Chapter 3

Drug Profiles

3.1 Ziprasidone

1) ***Introduction***

Ziprasidone is a new antipsychotic with combined dopamine and serotonin receptor antagonist activity, developed by Pfizer. Indeed its most potent action is action at the 5-HT2A site. Ziprasidone has an *in vitro* 5-HT_{2A}/dopamine D_2 receptor affinity ratio higher than most clinically available antipsychotic agents. Ziprasidone appears to have antipsychotic activity with a low liability for extrapyramidal side effects. Oral and intramuscular forms are available

2) ***Description***

a) *Chemical name*

5-[2-[4-(1, 2-Benzisothiazol-3-yl)-1-piperazinyl] ethyl]-6-chloro-1, 3-dihydro-2*H*-indol-2-one

b) *Formula*

- Empirical

$C_{21}H_{21}ClN_4OS$

- Structural

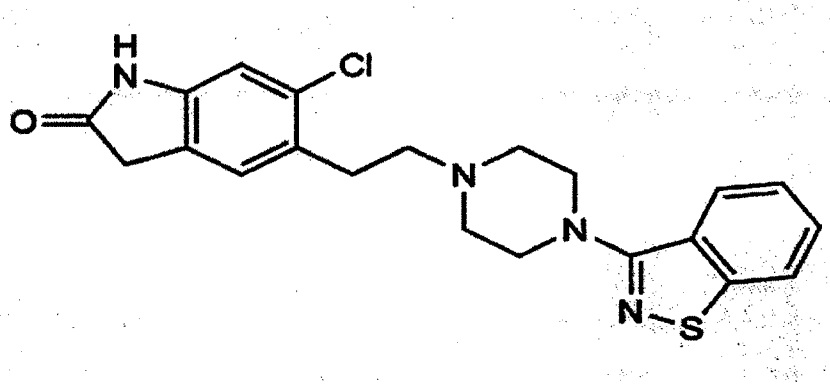

Figure 3.1: Ziprasidone

- Molecular weight

467.4

3) ***Appearance and color***

White to off white powder

4) ***Solubility***

Ziprasidone has a saturation solubility of 0.26μg/mL in phosphate buffer pH 7.4. It is practically insoluble in methanol and isopropyl alcohol. It is slightly soluble in ethyl acetate. It is freely soluble in dichloro methane, chloroform, tetrahydronfuran and acetonitrile. It shows pH dependent solubility by being more soluble at lower pH (acidic).

5) ***Ionization constant***

Ziprasidone has an apparent pKa of 6.5

6) ***Melting point***

226.64°C

7) ***Pharmacology***

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$ and $5HT_{1D}$ and α_1-adrenergic receptors (Ki's of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively) and moderate affinity for the histamine H_1 receptor (Ki = 47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC50 >1 μM). The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone. Ziprasidone's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of α1-

adrenergic receptors may explain the orthostatic hypotension observed with this drug.

8) ***Pharmacokinetics***

a) *Oral*

Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone is dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within one to three days of dosing. The mean apparent systemic clearance is 7.5 mL/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

- Absorption

  Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%

- Distribution

  Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. 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 minimal.

- Metabolism and Elimination

  Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield

four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide and S-methyldihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyl-dihydroziprasidone is generated in two steps. The data indicate that the reduction reaction is mediated by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

b) *Intramuscular*

The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($t_{½}$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

- Metabolism and Elimination

  Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

9) *Indications*

Ziprasidone is indicated for the treatment of schizophrenia. When deciding among the alternative treatments available for this condition, the prescriber should

consider the finding of Ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known.

Ziprasidone intramuscular is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Schizophrenic patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation. The efficacy of intramuscular ziprasidone for acute agitation in schizophrenia was established in single-day controlled trials of schizophrenic inpatients. Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

- Comparison with Parenteral Haloperidol

  A one week randomized, open label, parallel investigation involving 132 subjects was conducted in 19 centers. Ziprasidone and haloperidol were compared. Ziprasidone IM was said to be more effective in calming psychotic agitation than was injected haloperidol. A more trouble free transition to oral medication was cited with ziprasidone.

