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Spotlight on Ziprasidone in Schizophrenia and Schizoaffective Disorder[1]

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Contents

Abstract

Ziprasidone is a novel antipsychotic agent with a pharmacological profile distinct from that of other currently available novel or classical antipsychotics. In preclinical studies, ziprasidone was predicted to have efficacy against positive, negative and affective symptoms of schizophrenia with a favourable tolerability profile, including a low propensity to induce extrapyramidal adverse effects.

The drug has been administered orally to >300 patients with an acute exacerbation of schizophrenia or schizoaffective disorder in published 4- to 6-week randomised, double-blind trials. When given twice daily at dosages of between 80 and 160 mg/day, ziprasidone produced significantly greater improvements in overall symptomatology than placebo. In the largest study, ziprasidone 80 or 160 mg/day was also significantly more effective than placebo in reducing negative symptoms and, at 160 mg/day, was significantly more effective than placebo in improving depressive symptoms in patients with associated clinically significant depression. Data from a 4-week trial indicate that ziprasidone 160 mg/day has similar efficacy to haloperidol 15 mg/day.

Ziprasidone 40 to 160 mg/day was more effective than placebo with respect to prevention of impending relapse and improvement of negative symptoms in 294 stable patients with chronic schizophrenia who were treated for up to 1 year. In addition, significantly more ziprasidone than haloperidol recipients achieved

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a negative symptom response in a 28-week study involving 301 stable patients with chronic or subchronic schizophrenia.

In general, oral ziprasidone is well tolerated with an overall incidence of adverse events similar to placebo. Importantly, the drug has a low propensity to induce extrapyramidal effects and a negligible effect on bodyweight. Ziprasidone is associated with slight prolongation of the QTc interval; the clinical significance of this is not yet clear. The drug does not appear to be associated with sustained elevation of plasma prolactin levels. Preliminary data indicate that long-term oral ziprasidone treatment is well tolerated.

Ziprasidone is the only novel antipsychotic currently available in a rapid-acting intramuscular formulation. Short-term treatment with intramuscular ziprasidone was effective and well tolerated in patients with acute agitation associated with psychosis. In addition, intramuscular ziprasidone reduced agitation scores by a significantly greater extent than haloperidol in a study involving patients with acute agitation associated with psychosis.

Conclusions: Ziprasidone is a promising new antipsychotic that has shown significant efficacy in the oral treatment of patients with schizophrenia or schizoaffective disorder. The drug is well tolerated with a low propensity to induce extrapyramidal effects and a negligible effect on bodyweight. In addition, intramuscular ziprasidone shows efficacy and good tolerability in the treatment of acute agitation associated with psychotic disorders.

1. Pharmacodynamic Properties

Ziprasidone is a dopamine D_2 receptor antagonist and a serotonin 5-HT_{2A} receptor antagonist with a higher *in vitro* affinity for the 5-HT_{2A} receptor than for the D_2 receptor.[1,2] It is thought that a high 5-HT_{2A} to D_2 ratio may be partly responsible for the enhanced therapeutic efficacy and low propensity for extrapyramidal adverse effects seen with some of the newer antipsychotics.[3-10] The results of positron emission tomography studies in healthy volunteers indicate that single doses of oral ziprasidone of ≥40mg achieve high levels of occupancy of the D_2 and 5-HT_{2A} receptors.[11-15]

Ziprasidone also has high affinity for 5-HT_{2C}, 5-HT_{1A} and 5-HT_{1D} receptors, moderate affinity for α_1-adrenergic and histamine H_1 receptors, low affinity for α_2-adrenergic receptors and minimal affinity for muscarinic M_1 receptors.[1,2] Ziprasidone acts as an antagonist at 5-HT_{2C} receptors and as an agonist at 5-HT_{1A} receptors. Ziprasidone has also been shown to inhibit the reuptake of serotonin and noradrenaline (norepinephrine) into rat brain synaptosomes.[1]

The effects of ziprasidone in rat models were consistent with its *in vitro* pharmacology and predict clinical antipsychotic efficacy with a low potential for extrapyramidal adverse effects.[1,16,17]

Ziprasidone therapy does not appear to be associated with sustained elevation of prolactin levels. During treatment with ziprasidone 4 to 160 mg/day, mean predose serum prolactin levels did not significantly change from baseline and returned to baseline within 12 hours of drug administration in patients with schizophrenia or schizoaffective disorder in a 4-week study.[18] In contrast, mean predose prolactin levels rose significantly during administration of haloperidol 15 mg/day and were still elevated 12 hours after dosing. Mean prolactin levels decreased from 30.4 to 23.6 μg/L in patients with schizophrenia who received ziprasidone for 1 year.[19] Similarly, reductions from baseline in prolactin levels were seen in switching studies in which patients with schizophrenia or schizoaffective disorder were switched from treatment with classical antipsychotics or risperidone to treatment with ziprasidone.[20]

2. Pharmacokinetic Properties

In healthy volunteers who received multiple doses of ziprasidone 20 to 60mg twice daily, the maximum plasma concentration (C_{max}) of ziprasidone ranged from 44.6 to 139.4 μg/L, the area under the plasma concentration-time curve from 0 to 12 hours (AUC_{12}) ranged from 259.2 to 1027.9 μg • h/L and the time to C_{max} (t_{max}) ranged from 3.7 to 4.7 hours.[21] In general, C_{max} and AUC_{12} values increased proportionally with dose. Another study involving healthy men found that systemic exposure to ziprasidone was greater when the drug was administered directly after food compared with under fasting conditions.[22]

