

# Pharmacokinetics and Therapeutics of Acute Intramuscular Ziprasidone

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## Abstract

Patients with acute psychosis often exhibit agitation, which can be distressing and hazardous to others as well as to the patient. In such psychiatric emergencies, intramuscular antipsychotic agents can be easier to administer than oral formulations, and they have the added advantage of more rapid absorption and a faster onset of action. However, intramuscular formulations of conventional antipsychotics, which have been the standard treatment, are associated with acute dystonia and other movement disorder-related adverse events. Ziprasidone is the first atypical antipsychotic to be clinically available in both intramuscular and oral formulations in the US. The intramuscular formulation of ziprasidone, ziprasidone mesylate, uses sulfobutylether  $\beta$ -cyclodextrin to solubilise the drug by complexation. The pharmacokinetics of intramuscular ziprasidone include rapid attainment

of therapeutic drug level (time to reach peak serum concentration [ $t_{\max}$ ]  $\leq 60$  minutes postdose), a mean terminal elimination half-life ranging from 2 to 5 hours, bioavailability of approximately 100%, exposure to drug that increases in a dose-related manner and little drug accumulation even after 3 days of repeated intramuscular administration.

The metabolism and elimination of intramuscular ziprasidone have not been extensively evaluated. The principal difference between any oral versus intramuscular formulations of a drug is in first-pass metabolism. Oral ziprasidone is eliminated mainly via the hepatic route and  $<1\%$  is eliminated in urine and  $<4\%$  in faeces as unchanged drug. That would not be expected to change with the intramuscular route of administration. Low concentrations of ziprasidone are seen 12–18 hours after the last intramuscular injection. The rapid clearance of ziprasidone from plasma after an intramuscular administration results in little to no persistence of plasma drug level when switching from intramuscular to oral drug administration. No clinically significant age-, sex- or race-related effects on the pharmacokinetics of intramuscular or oral ziprasidone have been noted, and the tolerability and cardiovascular safety profiles of intramuscular ziprasidone have been well characterised in clinical trials.

Oral formulations of conventional and atypical antipsychotic medications provide symptom relief to patients with schizophrenia and schizoaffective disorder over the long term. However, the considerable agitation and anxiety that patients experience during an acute exacerbation can be distressing and may pose a safety problem for the patient, as well as for other patients and staff. In psychiatric emergencies, intramuscular formulations of antipsychotic agents can be easier to administer and have the added advantage of more rapid absorption and a faster onset of action.<sup>[1]</sup>

Although conventional antipsychotics available in intramuscular formulation are effective in controlling acute symptoms, they are associated with adverse effects that patients and clinicians can find intolerable or undesirable. For example, the use of chlorpromazine can cause substantial orthostatic hypotension, and haloperidol is associated with a propensity to cause disturbing and intolerable extrapyramidal symptoms (EPS), including acute dystonia.<sup>[2]</sup> To minimise the risk of EPS, acetylcholine receptor antagonists or benzodiazepines are frequently alternated with haloperidol; however, the use of these medications may result in sedation and

confusion, which may complicate assessment and treatment of the patient.

The low potential of atypical antipsychotics for movement disorders is a tolerability advantage over conventional agents. Ziprasidone is the first atypical antipsychotic to be clinically available in the US in both intramuscular formulation (for treatment of acute agitation in patients with schizophrenia) and in tablet formulation (for longer-term treatment of schizophrenia).<sup>[3]</sup>

Intramuscular ziprasidone has been shown to offer rapid effective treatment of acute agitation in patients with *Diagnostic and Statistical Manual of Mental Disorders (4th Edition)*-defined<sup>[4]</sup> schizophrenia or schizoaffective disorder, bipolar disorder with psychotic features or schizophreniform disorder, delusional disorder, brief psychotic disorder, or shared psychotic disorder or psychotic disorder not otherwise specified.<sup>[4-7]</sup>

This paper will review the therapeutic and tolerability features of the intramuscular formulation of ziprasidone in relation to its pharmacokinetic/pharmacodynamic characteristics and clinical trial evidence.

All published English language citations regarding intramuscular ziprasidone were retrieved using

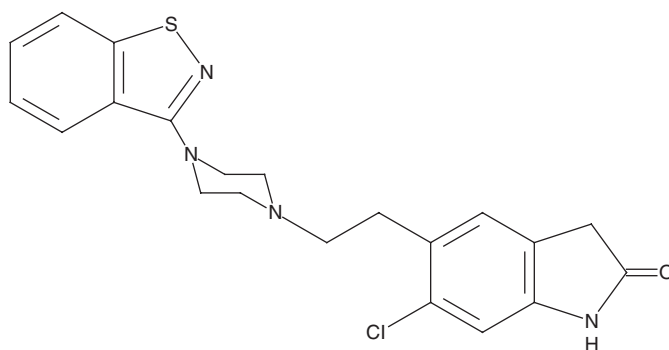


Fig. 1. Chemical structure of free-base ziprasidone.<sup>[3]</sup>

MEDLINE (citation search from January 1995 to May 2004). Primary search terms included 'IM (and intramuscular) ziprasidone', 'ziprasidone', 'IM ziprasidone pharmacokinetics', 'IM ziprasidone pharmacodynamics', 'IM ziprasidone and schizophrenia', 'ziprasidone and agitation', 'ziprasidone and psychosis', 'ziprasidone safety and tolerability', 'ziprasidone and QTc', and 'ziprasidone and psychiatric emergencies'. Additional references were identified from reference lists of published articles and from unpublished data requested from the developer of ziprasidone, Pfizer Inc., New York, NY, USA.

## 1. Formulations of Ziprasidone

Clinical development of ziprasidone has focused on an oral and acute intramuscular formulation, although an intravenous formulation has also been tested in pharmacokinetic studies.

The structural formula of free-base ziprasidone is shown in figure 1.<sup>[3]</sup> Ziprasidone hydrochloride, the oral formulation of ziprasidone chemically known as 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, monohydrochloride, monohydrate, is available as 20, 40, 60 and 80mg capsules and is currently recommended for the treatment of schizophrenia in doses of 40–160mg given with food.<sup>[3]</sup>

Ziprasidone mesylate, chemically known as 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, methanesulfonate, trihydrate, is the injectable intramuscular form of ziprasidone.<sup>[3]</sup> When reconstituted, each

millilitre of ziprasidone mesylate for intramuscular injection contains 20mg of ziprasidone and 4.7mg of methanesulfonic acid solubilised by 294mg of sulfobutylether  $\beta$ -cyclodextrin sodium (SBECD).

### 1.1 Use of Sulfobutylether $\beta$ -Cyclodextrin Sodium

The acute intramuscular formulation of ziprasidone was developed using SBECD, a complex carbohydrate, to solubilise the drug by complexation.<sup>[8]</sup> SBECD forms a highly water-soluble inclusion complex with ziprasidone mesylate. The complexation process is rapid and reversible.

In solution, the SBECD-ziprasidone mesylate complex remains in equilibrium with noncomplexed ziprasidone.<sup>[8]</sup> In the absence of competition from other dissolved solutes (i.e. in the dosage form), ziprasidone will remain primarily within the complex. After intramuscular injection of ziprasidone, endogenous solutes displace the drug from the complex. Thereafter, simple dilution, together with the extensive protein binding of ziprasidone, ensures that the drug rapidly enters the systemic circulation.

