Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

GEODON 20 mg/ml powder and solvent for solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains ziprasidone mesilate to deliver 20 mg of ziprasidone. After reconstitution, 1ml of solution for injection contains 20 mg ziprasidone.

Excipient(s) with known effects:
Contains less than 1 mmol of sodium (20 mg) per dose, and therefore is essentially sodium free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and Solvent for solution for injection.

White to off-white powder.
Clear colourless solvent.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ziprasidone powder and solvent for solution for injection is indicated for the rapid control of agitation in patients with schizophrenia, when oral therapy is not appropriate, for a maximum of 3 consecutive days.

Treatment with ziprasidone powder and solvent for solution for injection should be discontinued, and the use of oral ziprasidone should be initiated, as soon as clinically appropriate.

4.2 Posology and method of administration

Posology

For intramuscular use only.

Intravenous administration must be avoided.

Treatment with the intramuscular formulation should only be used in patients, where treatment with an oral formulation is considered to be inappropriate.

Adults
The recommended dose is 10 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours. Some patients may require an initial dose of 20mg, which can be followed by a further dose of 10 mg after 4 hours. Thereafter, doses of 10 mg may be given every 2 hours up to the maximum daily dose of 40 mg. Intramuscular administration of ziprasidone for more than 3 consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules, up to 80 mg twice daily, should replace the intramuscular administration as soon as possible.

Elderly
The clinical experience with intramuscular treatment in elderly patients (> 65 years) is limited. Treatment with

intramuscular injection is not recommended to these patients (see section 4.4).

Patients with renal impairment
Ziprasidone intramuscular injection should be administered with caution in patients with impaired renal function (see section 5.2).

Patients with hepatic impairment
In patients with hepatic insufficiency, lower doses should be considered (see section 4.4 and 5.2).

For instructions for reconstitution, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

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 section 4.4 and section 4.5).

4.4 Special warnings and precautions for use

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 section 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.

Paediatric Population
The safety and efficacy of ziprasidone intramuscular injection has not been evaluated in children and adolescents.

Elderly (> 65 years)
Elderly patients have not been included in clinical trials in sufficient numbers. Thus, no recommendations as regards dosing could be given and intramuscular treatment in these patients is not recommended.

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

Severe Cutaneous Adverse Reactions
Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with ziprasidone exposure. DRESS consists of a combination of three or more of the following:

cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis.

Other severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported with ziprasidone exposure.

Severe cutaneous adverse reactions are sometimes fatal. Discontinue ziprasidone if severe cutaneous reactions occur.

Cardiovascular disease
Patients with cardiovascular disease have not been included in the clinical trials in sufficient numbers. Thus, the safe use of the intramuscular product has not been established (see section 4.3).

Blood pressure
Dizziness, tachycardia and postural hypotension are not unusual in patients following intramuscular administration of ziprasidone. Single cases of hypertension have also been reported. Caution should be exercised, particularly in ambulatory patients.

Tardive dyskinesia
There is a potential for ziprasidone to cause tardive dyskinesia and other tardive extrapyramidal syndromes after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of ziprasidone should be considered.

Seizures
Caution is advised 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 section 4.2 and 5.2).

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. Geodon 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.

Geodon 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.

Post-marketing Reports of Mortality
As with other IM antipsychotics, fatalities with the use of ziprasidone IM, generally in patients with multiple confounding risk factors, have been reported. Although a causal relationship has not been established, ziprasidone IM should be used with caution.

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).

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
All interaction studies have been conducted with oral ziprasidone.

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.

Effects of other medicinal products on ziprasidone
The CYP3A4 inhibitor ketoconazole (400mg/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 co-administration of potent CYP3A4 inhibitors are unlikely to be of clinical importance, therefore no dosage adjustment is required.

Carbamazepine therapy, 200mg 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 with ziprasidone have shown undesirable effects on the reproductive process, at doses associated with maternal toxicity and/or sedation.
There was no evidence of teratogenicity (see section 5.3).

Pregnancy
No studies have been conducted in pregnant women. Women of child bearing potential should therefore be using an

appropriate method of contraception. As human experience is limited, administration of ziprasidone is not recommended during pregnancy unless the expected benefit to mother outweighs the potential risk to the foetus.

Antipsychotic class labelling
Neonates exposed to antipsychotics 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.

Breast-feeding
It is not known whether ziprasidone is excreted in breast milk. Patients should not breast feed if they are receiving 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 on the ability to drive and use machines. Patients likely to drive or operate machines should be cautioned appropriately**.**

