quinidine, itraconazole and ritonavir could cause increased plasma concentrations of ziprasidone. Co-administration with p-gp inducers such as rifampin and St John´s Wort could cause decreased concentrations of ziprasidone. This should be taken into account if co-administration is considered.

Carbamazepine therapy, 200 mg b.i.d for 21 days, resulted in a decrease of approximately 35% in the exposure to ziprasidone.

Antacid - multiple doses of aluminium and magnesium containing antacid or cimetidine have no clinically significant effect on the pharmacokinetics of ziprasidone under fed conditions.

Serotonergic medicinal products
In isolated cases, there have been reports of serotonin syndrome temporally associated with the therapeutic use of ziprasidone in combination with other serotonergic medicinal products such as SSRIs (see section 4.8). The features of serotonin syndrome can include confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.

Protein binding
Ziprasidone extensively binds to plasma proteins. The in vitro plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is unlikely.

4.6 Fertility, pregnancy and lactation

Reproductive toxicity studies have shown undesirable effects on the reproductive process, including fertility, at doses associated with maternal toxicity and/or sedation (see section 5.3). There was no evidence of teratogenicity (see section 5.3).

Pregnancy
No studies have been conducted in pregnant women. Women of child bearing potential receiving ziprasidone should therefore be advised to use an appropriate method of contraception. As human experience is limited, administration of ziprasidone is not recommended during pregnancy unless the expected benefit to the mother outweighs the potential risk to the foetus.

Antipsychotic class labeling: Neonates exposed to antipsychotics (including ziprasidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Ziprasidone should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Breastfeeding
It is not known whether ziprasidone is excreted in breast milk. Patients should not breast feed an infant if they are taking ziprasidone. If treatment is necessary, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

Ziprasidone may cause somnolence and may influence the ability to drive and use machines. Patients likely to drive or operate machines should be cautioned appropriately.

4.8 Undesirable effects

Oral ziprasidone has been administered in clinical trials (see section 5.1) to approximately 6500 adult subjects. The most common adverse reactions in schizophrenia clinical trials were sedation and akathisia. In bipolar mania clinical trials, the most common adverse reactions were sedation, akathisia, extrapyramidal disorder and dizziness.

The table below contains adverse events based on combined short term (4-6 week), fixed dose, schizophrenia studies and short term (3 week), flexible dose, bipolar mania studies with a probable or possible relationship to treatment with ziprasidone and which occur at an incidence greater than placebo. Additional reactions reported from the post-marketing experience are included as Frequency ‘Not known’ in italics in the list below.

All adverse reactions are listed by class and frequency: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1000 to < 1/100), *rare* (≥1/10000 to <1/1000); *very rare* (< 1/10000), *not known (cannot be estimated from the available data*).

The adverse reactions listed below may also be associated with the underlying disease and/or concomitant medications.