## 2. Pharmacokinetics

The pharmacokinetics of the acute intramuscular formulation of ziprasidone were investigated using population pharmacokinetic modelling in phase I and II development and in single- and multiple-dose studies. Two single-dose and one multiple-dose study utilised the lyophilised powder reconstituted to a 20 mg/mL solution, administered in repeated

doses, to a maximum of 80mg in 24 hours, to test the safety margin of the drug, particularly with regard to cardiovascular events.<sup>[9]</sup>

## 2.1 Population Pharmacokinetics Study

During efficacy trials for agitation associated with acute psychotic decompensation, frequent pharmacokinetic sampling is impractical. For this reason, population techniques were used to evaluate the pharmacokinetics of the intramuscular formulation of ziprasidone in these trials. The substantial amount of pharmacokinetic data collected from ziprasidone phase I, II and III studies that incorporated sparse serum sampling were used to develop a population-based pharmacokinetic model.<sup>[10]</sup> The objective of this modelling effort was to expand the understanding of intramuscular ziprasidone pharmacokinetics in a large clinical population and identify variables (i.e. age, sex, race, liver and renal function, bodyweight, body surface area, height and concomitant benzodiazepine use [presence or absence only]) that may significantly affect intramuscular ziprasidone pharmacokinetics. Serum concentration data obtained from nine trials, including the four pharmacokinetic studies<sup>[9]</sup> and the five phase II/III efficacy trials of intramuscular ziprasidone,<sup>[5,6,9,11-13]</sup> were used in this pharmacokinetic analysis.<sup>[10]</sup>

This analysis used 2250 samples obtained from a total of 483 healthy volunteers and patients with schizophrenia who participated in single- and multiple-dose intramuscular ziprasidone trials.<sup>[10]</sup> The initial pharmacokinetic model was based on data from phase I single-dose studies in which there was extensive serum sampling (762 samples from 47 healthy volunteers). The final pharmacokinetic model (with covariate analysis) was developed from combined data from phase I, II and III studies. Of the total data, 80% were used in the covariate analysis (1818 serum samples from 375 healthy volunteers and patients with schizophrenia). The remaining 20% of data were used for model validation (432 serum samples from 108 healthy volunteers and patients with schizophrenia). Data analysis was performed using nonlinear

mixed-effects modelling software NONMEM Version 4, level 2.1 (Globomax, Hanover, MD, USA).

Results of this nine-study data analysis confirm that the systemic clearance of ziprasidone following intramuscular administration is independent of dose over a range of 2–80 mg/day.<sup>[9,10]</sup> The exposure to intramuscular ziprasidone over this range is dose-related, which is consistent with previous studies of oral ziprasidone. Systemic clearance was found to be linearly related to both bodyweight and body surface area, although body surface area more reliably predicted clearance than bodyweight. Although the model showed that age, sex, race, renal and liver function, and concomitant benzodiazepine administration did not significantly affect intramuscular ziprasidone pharmacokinetic parameters, intramuscular ziprasidone has not been systematically evaluated in patients  $\geq 65$  years of age or in patients with renal or hepatic impairment.<sup>[3]</sup> Considering this caveat, the results are consistent with formal studies of oral ziprasidone in patients with normal and impaired renal and hepatic function that showed that area under the serum concentration-time curve (AUC), peak serum concentration ( $C_{max}$ ) and time to reach  $C_{max}$  ( $t_{max}$ ) were not altered to a clinically meaningful or statistically significant degree by mild-to-moderate renal<sup>[14]</sup> or hepatic<sup>[15]</sup> impairment. Nevertheless, the cyclodextrin excipient of intramuscular ziprasidone is cleared by renal filtration, and the drug's labelling advises that it should be administered with caution to patients with impaired renal function.<sup>[3]</sup>

## 2.2 Single-Dose Studies

Study 1 was a randomised, single-blind, placebo-controlled study in 24 healthy volunteers of escalating, single, intramuscular doses (5, 10 and 20mg).<sup>[9,16]</sup> Dosing groups were studied in a sequence of low- to high-dose intramuscular ziprasidone. Ziprasidone was administered as a single intramuscular injection in the morning after an overnight fast of at least 8 hours. Blood samples were collected immediately prior to and up to 24 hours after each intramuscular dose of study drug for the determination of ziprasidone concentrations. Blood

**Table 1.** Pharmacokinetic findings in two single-dose studies of intramuscular (IM) ziprasidone<sup>[9]</sup>

Dose (mg) and route of administration	No. of subjects	AUC <sub>∞</sub> (ng • h/mL) <sup>a</sup>	C <sub>max</sub> (ng/mL) <sup>a</sup>	t <sub>max</sub> (h) <sup>b</sup>	CL (mL • min/kg) <sup>a</sup>	t <sub>1/2β</sub> (h) <sup>c</sup>
<b>Study 1</b>						
5 IM	6	229 (23)	76 (7)	0.5 (38)	5.0 (28)	2.4
10 IM	6	463 (12)	156 (14)	0.7 (37)	4.7 (8)	2.2
20 IM	6	846 (29)	244 (37)	0.7 (52)	5.0 (28)	3.0
<b>Study 2</b>						
5 IM	12	223 (19)	80 (32)	0.5 (60)	4.9 (13)	3.0
5 IV	12	217 (20)	83 (21)	1 (12)	5.0 (15)	3.1
20 PO	12	514 (27)	64 (28)	8 (42)	NA	3.8

a Values are expressed as geometric mean (CV%).

b Values are expressed as arithmetic mean (CV%).

c Values are expressed as harmonic mean.

**AUC<sub>∞</sub>** = area under the serum concentration-time curve from time zero to infinity; **CL** = clearance; **C<sub>max</sub>** = peak serum concentration; **CV** = coefficient of variation; **IV** = intravenous; **NA** = not available; **PO** = oral; **t<sub>1/2β</sub>** = terminal elimination half-life; **t<sub>max</sub>** = time to reach C<sub>max</sub>.

samples were collected in tubes containing no preservative, anticoagulant or serum separator immediately prior to (time zero) and 0.08, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours following dose administration.<sup>[9]</sup>

In study 2, a single-dose, open-label study with a three-way crossover design, 12 healthy volunteers each received, in randomised sequence, intravenous ziprasidone 5mg infused over 1 hour, intramuscular ziprasidone 5mg and oral ziprasidone 20mg administered under fed conditions.<sup>[9,16]</sup> The dose administration periods for each dose route were separated by at least 7 days. Blood samples were collected at the following times for each formulation. For intravenous infusion, collection times were just prior to (time zero) and 0.25, 0.5, 0.75, 1 (immediately post-intravenous infusion), 1.25, 1.5, 1.75, 2, 4, 6, 8, 12, 16 and 24 hours following the start of the infusion. For intramuscular infusion, collection was just prior to (time zero) and 0.08, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours following dose administration. Finally, for oral administration, blood sample collection occurred prior to (time zero) and 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 30 and 36 hours following dose administration.<sup>[9]</sup>