4.8 Undesirable effects

Ziprasidone intramuscular
The table below contains adverse events with possible, probable or unknown relationship to ziprasidone in phase 2/3 trials. The most common reactions were nausea, sedation, dizziness, injection site pain, headache and somnolence. 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 (≥1/1,000 to <1/100), rare (≥1/10,000 to< 1/1,000)), very rare (< 1/10,000); 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	**Adverse drug reactions**
Frequency	
Metabolism and nutrition disorders	
Uncommon	Anorexia
Psychiatric disorders	
Uncommon	Agitation, antisocial behaviour, psychotic disorder, insomnia, tic
Not known	Mania/ hypomania
Nervous system disorders	
Common	Akathisia, dizziness, dystonia, headache, sedation, somnolence, ,extrapyramidal disorder*
Uncommon	Cogwheel rigidity, dizziness postural, dysarthria, dyskinesia, dyspraxia, parkinsonism, tremor
Not known	Neuroleptic malignant syndrome; serotonin syndrome (see section 4.5); facial droop
Cardiac disorders	
Uncommon	Bradycardia, tachycardia
Not known	Torsade de pointes (see section 4.4)
Ear and labyrinth disorders	
Uncommon	Vertigo
Vascular disorders	
Common	Hypertension, hypotension

Uncommon	Flushing, orthostatic hypotension,
Not known	Syncope, venous thromboembolism
Respiratory, thoracic and mediastinal disorders	
Uncommon	Laryngospasm
Gastrointestinal disorders	
Common	Nausea, vomiting
Uncommon	Constipation, diarrhoea, loose stools, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon	Hyperhidrosis
Not known	Hypersensitivity, angioedema, drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	
Common	Muscle rigidity
Renal and Urinary disorders	
Rare	Urinary incontinence, dysuria
Not known	Enuresis
Immune system disorders	
Not known	*Anaphylactic reaction*
Hepatobiliary disorders	
Uncommon	Hepatic enzyme increased
General disorders and administration site conditions	
Common	Asthenia, fatigue, Injection site burning, Injection site pain
Uncommon	Drug withdrawal syndrome, influenza like illness, injection site discomfort, injection site irritation
Investigations	
Uncommon	Blood pressure decreased
Pregnancy, puerperium and perinatal conditions	
Not known	Drug withdrawal syndrome neonatal (see section 4.6)

* frequency estimated from three post-marketing open-label controlled clinical trials

The most common cardiovascular adverse events reported from fixed dose clinical trials with intramuscular ziprasidone were: dizziness (10mg - 11%, 20mg – 12%), tachycardia (10mg - 4%, 20mg – 4%) and postural dizziness (10mg – 2%, 20mg – 2%), orthostatic hypotension, 20mg – 5%) and hypotension (10mg – 2%).

In premarketing fixed dose clinical trials with ziprasidone intramuscular injection, increased blood pressure and hypertension were observed in 2.2% of patients receiving 10 mg and increased blood pressure was observed in 2.8% of patients receiving 20 mg.

Ziprasidone capsules
Oral ziprasidone has been administered in clinical trials (see section 5.1) to approximately 6500 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 (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000)); very rare (< 1/10,000); 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, drug reaction with eosinophilia and systemic symptoms (DRESS)
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

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

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 overdosage 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 NO5A 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 oral 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 antipsychotic 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
In clinical trials, the safety and tolerability of intramuscular injection and subsequent continuation with oral therapy was demonstrated.

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.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 30-60 minutes post-dose. Exposure increases in a dose-related manner and following 3 days of intramuscular dosing, little accumulation is observed.

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 on the third day of dosing ranged from 8 to10 hours. The mean terminal half-life of ziprasidone after intravenous administration is 6 hours. 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 is extensively metabolised after oral administration with only a small amount excreted in urine (<1%) or

faeces (<4%) as unchanged drug. 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. *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 presumably 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 treated orally has not revealed any significant pharmacokinetic differences between smokers and non-smokers.

No clinically significant age- or gender-differences in the pharmacokinetics were observed following oral administration.

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 serum concentrations of the metabolites is unknown.

5.3 Preclinical safety data

Preclinical safety data on ziprasidone administered orally 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.

In parenteral studies of ziprasidone there were no adverse findings relevant to the clinical use of the product.

Skeletal variations, but no malformations, were observed in a rabbit teratology study of the excipient SBECD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: Sulphobutyl ether beta-cyclodextrin sodium.

Solvent: Water for Injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or solvents except Water for Injections mentioned in *Section 6.6.*

6.3 Shelf life

3 years.

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours up to 25°C and 7 days at 2 to 8 °C. However from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C.
Keep container in the outer carton.
Do not freeze.

6.5 Nature and contents of container

Type 1 flint glass vials containing powder (ziprasidone mesilate). The vials are sealed with butyl rubber lyophile stoppers and flip-off aluminium seals**.**
Type 1 flint glass ampoules containing solvent (Water for Injections).

Pack size: 1 vial and 1 ampoule per carton

6.6 Special precautions for disposal

The contents of the vial (powder) should be reconstituted by introduction of 1.2 ml of the supplied Water for Injections (solvent), affording a concentration of 20 mg ziprasidone per ml, and shaking until complete dissolution has occurred. Only clear solutions, free of visible particles, should be used. Only one dose (0.5 ml corresponding to 10 mg ziprasidone, or 1 ml corresponding to 20 mg ziprasidone) should be withdrawn from each vial and the remainder discarded.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
UK

8 MARKETING AUTHORISATION NUMBER

PA019/052/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 08 March 2002

Date of last renewal: 01 August 2010

10 DATE OF REVISION OF THE TEXT

January 2016