System Organ Class Frequency	Adverse drug reactions
Infections and Infestations	
Rare	Rhinitis
Metabolism and nutrition disorders	
Uncommon	Increased appetite
Rare	Hypocalcaemia
Psychiatric disorders	
Common	Restlessness
Uncommon	Agitation, anxiety, throat tightness, nightmare,
Rare	Panic attack, depressive symptom, bradyphrenia, flat affect, anorgasmia
Not known	Insomnia; mania/hypomania
Nervous system disorders	
Common	Dystonia, akathisia, extrapyramidal disorder, parkinsonism, (including cogwheel rigidity, bradykinesia, hypokinesia) tremor, dizziness, sedation, somnolence, headache
Uncommon	Generalised tonic clonic seizures, tardive dyskinesia, dyskinesia, drooling, ataxia, dysarthria, oculogyric crisis, disturbance in attention, hypersomnia, hypoaesthesia, paraesthesia, lethargy
Rare	Torticollis, paresis, akinesia, hypertonia, restless legs syndrome
Not known	Neuroleptic malignant syndrome; serotonin syndrome (see section 4.5); facial droop
Blood and lymphatic system disorders	
Rare	Lymphopenia, eosinophil count increased
Cardiac disorders	
Uncommon	Palpitations, tachycardia
Rare	Electrocardiogram QT corrected interval prolonged
Not known	Torsade de pointes (see section 4.4*)*
Eye disorders	
Common	Vision blurred
Uncommon	Photophobia.
Rare	Amblyopia, visual disturbance, eye pruritis, dry eyes
Ear and labyrinth disorders	
Uncommon	Vertigo, tinnitus
Rare	Ear pain
Vascular disorders	
Uncommon	Hypertensive crisis, hypertension, orthostatic hypotension, hypotension
Rare	Systolic hypertension, diastolic hypertension, labile blood pressure
Not known	Syncope, venous thromboembolism
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, sore throat
Rare	Hiccups
Gastrointestinal disorders	
Common	Nausea, vomiting, constipation, dyspepsia, dry mouth, salivary hypersecretion
Uncommon	Diarrhoea, dysphagia, gastritis, gastrointestinal discomfort, swollen tongue, tongue thick, flatulence
Rare	Gastro-oesophageal reflux, loose stools
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria, rash, rash maculo-papular, acne
Rare	Psoriasis, dermatitis allergic, alopecia, swelling face, erythema, rash

	papular, skin irritation
Not known	Hypersensitivity, angioedema
Musculoskeletal and connective tissue disorders	
Common	Musculoskeletal rigidity
Uncommon	Musculoskeletal discomfort, muscle cramp, pain in extremity, joint stiffness
Rare	Trismus
Renal and urinary disorders	
Rare	Urinary incontinence, dysuria
Not known	Enuresis
Reproductive system and breast disorders	
Rare	Erectile dysfunction, erection increased, galactorrhoea, gynaecomastia
Not known	Priapism
Immune system disorders	
Not known	Anaphylactic reaction
Hepatobiliary disorders	
Uncommon	Hepatic enzyme increased
Rare	Liver function test abnormal
General disorders and administration site conditions	
Common	Asthenia, fatigue
Uncommon	Chest discomfort, gait abnormal, pain, thirst
Rare	Pyrexia, feeling hot
Investigations	
Rare	Blood lactate dehydrogenase increased
Pregnancy, puerperium and perinatal conditions	
Not known	Drug withdrawal syndrome neonatal (see section 4.6)

In short-term and long-term ziprasidone schizophrenia and bipolar mania clinical trials, the incidence of tonic clonic seizures and hypotension was uncommon, occurring in less than 1% of ziprasidone treated patients.

Ziprasidone causes a mild to moderate dose-related prolongation of the QT interval (see section 5.1). In schizophrenia clinical trials, an increase of 30 to 60 msec was seen in 12.3% (976/7941) of ECG tracings from ziprasidone-treated and 7.5% (73/975) of ECG tracings from placebo-treated patients. A prolongation of >60 msec was seen in 1.6% (128/7941) and 1.2% (12/975) of tracings from ziprasidone and placebo-treated patients, respectively. The incidence of QTc interval prolongation above 500 msec was 3 in a total of 3266 (0.1%) in ziprasidone treated patients and 1 in a total of 538 (0.2%) in placebo treated patients. Comparable findings were observed in bipolar mania clinical trials.

In long term maintenance treatment in schizophrenia clinical trials, prolactin levels in patients treated with ziprasidone were sometimes elevated, but, in most patients, returned to normal ranges without cessation of treatment. In addition, potential clinical manifestations (e.g. gynaecomastia and breast enlargement) were rare.

Paediatric and Adolescent population with Bipolar mania and Adolescents with Schizophrenia

In a placebo-controlled bipolar disorder trial (ages 10-17 years), the most frequent adverse reactions (reported with a frequency >10%) were sedation, somnolence, headache, fatigue, nausea, and dizziness. In a placebo-controlled schizophrenia trial (ages 13-17 years), the most frequent adverse reactions (reported with a frequency >10%) were somnolence and extrapyramidal disorder. The frequency, type and severity of adverse reactions in these subjects were generally similar to those in adults with bipolar disorder or schizophrenia who are treated with ziprasidone.