Pharmacokinetic parameters for intramuscular ziprasidone were consistent across the single-dose studies (table I).<sup>[9]</sup> In study 2, mean ziprasidone serum C<sub>max</sub> values were similar for both the intra-

muscular and intravenous formulations, at 80 ng/mL and 83 ng/mL, respectively; both differed significantly from the mean C<sub>max</sub> value of 64 ng/mL observed with the oral formulation.<sup>[9,16]</sup> C<sub>max</sub> following the intramuscular dose occurred approximately 30 minutes after dose administration (range 10–60 minutes).<sup>[9]</sup> The terminal elimination half-life (t<sub>1/2β</sub>) was also similar in the intramuscular and intravenous formulations (3.0 and 3.1 hours, respectively), but slightly longer (3.8 hours) in the oral formulation. This difference was attributed to continued drug absorption during the later portion of the sampling period after oral administration.<sup>[9]</sup> The mean bioavailability of a single 5mg intramuscular dose of ziprasidone was approximately 100% (range 86–113%).<sup>[9]</sup>

In study 1, peak serum concentrations of ziprasidone were generally reached in <1 hour (range 20–90 minutes) after intramuscular injection for each of the three doses of ziprasidone tested.<sup>[9]</sup> Mean AUC increased in a dose-proportional manner, with an approximate doubling of the mean AUC with each 2-fold dose increment. The increase in mean C<sub>max</sub> was also dose proportional from 5–10mg, increasing from 76 to 156 ng/mL. The exception occurred with the doubling in dose from 10 to 20mg in which the mean C<sub>max</sub> increased approximately 1.6-fold. Mean t<sub>1/2β</sub> was approximately 2.5 hours across the 5–20mg dose range.

### 2.3 Multiple-Dose Study

Another pharmacokinetic study utilised a population pharmacokinetic model to evaluate the effects of multiple doses of intramuscular ziprasidone (20–80 mg/day [5, 10 or 20mg four times daily] for 3 days) in 24 enrolled subjects with mildly symptomatic schizophrenia.<sup>[9,17]</sup> This multiple-dose study expanded on a population pharmacokinetic model from phase I and II single-dose studies, which included data from 375 subjects (aged 18–76 years). The sample-derived values from the small multiple-dose study population were then compared with the predictive values from the population model. AUC during a 24-hour dose administration interval (AUC<sub>24</sub>), accumulation ratio (i.e. ratio of day 3 to day 1 AUC<sub>24</sub>), elimination rate constant ( $k_{el}$ ), and serum  $t_{1/2\beta}$  were estimated from individual observed and model-predicted ziprasidone concentration-time curves.<sup>[17]</sup>

All antipsychotic medication was discontinued in the 24 subjects 5 days before initiation of ziprasidone therapy. Six subjects were randomly assigned to each dosage group and an additional two subjects in each group were given placebo. Subjects in the 5mg and 10mg four-times-daily groups were given intramuscular ziprasidone at 2-hour intervals. Those in the 20mg four-times-daily group received an initial 10mg dose on day 1, followed by three 20mg doses given 4 hours apart and successive 20mg doses given four times daily on days 2 and 3. Twelve blood samples were taken immediately before and at varying intervals (up to 24 hours) after each dose on day 1 to determine pharmacokinetic parameters.<sup>[9,17]</sup> In the 5mg and 10mg four-times-daily groups, blood samples were collected immediately prior to (time zero) and at 1, 2 (just prior to second injection), 3, 4 (just prior to third injection), 5, 6 (just prior to fourth injection), 8, 10, 12, 16 and 24 hours following the first injection.<sup>[9]</sup> In the 20mg four-times-daily group, blood samples were collected immediately prior to (time zero) and at 2, 4 (just prior to second injection), 6, 8 (just prior to third injection), 10, 12 (just prior to fourth injection), 14, 16, 18, 20 and 24 hours following the first injection. On day 3, additional blood samples were to be

obtained at 30 and 36 hours following the first injection for all three dosage groups.<sup>[9]</sup>

Given the limited pharmacokinetic sampling ( $C_{max}$  and  $t_{max}$ ), the time to the first occurrence of  $C_{max}$  was not precisely characterised in this small multiple-dose study. However, dose-related increases in total systemic exposure, as determined by AUC<sub>24</sub>, were observed on days 1 and 3 (table II).<sup>[9]</sup> As determined from the pharmacokinetic model,  $t_{max}$  was comparable to  $t_{max}$  from previous single-dose, data-rich studies (mean values ranging from 0.2–0.6 hours).<sup>[17]</sup> Based on the ratio of day 3 and day 1 AUC<sub>24</sub> values, drug accumulation was minimal or absent, regardless of dosage.<sup>[9]</sup> Mean serum drug concentrations at 12 and 18 hours after the fourth intramuscular injection on day 3 were low, ranging from 4–27 ng/mL for all dosage groups. Dose did not appear to affect  $t_{1/2\beta}$  on days 1 or 3. The mean  $t_{1/2\beta}$  ranged from 3–5 hours on day 1 and from 7–13 hours on day 3. The  $t_{1/2\beta}$  values observed in this multiple-dose study on day 1 were comparable to those observed in the single-dose intramuscular studies.<sup>[9]</sup> Increased  $t_{1/2\beta}$  values observed in each dosage group on day 3 may be attributable to an additional dispositional phase; however, a decrease in clearance with multiple-dose administration cannot be ruled out.<sup>[9]</sup>

**Table II.** Pharmacokinetic parameters after multiple doses of intramuscular ziprasidone in schizophrenic patients<sup>[9]</sup>

Treatment arm	No. of patients	AUC <sub>24</sub> (ng • h/mL) <sup>a</sup>	Mean $t_{1/2\beta}$ (h) <sup>b</sup>
5mg qid	6		
day 1		648	4.6
day 3		590	8.1
10mg qid	6		
day 1		1363	3.9
day 3		1116	10.4
20mg qid	6		
day 1		1560	3.8
day 3		1504	ND

a Values are expressed as geometric mean.

b Calculated as  $0.693/k_{el}$ .

**AUC<sub>24</sub>** = area under the serum concentration-time curve from 0 to 24 hours;  **$k_{el}$**  = terminal elimination rate constant; **ND** = not determined because half-lives were not estimable for the 80 mg/day group owing to the shorter time interval over which to assess them during the terminal phase; **qid** = four times daily;  **$t_{1/2\beta}$**  = terminal elimination half-life.