  In research conducted by the manufacturer, changes in the QTc were assessed with both intramuscular ziprasidone and haloperidol. At 24 hours post IM administration of ziprasidone, there was an average increase in the QTc of 3.4

msec as compared to 6.3 msec with haloperidol. Ziprasidone was reported to induce less movement disorders (e.g, dystonia) than haloperidol.

10) ***Dosage and administration***

a) Oral Therapy

Ziprasidone capsules are administered as an initial daily dose of 20 mg BID with food. In some patients daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg BID. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, ordinarily patients should be observed for improvement for several weeks before upward dosage adjustment. Efficacy in schizophrenia was demonstrated in a dose range of 20 to 100 mg BID in short-term, placebo controlled clinical trials. There were trends toward dose response within the range of 20 to 80 mg BID, but results were not consistent. An increase to a dose greater than 80 mg BID is not generally recommended. The safety of doses above 100 mg BID has not been systematically evaluated in clinical trials.

While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, systematic evaluation of ziprasidone has shown that its efficacy in schizophrenia is maintained for periods of up to 52 weeks at a dose of 20 to 80 mg BID. No additional benefit was demonstrated for doses above 20 mg BID. Patients should be periodically reassessed to determine the need for maintenance treatment.

b) Intramuscular Administration

The recommended dose is 10 to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible. Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

c) Dosing in Special Populations

Oral: Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment. Intramuscular: Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race.

11) ***Contraindications***

Because of Ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure. Pharmacokinetic/ pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other Class IA and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. Ziprasidone is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning

12) ***Analytical methods for ZB***

Analyte	Method / Mobile Phase / Column/ Remarks	Type of sample	Detection by	Reference
Ziprasidone	RP HPLC / 72:28 phosphate buffer: acetonitrile / trimethylsilyl bonded silica column / Detection limit: 0.5ng/mL – 200ng/mL	Human Plasma	Fluoresence Detection excitation and emission λ 320 and 410 nm	Suckow RF et al., 2004
Ziprasidone	RP HPLC / 8% v/v acetonitrile in deionized water / C8 silica column / Limit of quantification – 10ng/mL	Human Plasma	UV detection at 254nm	Sachse J et al., 2005
Ziprasidone	RP HPLC / Luna® phenyl-hexyl column/ Acetonitrile: Methanol: dipotassium hydrogen phosphate (10:35:55, V/V, pH 9) / -	Human Plasma	Digital electrochemical amperometric detector	Melchner W et al., 2005
Ziprasidone and its metabolites	RP HPLC / YMC basic HPLC column / binary mixture of 20 mM ammonium acetate (pH 5.0, solvent A) and methanol (solvent B). The mobile phase initially consisted of solvent A/solvent B at 90:10 for 10 min. It was then linearly programmed to solvent A/solvent B at 20:80 over 50 min.	Human Plasma	Mass Spectrometry	Prakash C., 1997

3.2 Olanzapine

1) Introduction

Olanzapine is a selective monoaminergic antagonist developed by Eli Lilly and Company, with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (Ki=4 and 11 nM, respectively), dopamine D_{1-4} (Ki=11-31 nM), muscarinic M_{1-5} (Ki=1.9-25 nM), histamine H1 (Ki=7 nM), and adrenergic α1 receptors (Ki=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (Ki > 10 mM).

2) Description

a. *Chemical name*

The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno [2, 3-*b*] [1, 5] benzodiazepine.

b. *Formula*

- Empirical

  $C_{17}H_{20}N_4S$

- Structural

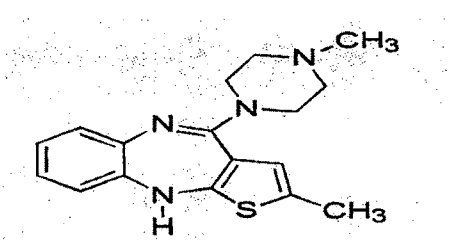

Figure 3.2: Olanzapine

- Molecular weight

  312.44

3) Appearance and color

Yellow crystalline solid

4) Solubility

Olanzapine has a saturation solubility of 8.87μg/mL in phosphate buffer pH 7.4. It is practically insoluble in water; it is soluble in methanol and isopropyl alcohol. It is freely soluble in dichloro methane, chloroform, tetrahydronfuran and acetonitrile. It shows pH dependent solubility by being more soluble at lower pH. But olanzapine is not stable in solution state. Aqueous solutions of olanzapine shows color change from yellow to violet within 7 days.