Ziprasidone was associated with a similar mild to moderate dose-related prolongation of the QT interval in the paediatric bipolar and schizophrenia clinical trials to those seen in the adult population. Tonic clonic seizures and hypotension were not reported in the placebo-controlled paediatric bipolar clinical trials.

4.9 Overdose

Experience with ziprasidone in overdose is limited. The largest confirmed single ingestion of ziprasidone is 12,800 mg. In this case, extrapyramidal symptoms and a QTc interval of 446 msec (with no cardiac sequelae) were reported. In general, the most commonly reported symptoms following overdose are, extrapyramidal symptoms, somnolence, tremor and anxiety.

The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. There is no specific antidote to ziprasidone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group*:* Antipsychotic, indole derivatives, ATC code N05A E04.

Ziprasidone has a high affinity for dopamine type 2 (D_2) receptors and substantially higher affinity for serotonin type 2_A ($5HT_{2A}$) receptors. Receptor blockade, 12 hours after a single dose of 40 mg, was greater than 80% for serotonin type 2_A and greater than 50% for D_2 using positron emission tomography (PET). Ziprasidone also interacts with serotonin $5HT_{2C}$, $5HT_{1D}$ and $5HT_{1A}$ receptors where its affinities for these sites are equal to or greater than its affinity for the D_2 receptor. Ziprasidone has moderate affinity for neuronal serotonin and norepinephrine transporters. Ziprasidone demonstrates moderate affinity for histamine H(1)- and alpha(1)-receptors. Ziprasidone demonstrates negligible affinity for muscarinic M(1)-receptors.

Ziprasidone has been shown to be an antagonist at both serotonin type 2_A ($5HT_{2A}$) and dopamine type 2 (D_2) receptors. It is proposed that the therapeutic activity is mediated, in part, through this combination of antagonist activities. Ziprasidone is also a potent antagonist at $5HT_{2C}$ and $5HT_{1D}$ receptors, a potent agonist at the $5HT_{1A}$ receptor and inhibits neuronal reuptake of norepinephrine and serotonin.

Further information on clinical trials

Schizophrenia
In a 52 week study, ziprasidone was effective in maintaining the clinical improvement during continuation therapy in patients who showed an initial treatment response: there was no clear evidence for a dose-response relationship amongst the ziprasidone groups. In this study, which included patients with both positive and negative symptoms, ziprasidone's efficacy was demonstrated in both positive and negative symptoms.

The incidence of body weight gain, reported as an adverse event in short term (4-6 week) schizophrenia studies was low and identical in ziprasidone-treated and placebo-treated patients (both 0.4%). In a one-year placebo-controlled study a median weight loss of 1-3 kg was observed in ziprasidone-treated patients compared to a 3 kg median loss in placebo-treated patients.

In a double-blind comparative schizophrenia study, metabolic parameters including weight and fasting levels of insulin, total cholesterol and triglycerides and an insulin resistance (IR) index were measured. In patients receiving ziprasidone no significant changes from baseline were observed in any of these metabolic parameters.

Results of a large post-marketing safety study:
A randomised post-approval study of 18,239 schizophrenic patients with observational follow-up for 1 year was conducted to determine whether ziprasidone´s effect on the QTc interval is associated with an increased risk of non-suicide mortality. This study, which was conducted in naturalistic clinical practice settings, showed no difference in the rate of over-all non-suicide mortality between ziprasidone and olanzapine treatments (primary end-point). The study also showed no difference in secondary end-points of all-cause mortality, mortality due to suicide, mortality due to sudden death, however, a non-significant numerically higher incidence of cardiovascular mortality was observed in the ziprasidone group. A statistically significantly higher incidence of all-cause hospitalisation, mainly due to differences in the number of psychiatric hospitalisations, was also observed in the ziprasidone group.