The overall pharmacokinetic characteristics of the intramuscular ziprasidone formulation demonstrated in these single- and multiple-dose studies support its suitability for use in the acute situation: bioavailability is approximately 100%, peak serum concentrations are reached rapidly (usually within 30–60 minutes following a single dose), which would predict a timely onset of action, and the formulation exhibits predictable pharmacokinetics, with exposure increasing in a dose-related fashion.<sup>[9]</sup> The absence of significant drug accumulation and observed low concentrations 12–18 hours after the last intramuscular dose means that the clinician does not have to adjust the starting oral dose to take into account levels persisting from the intramuscular drug administration. As discussed in section 4.2, ease of transition from intramuscular to oral ziprasidone therapy was documented in two clinical studies comparing ziprasidone and haloperidol.<sup>[9]</sup>

## 2.4 Metabolism

Ziprasidone is extensively metabolised in humans via the liver, with small amounts excreted in urine (<1%) and faeces (<4%) as unchanged drug.<sup>[3,9]</sup> Metabolism proceeds along three main pathways and is mediated by two enzymes – reduction by aldehyde oxidase along one pathway, which accounts for approximately two-thirds of ziprasidone metabolism, and oxidation by cytochrome P450 (CYP) 3A4 along two pathways, which accounts for the remainder of ziprasidone metabolism (figure 2).<sup>[9,18]</sup> Four major circulating metabolites result: *S*-methyl dihydroziprasidone (M9; formed by aldehyde oxidase-mediated reduction) and ziprasidone sulfoxide (M10; formed by CYP3A4-mediated oxidation) and two other metabolites, benzisothiazole piperidine (BITP) sulfoxide (M2) and BITP sulfone (M1), both mediated by CYP3A4 oxidation.<sup>[9,18]</sup>

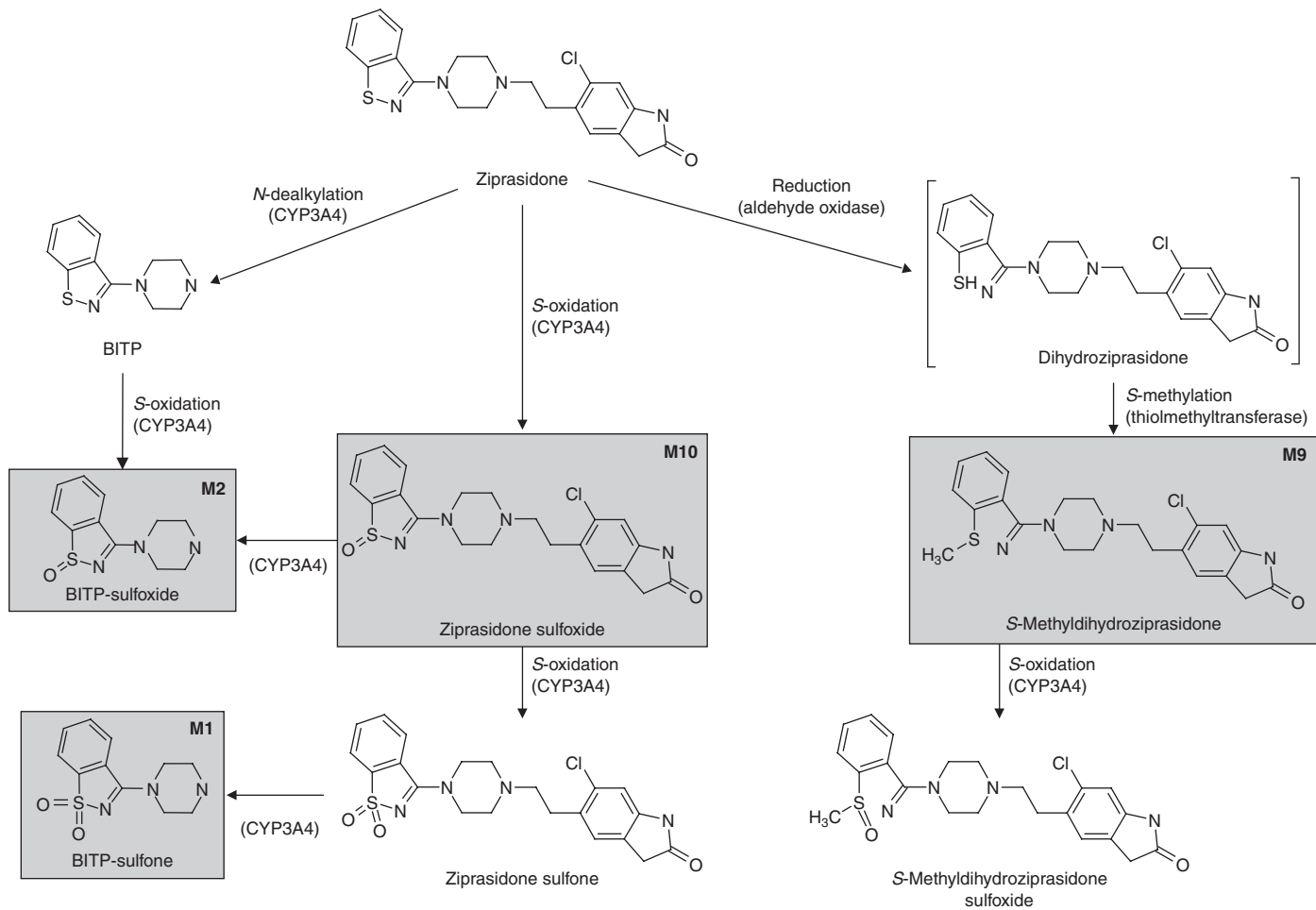
Oral ziprasidone undergoes first-pass hepatic metabolism; an estimated 30–40% of a single oral dose is converted to metabolites before reaching the systemic circulation.<sup>[9]</sup> In contrast, intramuscular ziprasidone enters the systemic circulation prior to passing through the hepatic system. For this reason,

the concentration ratio of metabolites to unchanged drug are lower with intramuscular administration compared with oral administration. Pharmacokinetic studies and clinical trial data show that the mean serum concentration ratios for M9 : ziprasidone are 0.23 and 0.95 following intramuscular and oral administration, respectively. The corresponding mean M10 : ziprasidone ratios are 0.03 and 0.30, respectively.<sup>[9]</sup> Eventually, all circulating ziprasidone is cleared by hepatic metabolism, regardless of route of administration.

## 3. Pharmacodynamics

### 3.1 Receptor-Binding Profile

The receptor-binding affinities of ziprasidone are relatively unique.<sup>[19–22]</sup> Like some of the newer antipsychotics, and in contrast to conventional agents such as haloperidol, ziprasidone binds more avidly to serotonin 5-HT<sub>2A</sub> (dissociation constant [K<sub>i</sub>] = 0.39 nmol/L) than to dopamine D<sub>2</sub> receptors (K<sub>i</sub> = 3.1 nmol/L), i.e. with 8-fold greater affinity.<sup>[22]</sup> Ziprasidone has a high receptor-binding affinity for 5-HT<sub>2A</sub> and D<sub>2</sub> receptors, and a higher 5-HT<sub>2A</sub>/D<sub>2</sub> receptor affinity ratio than most other antipsychotic agents (table III).<sup>[22]</sup> Ziprasidone is an antagonist of the 5-HT<sub>2C</sub> (K<sub>i</sub> = 0.72 nmol/L) and 5-HT<sub>1B/1D</sub> (K<sub>i</sub> = 2.0 nmol/L) receptors and exhibits 5-HT<sub>1A</sub> receptor agonist activity (K<sub>i</sub> = 2.5 nmol/L).<sup>[22]</sup> In addition, ziprasidone modestly inhibits neuronal reuptake of serotonin (K<sub>i</sub> = 53 nmol/L) and norepinephrine (K<sub>i</sub> = 48 nmol/L), and has modest binding affinity for histamine H<sub>1</sub> receptors and  $\alpha_1$ -adrenoceptors (K<sub>i</sub> = 47 nmol/L and 13 nmol/L, respectively).<sup>[22]</sup> Its affinity for the serotonin and norepinephrine uptake pumps is approximately 100-fold less than its affinity for the 5-HT<sub>2A</sub> receptor.<sup>[22–24]</sup> The binding affinity of ziprasidone for  $\alpha_2$ -adrenoceptors and acetylcholine muscarinic (M<sub>1</sub>) receptors is negligible (K<sub>i</sub> = 310 nmol/L and 5100 nmol/L, respectively). Likewise, ziprasidone has little or no activity (50% inhibitory concentration >1  $\mu$ mol/L) at  $\beta$ -adrenoceptor, GABA/benzodiazepine and opioid receptor sites.<sup>[23,25]</sup>



**Fig. 2.** Summary of the metabolic pathways of ziprasidone in humans (shaded boxes indicate metabolites present in circulation).<sup>[9]</sup> **BITP** = benzothiazole piperidine; **CYP** = cytochrome P450.