5) Ultra violet and visible spectrum

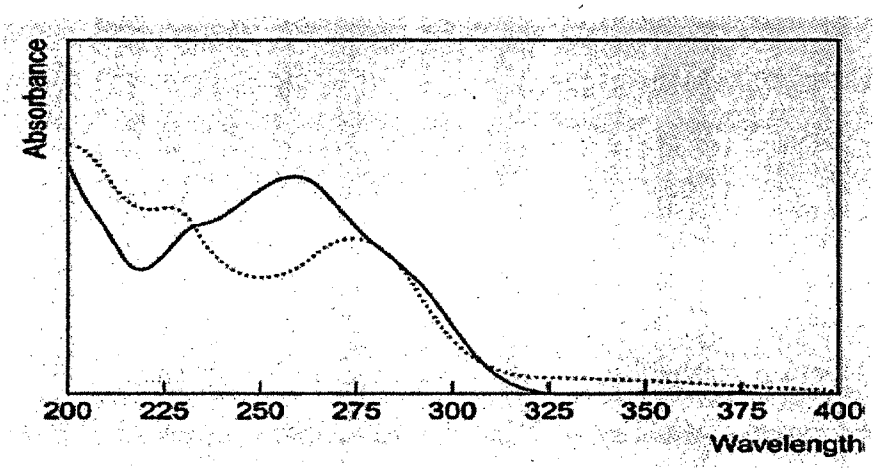

Figure 3.3: Ultra Violet Scan of Olanzapine in 0.1N Hydrochloric Acid showing λ_{max} at 258nm (smooth line) and Olanzapine in phosphate buffer pH 7.4 showing λ_{max} at 276nm (dotted line)

6) Ionization constant

pK_{a1}, 5.0; pK_{a2}, 7.4

7) Melting point

195°C

8) Log P value

2.199

9) Pharmacology

Olanzapine displays a very broad pharmacological profile, with potent activity at dopamine, serotonin, muscarinic, histamine and adrenergic receptors. Its antagonism to muscarinic receptors may explain its anticholinergic properties. Animal behavioral studies show that olanzapine has atypical antipsychotic characteristics, by virtue of its *in vitro* receptor profile. The initial animal screening tests suggested that olanzapine possessed antipsychotic efficacy by virtue of its dopaminergic blocking properties. Furthermore, the animal tests suggest that the clinical efficiency with minimum EPS could be due to its specific action on the firing of the A10 region of the hippocampus the brain. The animal behavioral and electrophysiological studies show that at low doses, it might act as an atypical antipsychotic whereas at very high doses, it might resemble the typical antipsychotic.

10) Pharmacokinetics

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA (Eli Lilly and Company, USA) tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) (Eli Lilly and Company, USA) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses.

Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age. Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Intramuscular administration of olanzapine results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, administration of 5 mg dose of intramuscular olanzapine for injection produced, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics is linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

11) Metabolism

It is metabolized extensively in humans via glucuronidation, allylic hydroxylation, N-oxidation, N-dealkylation and a combination thereof. This is the most important pathway both in terms of contribution to drug related circulating species and as an excretory product in the species. The major metabolites found in humans are 10-N-glucuronide and 4-desmethylolanzapine. In vitro evaluations of the human cytochrome P450 isoenzymes involved in the formation of the three major metabolites of olanzapine have found that CYP 1A2, CYP 2D6, and the flavin containing mono-oxygenase system are involved in the oxidation of olanzapine. The major route of elimination seems to be urine (first pass metabolism) in humans. It displays linear kinetics over the clinical dosing range. The systemic clearance of olanzapine takes about 26.1 ± 12.1 hrs. The plasma elimination half-life (t1/2b) is 33.1 ± 10.3 hrs. Compared with young men, young women

demonstrated decreased clearance. Similarly, elderly subjects showed a decreased clearance compared to younger patients.