Bipolar mania
The efficacy of ziprasidone in adults with mania was established in two placebo controlled, double blind, 3 week studies which compared ziprasidone with placebo and one double blind, 12 week study which compared ziprasidone to haloperidol and placebo. These studies included approximately 850 patients meeting DSM-IV criteria for bipolar I disorder with an acute manic or mixed episode, with or without psychotic features. The baseline presence of psychotic features in the studies was 49.7%, 34.7% or 34.9%. Efficacy was assessed using the Mania Rating Scale (MRS). The Clinical Global Impression-Severity (CGI-S) scale was either a co-primary or key secondary efficacy variable in these studies. Ziprasidone treatment (40-80 mg BID, mean daily dose 120 mg) resulted in statistically significantly greater improvement in both MRS and CGI-S scores at Last Visit (3 weeks) compared with placebo. In the 12 week study, haloperidol treatment (mean daily dose 16 mg) produced significantly greater reductions in MRS scores compared with ziprasidone (mean daily dose 121 mg). Ziprasidone demonstrated comparable efficacy to haloperidol in terms of the proportion of patients maintaining a response to treatment from week 3 to week 12.

The efficacy of ziprasidone in the treatment of Bipolar I Disorder in paediatric patients (10 to 17 years of age) was evaluated in one four-week placebo-controlled trial (n=237) of inpatients or outpatients who met DSM-IV criteria for Bipolar I Disorder manic or mixed episodes with or without psychotic features and had a Y-MRS score ≥17 at baseline. This double-blind, placebo-controlled trial compared flexibly-dosed oral ziprasidone (80-160 mg/day (40-80 mg BID) in two divided doses for patients weighing ≥45 kg; 40-80 mg/day (20-40 mg BID) for patients weighing <45 kg) to placebo. Ziprasidone was administered as a single dose of 20 mg on the first day, then titrated over 1-2 weeks, in two daily doses, to a target range of 120-160 mg/day for patients weighing ≥45 kg, or 60-80 mg/day for patients weighing <45 kg. Asymmetric dosing, with morning doses 20 mg or 40 mg less than evening doses, was permitted. Ziprasidone was superior to placebo in change from baseline to week 4 on the Y-MRS total score.

In this clinical trial, the mean daily doses administered were 119 mg and 69 mg in the patients weighing ≥45 kg and <45 kg, respectively.

Ziprasidone has been evaluated for safety in 267 paediatric patients (age 10 to 17 years) who participated in multiple-dose, clinical trials in bipolar mania; a total of 82 paediatric patients with Bipolar I Disorder were dosed with oral ziprasidone for at least 180 days.

In a 4-week trial in paediatric patients (10-17 years) with bipolar mania, there were no differences between ziprasidone and placebo patients in the mean change from baseline in body weight fasting glucose, total cholesterol, LDL cholesterol, or triglyceride levels.

There are no long-term double-blind clinical studies investigating the efficacy and tolerability of ziprasidone in children and adolescents.

There are no long-term clinical studies investigating the efficacy of ziprasidone in the prevention of recurrence of manic/depressive symptoms.

5.2 Pharmacokinetic properties

Absorption: Following oral administration of multiple doses of ziprasidone with food, peak serum concentrations typically occur 6 to 8 hours post-dose. . The absolute bioavailability of a 20 mg dose is 60% in the fed state. Pharmacokinetic studies have demonstrated that the bioavailability of ziprasidone is increased by up to 100% in the presence of food. It is therefore recommended that ziprasidone should be taken with food.

Distribution: The volume of distribution is approximately 1.1 L/kg. Ziprasidone is more than 99% protein bound in serum.

Biotransformation and elimination: The mean terminal half-life of ziprasidone after oral administration is 6.6 hours. Steady state is reached within 1-3 days. Mean clearance of ziprasidone administered intravenously is 5 ml/min/kg. Approximately 20% of the dose is excreted in urine, and approximately 66% is eliminated in faeces.

Ziprasidone demonstrates linear kinetics over the therapeutic dose range of 40 to 80 mg twice daily in fed subjects.