**Table III.** Receptor-binding affinities (nmol/L) of antipsychotic agents (reproduced from Schmidt et al.,<sup>[22]</sup> with permission from Elsevier)

Receptor	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine	Haloperidol
Serotonin 5-HT <sub>1A</sub>	2.5	210	2100	230	140	3600
5-HT <sub>2A</sub>	0.39	0.29	3.3	220	8.9	120
Dopamine D <sub>2</sub>	3.1	2.2	20	180	130	1.4
5-HT <sub>1B/1D</sub>	2.0	170	530	>5100	1700	>5000
5-HT <sub>2C</sub>	0.72	10	10	1400	17	4700
$\alpha_1$ -Adrenoceptor	13	1.4	54	15	4.0	4.7
$\alpha_2$ -Adrenoceptor	310	5.1	170	1000	33	1200
Histamine H <sub>1</sub>	47	19	2.8	8.7	1.8	440
Muscarinic M <sub>1</sub>	5100	2800	4.7	100	1.8	1600
GABA/benzodiazepine	IC <sub>50</sub> >1 $\mu$ mol/L	NA	NA	NA	NA	NA
Opioid	IC <sub>50</sub> >1 $\mu$ mol/L	NA	NA	NA	NA	NA
$\beta$ -Adrenoceptor	IC <sub>50</sub> >1 $\mu$ mol/L	NA	NA	NA	NA	NA

IC<sub>50</sub> = 50% inhibitory concentration; NA = not available.

### 3.2 Clinical Implications of Receptor-Binding Affinities

A high binding ratio for 5-HT<sub>2A</sub>/D<sub>2</sub> receptors has been proposed as the potential mechanism explaining a lower risk of troublesome EPS with ziprasidone and some of the newer versus traditional antipsychotics, as well as greater efficacy in alleviating negative symptoms of schizophrenia.<sup>[20,25-28]</sup> The 5-HT<sub>1A</sub>-receptor agonism, 5HT<sub>1B/1D</sub>-receptor antagonism and serotonin/norepinephrine uptake inhibition are mechanisms associated with anxiolytic and antidepressant efficacy.<sup>[20,22,24,25,29,30]</sup> However, it has not been established whether ziprasidone, under clinically relevant dosing conditions, affects these targets to a clinically meaningful degree.

Based on the 4-fold lower affinity of ziprasidone for  $\alpha_1$ -adrenoceptors compared with D<sub>2</sub> receptors, an intramuscular formulation of ziprasidone might have a lower potential to cause orthostatic hypotension and sedation than would intramuscular formulations of other atypical antipsychotics, such as risperidone, clozapine and quetiapine, which have higher binding affinities for  $\alpha_1$ -adrenoceptors compared with D<sub>2</sub> receptors.<sup>[22]</sup> However, this possibility has not been empirically established.

The modest binding affinity of ziprasidone for H<sub>1</sub> receptors and negligible binding affinity for the M<sub>1</sub> receptor are consistent with its low potential for causing anticholinergic effects, including cognitive dysfunction and adverse memory effects, as well as

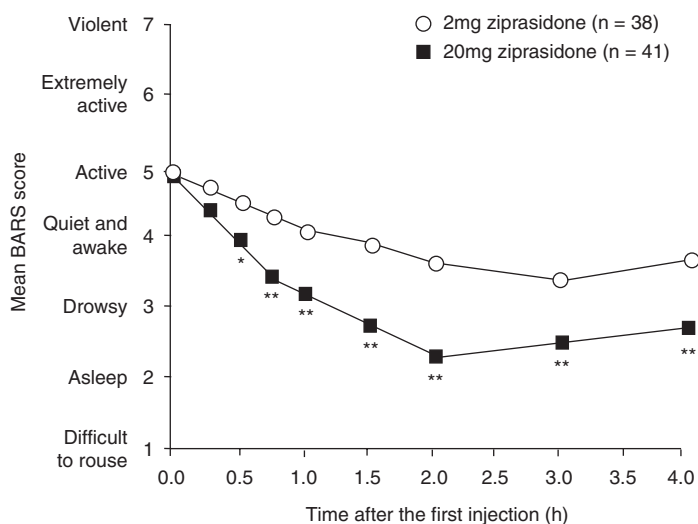
excessive sedation.<sup>[20,22]</sup> While a certain degree of sedation may be a desired feature in a drug being used to calm a patient during periods of acute agitation and anxiety, excessive sedation may complicate assessment of the patient.

## 4. Clinical Efficacy of Intramuscular Ziprasidone

The clinical efficacy of intramuscular ziprasidone was evaluated in several phase II/III clinical trials.

### 4.1 Agitation in Psychotic Patients

The results of several clinical trials showed that rapid acting intramuscular ziprasidone is effective and well tolerated in the treatment of acute agitation associated with psychosis.<sup>[5-7]</sup> In two 24-hour, randomised, double-blind studies of agitated patients hospitalised with schizophrenia, schizoaffective disorder or bipolar disease, intramuscular ziprasidone was given, as needed, in doses of 2 and 10mg,<sup>[6]</sup> and 2 and 20mg<sup>[5]</sup> up to total daily doses of 80mg. In each study, patients given 2mg doses served as a control group. Results in both studies demonstrated a rapid calming effect produced without excessive sedation. Compared with the 2mg dose, patients given both 10 and 20mg doses demonstrated improvement in symptoms of agitation, as measured by the Behavioural Activity Rating Scale (score range 1–7; 1 = difficult to rouse, to 7 =



**Fig. 3.** Mean Behavioural Activity Rating Scale (BARS) scores 0–4 hours after the initial injection of intramuscular ziprasidone 2mg and 20mg (reproduced from Daniel et al.<sup>[6]</sup> with permission). \*  $p < 0.01$ , \*\*  $p < 0.001$  vs 2mg.

violent, requires restraint),<sup>[31]</sup> within 15 minutes of dose administration (figure 3 and figure 4). Improvement with the 20mg dose was significant ( $p < 0.01$ ) 30 minutes postdose, and improvement with both 10 and 20mg doses was sustained for up to 4 hours postdose ( $p \leq 0.001$ ) compared with the control group.