12) Toxicology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on an mg/m^2 basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on an mg/m^2 basis) in studies of 3 months duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on an mg/m^2 basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m^2 basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

13) Indications

Schizophrenia

Oral Olanzapine is indicated for the treatment of schizophrenia. The efficacy of olanzapine was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effectiveness of oral olanzapine at maintaining a treatment response in schizophrenic patients who had been stable on olanzapine for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial Nevertheless, the physician who elects to use olanzapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar Disorder

Acute Monotherapy — Oral olanzapine is indicated for the treatment of acute mixed or manic episodes associated with Bipolar I Disorder.

Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral olanzapine after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial

Agitation Associated with Schizophrenia and Bipolar I Mania

Olanzapine IM is indicated for the treatment of agitation associated with schizophrenia and bipolar I mania. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation. The efficacy of olanzapine IM for the treatment of agitation associated with schizophrenia and bipolar I mania was established in 3 short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia or Bipolar I Disorder (manic or mixed episodes)

14) Dosage and administration

Schizophrenia

Usual Dose — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Bipolar Disorder

Usual Monotherapy Dose — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg.

Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended. Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Agitation Associated with Schizophrenia and Bipolar I Mania

Usual Dose for Agitated Patients with Schizophrenia or Bipolar Mania — The efficacy of olanzapine IM for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of olanzapine IM for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., three doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension. Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended. If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate

15) Analytical methods for OL

Analyte	Method / Mobile Phase / Column/ Remarks	Type of sample	Detection by	Reference
Olanzapine	RP-HPLC / - / - / Detection limits – 0.25ng/mL for 1mL human serum	Human Serum	Electrochemical	Catlow JT et al., 1995
	HPLC/ C8 column / Mobile phase – acetonitrile: tetramethylammonium perchlorate		UV detection at 260nm	
	Derivative Spectrophotometry / -/ -/ -	Tablets	At 298nm	Raggi MA et al., 2000
Olanzapine	Linear Voltammetric method		Measurement of oxidation wave at +495mV	
Olanzapine and two metabolites	RP-HPLC / - / - / Detection limits: 1 - 100ng/mL	Rat Plasma	Electrochemical	Chiu JA and Franklin RB., 1996
Olanzapine	Gas Chromatography / Carrier gas: helium /50% phenyl–50% methyl polysiloxane capillary column / Column temperature: 130° for 3 min, to 270° at 10°/min, held for 10 min; then to 295° at 10°/min and held for 5 min. Injector and detector temperature: 250° and 300°, respectively.	Bulk Drug	Nitrogen – phosphorus Internal Standard – Promazaine	Jenkins A., 1998
Olanzapine	RP – HPLC / acetonitrile: methanol: sodium phosphate buffer (50 mM, pH 6.5) (5:28:67) / Microsorb CN - Column temperature: 37°C / -	Bulk Drug	Internal Standard – Clozapine	Prieto I et al., 1997

Analyte	Method / Mobile Phase / Column/ Remarks	Type of sample	Detection by	Reference
Olanzapine	RP HPLC / Methanol–deionized water mixture (70:30 by volume) containing 0.110 mL/L butylamine / Ultremex silica column [250 3 4.6 mm (i.d.); Phenomenex / Detection limit 1.25µg – 80µg/L	Human Plasma	Photodiode array	Lloraca PM et al., 2001
Olanzapine	RP HPLC / phosphate buffer of pH: 5.5 and acetonitrile (7:3 v/v) / RP-YMC pack ODS A -132 C18 column/	Tablets	Diode array detector at 275nm	
	BAS 100 W/B electrochemical analyzer; Working electrode: BAS MF 2012 glassy carbon disc; Counter electrode: BAS MV 1032 platinum; Reference electrode: BAS MF 1063 type silver/silver chloride electrode		Voltammetry	Biryol I and Erk N., 2003
	Derivative Spectrophotometry / -/ -/ -		At 234.3nm and 290.7nm	

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