Ziprasidone is extensively metabolised after oral administration with only a small amount excreted in urine (<1%) or faeces (<4%) as unchanged ziprasidone. Ziprasidone is primarily cleared via three proposed metabolic routes to yield four major circulating metabolites, benzisothiazole piperazine (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide and S-methyl-dihydroziprasidone. Unchanged ziprasidone represents about 44% of total drug-related material in serum.

Ziprasidone is primarily metabolised by two pathways: reduction and methylation to generate S-methyldihydroziprasidone which accounts for approximately two-thirds of the metabolism, and oxidative metabolism accounting for the other third. *In vitro* studies using human liver subcellular fractions indicate that S-methyldihydroziprasidone is generated in two steps. These studies indicate that the first step is mediated primarily by chemical reduction by glutathione as well as by enzymatic reduction by aldehyde oxidase. The second step is methylation mediated by thiol methyltransferase *I In vitro* studies indicate that CYP3A4 is the major cytochrome P450 catalysing the oxidative metabolism of ziprasidone with a potential minor contribution of CYP1A2.

Ziprasidone, S-methyl-dihydroziprasidone, and ziprasidone sulphoxide, when tested *in vitro*, share properties which may predict a QTc-prolonging effect. S-methyl-dihydroziprasidone is mainly eliminated in faeces by biliary excretion with a minor contribution by CYP3A4 catalysed metabolism. Ziprasidone sulphoxide is eliminated through renal excretion and by secondary metabolism catalysed by CYP3A4.

Special populations
Pharmacokinetic screening of patients has not revealed any significant pharmacokinetic differences between smokers and non-smokers.

No clinically significant age- or gender-differences in the pharmacokinetics of ziprasidone has been observed. The pharmacokinetics of ziprasidone in paediatric patients 10 to17 years of age were similar to those in adults after correcting for the differences in body weights.

Consistent with the fact that renal clearance contributes very little to its overall clearance, no progressive increases in ziprasidone exposure were noted when ziprasidone was administered to subjects with varying degrees of renal function. Exposures in subjects with mild (creatinine clearance 30-60 ml/min), moderate (creatinine clearance 10-29 ml/min) and severe impairment (requiring dialysis) were 146%, 87% and 75% those of healthy subjects (creatinine clearance >70 ml/min) following oral administration of 20 mg BID for seven days. It is unknown whether serum concentrations of the metabolites are increased in these patients.

In mild to moderate impairment of liver function (Child Pugh A or B) caused by cirrhoses, the serum concentrations after oral administration were 30% higher and the terminal half-life was about 2 hours longer than in normal patients. The effect of liver impairment on the serum concentrations of the metabolites is unknown.

5.3 Preclinical safety data

Preclinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. In reproductive studies in rats and rabbits, ziprasidone has shown no evidence of teratogenicity. Undesirable effects on fertility and decreased pup weights were observed at doses causing maternal toxicity such as decreased body weight gain. Increased perinatal mortality and delayed functional development of offspring occurred at maternal plasma concentrations extrapolated to be similar to the maximal concentrations in humans given therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contents:
Lactose monohydrate
Pregelatinised maize starch
Magnesium stearate.

Capsule shell:
Gelatin
Titanium dioxide (E171)
Sodium laurilsulfate (sodium dodecylsulfate)
Indigotin (E132)

Printing ink:
Shellac
Ethyl alcohol anhydrous
Isopropyl alcohol
n-butyl alcohol
Propylene glycol
Purified water
Ammonium hydroxide
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Blister
Ziprasidon Pfizer capsules are presented in aluminium PVC/PA blisters with aluminium foil lids, in cartons containing 14, 20, 28, 30, 50, 56, 60, 98 or 100 capsules.

Bottles
Ziprasidon Pfizer capsules are presented in HDPE bottles containing 100 capsules and desiccant, with two-piece polypropylene screw-cap child-resistant closures. A heat induction seal may be used as a closure, in which case no desiccant is included.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road,
Sandwich,
Kent CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA19/94/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 5th November 2012

10 DATE OF REVISION OF THE TEXT

March 2014