#### 4.2 Transition from Intramuscular to Oral Therapy

A 6-week, multicentre, parallel-group study compared the efficacy of sequential intramuscular/oral ziprasidone with that of sequential intramuscular/oral haloperidol in patients with acute exacerbation of schizophrenia or schizoaffective disorder.<sup>[11]</sup> Patients ( $n = 567$ ) received either ziprasidone or haloperidol on an open-label basis and assessments were conducted by evaluators who were blinded with respect to drug allocation. Efficacy was evaluated using changes in scores on the Brief Psychiatric Rating Scale (BPRS) total, the Clinical Global Impression-Improvement (CGI-I) scale, the CGI-Severity (CGI-S) scale and the Covi Anxiety Scale. Scores were compared from baseline to the end of the intramuscular phase (days 1–3) and from base-

line to study endpoint (week 6, or early discontinuation).

Mean daily intramuscular doses of ziprasidone and haloperidol were 21.9mg and 7.0mg, respectively, and median duration of intramuscular treatment was 2 days for both groups.<sup>[9]</sup> Patients could be transferred to oral therapy after (i) a minimum of two intramuscular doses; (ii) evaluation by the investigator; and (iii) completion of applicable rating instruments.<sup>[9,11]</sup> A patient could continue to the oral phase of the study at the discretion of the investigator despite refusal of a second intramuscular administration.<sup>[9]</sup> Oral dosages ranged from 40–80mg twice daily for ziprasidone and from an initial dosage of haloperidol 5mg twice daily, with subsequent adjustment within the range of 5–20 mg/day, depending on patient's clinical status.

At the end of the intramuscular phase, significantly greater changes were noted for ziprasidone compared with haloperidol on the BPRS total {–6.15 (effect size [ES] –13.7) vs –4.13 (ES –6.3), respectively;  $p < 0.01$ }<sup>[11]</sup> and Covi Anxiety Scale (–0.980 [ES –0.36] vs +0.513 [ES 0.19], respectively;  $p < 0.01$ ).<sup>[9]</sup> Improvements in CGI-S and CGI-I at the end of intramuscular treatment were similar for both groups.<sup>[11]</sup>

Daniel et al.<sup>[32]</sup> analysed data from three multicentre blinded studies (two 7-day studies<sup>[12,13]</sup> and the 6-week study discussed earlier<sup>[11]</sup>) in which patients transitioned from intramuscular to oral therapy (n = 1005; sequential intramuscular/oral ziprasidone [n = 725] or sequential intramuscular/oral haloperidol [n = 280]). In the two 7-day studies, discontinuation rates due to adverse events were comparable in ziprasidone- and haloperidol-treated patients (1.5% vs 0.7%). However, in the 6-week trial, discontinuation rates at 2 weeks due to adverse events were lower in the ziprasidone group compared with the haloperidol group (4.2% vs 9.6%); rates of discontinuations due to lack of efficacy were low in both treatment groups at 2 weeks (3.5% for ziprasidone and 1.5% for haloperidol). No patient withdrew because of lack of efficacy during the intramuscular phase. The investigators concluded that ziprasidone was well tolerated and was at least as effective as haloperidol during the transition and continued to sustain or increase improvement in symptoms.<sup>[13]</sup>

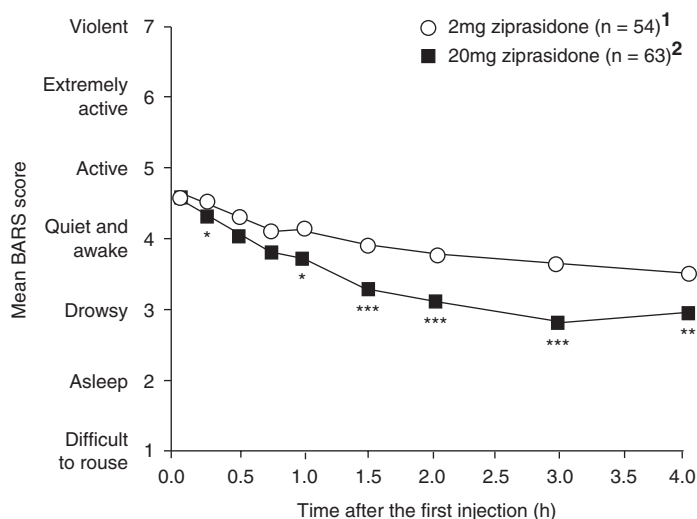
## 5. Tolerability

### 5.1 Overall Adverse Events

Safety data from five clinical trials in 921 adult patients who received intramuscular ziprasidone for acute psychosis were reviewed.<sup>[33,34]</sup> Ziprasidone doses ranged from 2–20mg, up to 80 mg/day, over a duration of not more than 3 days. The most common adverse events reported in these five studies were nausea, headache, dizziness, anxiety, somnolence, insomnia and injection-site pain. The majority of adverse events were mild or moderate in severity, and the rate of treatment discontinuations due to treatment-emergent adverse events for intramuscular ziprasidone ranged from 1.1% to 6.1%.<sup>[33]</sup>

### 5.2 Movement Disorders

Atypical antipsychotics have demonstrated a relatively low incidence of distressing adverse effects, such as EPS and acute dystonia, which have been associated with the use of conventional antipsychotic agents. In the study of 2mg (control dose) versus 10mg of intramuscular ziprasidone in acutely agitated patients by Lesem et al.,<sup>[6]</sup> no instances of acute dystonia were reported, although 1 of 63 (1.6%)



**Fig. 4.** Mean Behavioural Activity Rating Scale (BARS) scores 0–4 hours after the initial injection of intramuscular ziprasidone 2mg and 10mg (reproduced from Lesem et al.,<sup>[6]</sup> with permission). **1** At baseline, n = 54; at 2 hours, n = 54; at 4 hours, n = 45; **2** At baseline, n = 63; at 2 hours, n = 62; at 4 hours, n = 55; \* p < 0.05, \*\* p < 0.01, \*\*\* p ≤ 0.001 vs 2mg.

patients in the 10mg group experienced akathisia. Further, improvements were noted in assessments of parkinsonism and akathisia overall. In the study of 2mg versus 20mg of intramuscular ziprasidone in acutely agitated patients by Daniel et al.,<sup>[5]</sup> no instances of EPS, dystonia, akathisia, respiratory depression or excessive sedation were noted with either the 2mg or 20mg dose of intramuscular ziprasidone.

Intramuscular ziprasidone has consistently demonstrated low rates of movement disorders compared with intramuscular haloperidol.<sup>[11-13,33,35,36]</sup> The low rate of movement disorders associated with ziprasidone is reflected in patients' requirements for acetylcholine receptor antagonists. For example, in the 7-day comparative study,<sup>[13]</sup> far fewer ziprasidone-treated patients required concomitant acetylcholine receptor antagonists than did haloperidol-treated patients (14.4% vs 47.6%). These findings are consistent with the receptor binding profile of ziprasidone, as previously discussed.

### 5.3 Cardiovascular Safety

#### 5.3.1 QT Interval

An important concern with antipsychotic medications has been adverse effects on intracardiac conduction, such as prolongation of the QT interval. For this reason, the safety evaluation of intramuscular

ziprasidone incorporated extensive ECG data recorded at baseline, at random times relative to intramuscular ziprasidone administration and at last assessments during seven of the phase II/III clinical trials discussed earlier.<sup>[9]</sup>

Mean changes in corrected QT (QTc) interval values from baseline to last assessment for intramuscular ziprasidone (all doses  $\geq 5$ mg) versus intramuscular haloperidol (2.5mg to a maximum of 40 mg/day) are shown in table IV.<sup>[9]</sup> For all intramuscular ziprasidone doses  $\geq 5$ mg, mean QTc interval change was 0.1 milliseconds compared with 0.6 milliseconds for haloperidol. No relation between QTc change and ziprasidone dose was observed across doses of 2–20mg in the fixed-dose trials.

The effects of multiple intramuscular injections of ziprasidone and haloperidol on QTc interval at observed  $C_{max}$  were evaluated in a randomised, single-blind study.<sup>[34,37]</sup> Among those subjects who completed the study, mean increases in QTc interval at  $C_{max}$  were 4.6 milliseconds for ziprasidone (n = 25) and 6.0 milliseconds for haloperidol (n = 24) after injection 1, and 12.8 milliseconds and 14.7 milliseconds after injection 2, respectively. Mean QTc interval increases over 24 hours after initial injection were 3.4 milliseconds (95% CI 0.86, 5.92) for ziprasidone and 6.3 milliseconds (95% CI 3.58,

**Table IV.** Change in corrected QT interval (QTc) from baseline to last observation in phase II/III intramuscular ziprasidone trials<sup>[9]</sup>

Treatment group	No. of patients	Baseline QTc (msec) <sup>a</sup>	Final QTc (msec) <sup>a</sup>	Mean change
All trials, ziprasidone doses $\geq 5$ mg	445	405.2 (335.0–465.1)	405.3 (334.8–494.8)	0.1
Haloperidol doses ranged from 2.5mg to a maximum of 40 mg/day	137	405.5 (335.0–465.1)	406.1 (348.7–454.3)	0.6
<b>Fixed-dose trials</b>				
Ziprasidone				
2mg	91	413.2 (377.5–460.0)	413.3 (362.6–452.1)	0.1
5mg	74	410.4 (349.9–455.5)	410.7 (357.1–494.8)	0.3
10mg	138	412.7 (353.2–465.1)	411.4 (372.3–445.1)	-1.3
20mg	109	410.7 (364.5–454.3)	411.5 (361.3–466.2)	0.8
all doses $\geq 5$ mg	321	411.5 (349.9–465.1)	411.2 (357.1–494.8)	-0.2
Haloperidol	95	411.1 (368.2–465.1)	411.1 (349.9–454.3)	-0.1
<b>Flexible-dose trials</b>				
Ziprasidone	124	389.0 (335.0–433.6)	390.0 (334.8–437.0)	1.0
Haloperidol	42	392.8 (335.0–437.6)	395.0 (348.7–436.2)	2.3

a Values are expressed as mean (range).

8.95) for haloperidol. No subject had a QTc interval >500 milliseconds.

Another way of assessing safety in terms of QT interval prolongation is to examine the percentage of patients who experience a QTc interval >500 milliseconds, which is indicative of a higher risk of torsade des pointes.<sup>[38]</sup> In a clinical trial evaluating the QT/QTc-interval prolonging effect of intramuscular ziprasidone in patient volunteers, no QTc interval values >500 milliseconds were recorded, compared with 2 of 2988 patients (0.06%) for oral ziprasidone versus 1 of 440 patients (0.23%) for placebo in the clinical trial database for the oral formulation.<sup>[3]</sup>

### 5.3.2 Blood Pressure

Clinically significant orthostatic hypotension was a significant limitation to intramuscular administration of chlorpromazine, and contributed to the decline in its use. In contrast to chlorpromazine, the binding affinity of ziprasidone for  $\alpha_1$ -adrenoceptors is 30- and 4-fold weaker than its binding affinity for 5-HT<sub>2A</sub> and D<sub>2</sub> receptors, respectively (table III).<sup>[22]</sup> Consistent with this weak antagonist binding, ziprasidone has a modest potential to induce orthostatic hypotension, which can result in dizziness, tachycardia and syncope.<sup>[3]</sup> The incidence of ziprasidone-associated postural hypotension was 5% in two short-term, open-label trials of sequential intramuscular/oral ziprasidone (one fixed-dose [5, 10 or 20mg four times daily; n = 306] and 1 flexible-dose [5–20mg up to four times daily; n = 132]).<sup>[9,33]</sup> In the fixed-dose study, ziprasidone was given over 3 days, in doses up to 80mg at the shortest recommended intervals, to 306 clinically-stable patients with psychosis. Blood pressure measurements were obtained prior to each intramuscular dose, and 30 and 60 minutes following each dose. Median changes in systolic and diastolic blood pressures ranged from -1 to 5mm Hg for ziprasidone and from -1 to 4mm Hg for haloperidol. Haloperidol was administered in a clinically determined flexible dose with median number of doses 2 (range 1–4) and mean daily dose of 11mg. Significant changes in blood pressure were isolated and transient, and not considered clinically meaningful.<sup>[9,33]</sup>

Two of 281 patients receiving ziprasidone in these two sequential intramuscular/oral trials discontinued ziprasidone because of hypertension, and one patient discontinued because of tachycardia. Tachycardia was reported as a treatment-emergent adverse event in the 5, 10 and 20mg dose groups (2.9%, 11.3% and 7.6%, respectively), compared with 6.0% for haloperidol. No patient withdrew because of hypotension.<sup>[9,33]</sup>

Observed rates of changes in standing diastolic blood pressure and tachycardia appeared higher in the ziprasidone group than in the haloperidol group. However, that could represent an artifact of the sampling difference rather than a meaningful increased risk, because patients receiving ziprasidone had more vital sign measurements than haloperidol patients per trial design.<sup>[9]</sup> Thus, a sampling bias could have inflated the risk attributable to ziprasidone relative to haloperidol. Results from a database of >5000 appropriately-timed measurements of the effect of intramuscular ziprasidone (up to 80 mg/day) showed no clinically meaningful adverse effects on blood pressure and heart rate.

## 6. Drug-Drug Interactions

Drug-drug interactions (DDIs) can be pharmacodynamic and/or pharmacokinetic. The potential for ziprasidone to inhibit the metabolism of other drugs is low because it has little effect on drug metabolising enzymes. Inferences about the potential for the intramuscular formulation of ziprasidone to interact with other drugs is extrapolated from studies of oral ziprasidone, as all DDI studies were conducted with the oral formulation.<sup>[3]</sup>

### 6.1 Pharmacokinetic Considerations

Aldehyde oxidase, which mediates two-thirds of the metabolism of ziprasidone, is well characterised and does not appear to play as important a role in the metabolism of drugs overall as do CYP enzymes, which mediate the bulk of the metabolism of most other drugs, including all other atypical and conventional antipsychotics. DDIs mediated by an effect on aldehyde oxidase are not known. CYP3A4 isoenzyme is responsible for an estimated 50% of all

known drug metabolism. Inhibition and induction of this enzyme is a clinically important mechanism in some pharmacokinetic DDIs. Based on *in vitro* studies using human liver microsomes, CYP3A4 plays a minor role in the metabolism of ziprasidone.<sup>[3,18]</sup> Consistent with these *in vitro* data, results of two clinical interaction studies in 31 patients with schizophrenia<sup>[39]</sup> and in 14 healthy volunteers<sup>[40]</sup> showed only a 35–40% increase in ziprasidone exposure with concomitant administration of ketoconazole, a virtual knockout CYP3A4 inhibitor. Additionally, a placebo-controlled trial in 25 healthy volunteers<sup>[41]</sup> found a 35% decrease in ziprasidone exposure with concomitant administration of carbamazepine, a CYP3A4 inducer. Hence, drugs that affect CYP3A4 would not be expected to significantly cause changes in exposure to ziprasidone.<sup>[18]</sup> By avoiding first-pass metabolism, the above effects seen with oral ziprasidone would predictably be less with intramuscular ziprasidone.

Whereas CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone, CYP1A2 may contribute to a much lesser extent.<sup>[18]</sup> Hence, cigarette smoking, which induces CYP1A2,<sup>[3,42]</sup> is unlikely to influence its pharmacokinetics. *In vivo* studies demonstrated no effect of ziprasidone on the pharmacokinetics of dextromethorphan, estrogen, progesterone or lithium.<sup>[3]</sup> No clinically significant interactions with alcohol (ethanol) have been reported. The potential for interaction with commonly used street drugs, including amphetamines, phencyclidine, cannabis and some opioids, has not been studied. Cocaine and heroin are primarily metabolised by carboxyesterases through ester hydrolysis to benzoylecgonine and morphine, respectively.<sup>[43]</sup> Although the effect of ziprasidone on the activity of these enzymes is unknown, there is nothing in the chemical structure of ziprasidone to suggest a possible interaction. Morphine is metabolised by glucuronidation and CYP N-demethylation. There is no information regarding the effects of ziprasidone on glucuronyltransferases.

## 6.2 Pharmacodynamic Considerations

In assessing potential DDIs with intramuscular ziprasidone, the pharmacodynamics are likely to be more important than pharmacokinetics because the intramuscular formulation does not undergo first-pass metabolism and short-term administration of the intramuscular preparation (i.e. limited to 1–3 days) does not lead to any appreciable build-up of the drug. In contrast, a rapid increase in drug concentration at receptor sites can acutely alter human physiology and thus interact pharmacodynamically with other drugs. For example, significant lowering of blood pressure as a result of the high binding affinity of a drug, such as clozapine, for  $\alpha_1$ -adrenoceptors compared with D<sub>2</sub> receptors can be increased by concomitant treatment with a  $\beta$ -adrenoceptor antagonist or diuretic. Also, the high affinity of clozapine for H<sub>1</sub> receptors can cause sedation and potentiate the sedative effects of agents such as alcohol and benzodiazepines. In contrast, the relatively low affinity of ziprasidone for  $\alpha_1$ -adrenoceptors and even lower relative affinity for H<sub>1</sub> receptors compared with D<sub>2</sub> receptors is consistent with the observation that intramuscular ziprasidone has a low potential to cause orthostatic hypotension or sedation and predicts lower potential for having additive or synergistic effects with other blood pressure-lowering or sedative agents.

Although there is no evidence of any adverse pharmacodynamic interaction between drugs known to prolong the QTc interval and ziprasidone, there is a caution against prescribing ziprasidone in combination with other drugs that are known to prolong the QT interval (i.e. arsenic trioxide, dofetilide, dolasetron, gatifloxacin, halofantrine, levacetylmethadol, mefloquine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin or tacrolimus).<sup>[3]</sup> There are no data regarding the safety of administering intramuscular ziprasidone to patients already taking oral ziprasidone, thus this practice is not recommended.<sup>[3]</sup>

## 7. Conclusion

Rapid and effective control of agitation in patients with acute psychosis is required to minimise

the risk of harm and allow for the initiation of long-term management. Ziprasidone, which is approximately 100% bioavailable in the intramuscular formulation, has been shown to be an effective treatment for the acute control of agitation. After a single intramuscular injection, peak serum concentrations are typically reached within 30–60 minutes and the mean  $t_{1/2\beta}$  is between 2–5 hours.

Exposure to intramuscular ziprasidone is linear and hence predictable. Change in AUC is dose proportional and  $C_{\max}$  has been shown to increase in a dose-related fashion between ziprasidone 5 and 10mg, although the increase was somewhat less than proportional between ziprasidone 10 and 20mg. Little to no drug accumulation occurs with repeated administration for up to 3 days and serum concentrations are low 12–18 hours after the last intramuscular injection. Once improvement on measures of psychopathology has been noted, the lack of significant drug accumulation means that persistent levels of ziprasidone do not have to be considered when switching from intramuscular to oral ziprasidone therapy.

Although intramuscular ziprasidone has not been systematically evaluated in patients  $\geq 65$  years of age or in patients with renal or hepatic impairment,<sup>[3]</sup> results from the nine-study pharmacokinetic model discussed<sup>[10]</sup> indicate that age, sex, race and concomitant benzodiazepine administration do not significantly affect intramuscular ziprasidone pharmacokinetic parameters. In addition, the model showed that baseline liver and renal functions were not significantly affected by the drug. These results are consistent with those from other clinical studies of oral ziprasidone; however, hepatic impairment would be expected to increase the AUC of ziprasidone since ziprasidone is cleared substantially by the liver. The tolerability and efficacy of ziprasidone has not been established in paediatric populations.<sup>[3]</sup>

There is low risk of pharmacokinetic DDIs which is further reduced by the metabolic profile of ziprasidone, which is primarily metabolised via aldehyde oxidase-mediated reduction, whereas CYP-mediated pathways that may pose a major risk of

DDIs, play a less important role. No inhibitors or inducers of aldehyde oxidase have been identified. To date, clinical interactions with the oral formulation have been reported with only two drugs, ketoconazole and carbamazepine. In neither case was the magnitude of the interaction considered clinically relevant. No interactions are expected with compounds often used by patients with schizophrenia, including lithium and lorazepam, or with commonly used street drugs, alcohol or tobacco. Unlike conventional antipsychotics, ziprasidone has not been associated with a high incidence of EPS. Clinically significant prolongation of the QTc interval is rare.

Once an acute episode is controlled, data indicate that patients can be safely moved to maintenance therapy with oral ziprasidone. Given the need for a rapid-acting intramuscular antipsychotic with good tolerability, intramuscular ziprasidone has the potential to be valuable in the management of patients with acute psychotic agitation.

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Dr Preskorn personally owns no stock in any pharmaceutical company other than what might have been purchased in externally managed accounts.

His activities with the pharmaceutical industry have included serving as a consultant and researcher at all phases of drug development (preclinical through to registration) and as a sponsored speaker at a wide variety of educational programmes. He has served, or is serving in one or more of the following capacities: as a principal investigator, on the Speakers' Bureau, and/or as a consultant for the following companies: Abbott Laboratories, AstraZeneca, Aventis, Bayer, Biovail, Boehringer-Ingelheim, Bristol-Myers Squibb, E. Merck, Eisai, Eli Lilly, GlaxoSmithKline, Forest, Hoffman-LaRoche, Innapharma, Janssen, Johnson & Johnson, Lundbeck, Merck, Neurosearch, Novartis, Organon, Otsuka, Pfizer Inc., Sention, Solvay, Sommerset, Sumitomo, Wyeth, and Yamanouchi.

Dr Preskorn was the principal investigator on a number of phase I studies with both intravenous and intramuscular for-

mulations of ziprasidone, as well as phase II and III efficacy trials of the intramuscular formulation.

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