Approximately two-thirds of the metabolic clearance of ziprasidone occurs via aldehyde oxidase-mediated reduction, and less than one-third of the metabolic clearance of the drug is accounted for by cytochrome P450 (CYP)–mediated oxidation.[23] CYP3A4 is the principal enzyme thought to be responsible for the formation of ziprasidone sulphoxide and ziprasidone sulphone, two of the major ziprasidone metabolites.[24] The terminal phase half-life ($t_{½}$) of the drug following multiple administration of ziprasidone 20 to 60mg twice daily ranged from 4.8 to 10 hours.[21]

Differences in pharmacokinetics between healthy volunteers and patients with mild to moderate hepatic impairment or varying degrees of renal impairment, or in the elderly were not considered clinically significant.[25-27]

Studies in healthy volunteers showed that coadministration of ziprasidone did not affect the pharmacokinetics of dextromethorphan,[28] a combined oral contraceptive (levonorgestrel plus ethinylestradiol)[29] or lithium.[30] In addition, coadministration of cimetidine or an aluminium hydroxide/magnesium hydroxide preparation did not affect the pharmacokinetics of ziprasidone to a clinically significant extent.[31] Coadministration of ketoconazole[32] or carbamazepine[33] had statistically significant effects on the pharmacokinetics of ziprasidone, but these were not considered clinically relevant.

Following administration of intramuscular ziprasidone 5 to 20mg, the C_{max} ranged from 76 to 244 μg/L, the AUC_{∞} ranged from 229 to 846 μg • h/L and the t_{max} ranged from 0.5 to 0.7 hours. The $t_{½}$ was ≤3 hours (2.2 to 3 hours).[34]

3. Therapeutic Efficacy

3.1 Short-Term Treatment

When given twice daily, oral ziprasidone 80 to 160 mg/day demonstrated significantly greater clinical efficacy than placebo in two short-term (4- or 6-week), double-blind, randomised, fixed-dose, multicentre studies involving patients with an acute exacerbation of schizophrenia or schizoaffective disorder.[35,36] Results from both trials revealed significantly greater reductions from baseline in Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI) severity scores in ziprasidone 80, 120 and 160 mg/day recipients, compared with placebo recipients, with a trend towards dose response.[35,36] In addition, Positive and Negative Syndrome Scale (PANSS) total scores were significantly reduced from baseline in ziprasidone 80 and 160 mg/day recipients in one of the studies.[36] With regard to negative symptoms, significantly greater reductions from baseline in PANSS negative subscale scores were seen in ziprasidone 80 and 160 mg/day recipients, compared with placebo recipients, in one of the studies.[36] However, no significant between-group difference in the change in Scale of Assessment of Negative Symptoms scores was seen in the other study.[35] Among patients with clinically significant depressive symptoms at baseline, a significantly greater reduction from baseline in Montgomery-Åsberg Depression Rating Scale scores was seen in ziprasidone 160 mg/day recipients, compared with placebo recipients, in one study,[36] and a significantly greater reduction from baseline in BPRS depression cluster scores was seen in ziprasidone 120 mg/day recipients, compared with placebo recipients, in the other study.[35]

In terms of improvement in BPRS and CGI severity scores, oral ziprasidone 160 mg/day had

similar efficacy to haloperidol 15 mg/day in a 4-week, double-blind, randomised, multicentre study involving patients with chronic or subchronic schizophrenia or schizoaffective disorder who either had an acute exacerbation of their illness or had experienced only a partial response to prior antipsychotic therapy.[18] Furthermore, oral ziprasidone 80 or 160 mg/day had similar efficacy to olanzapine 5 to 15 mg/day at improving BPRS scores, CGI severity scores and PANSS total and PANSS positive and negative subscale scores, according to the results of a 6-week, double-blind, randomised, multicentre study, available as an abstract, involving patients with an acute exacerbation of schizophrenia or schizoaffective disorder.[37]

Switching from classical antipsychotics, risperidone or olanzapine to flexible-dose ziprasidone was associated with improved symptom control in three uncontrolled 6-week studies, available as abstracts and posters, involving stable patients with schizophrenia or schizoaffective disorder who switched treatment because of inadequate efficacy or poor tolerability.[20,38] In two other uncontrolled switching studies (of 6 and 12 weeks' duration), switching from haloperidol[39] or intramuscular depot antipsychotics[40] to ziprasidone was associated with sustained symptom control in patients with chronic schizophrenia or schizoaffective disorder.

3.2 Long-Term Treatment

Long-term treatment with oral ziprasidone appears to be effective in the treatment of stable patients with chronic schizophrenia, according to the results of two double-blind, randomised studies. In the 1-year, placebo-controlled study, significantly greater improvements from baseline in PANSS negative subscale scores were seen in ziprasidone 40, 80 or 160 mg/day recipients, compared with placebo recipients.[41] Moreover, improvement from baseline in Global Assessment of Functioning scores was significantly greater in ziprasidone 80 or 160 mg/day recipients than in placebo recipients. Ziprasidone 40, 80 and 160 mg/day recipients were also significantly less likely than placebo recipients to experience impending relapse (40.5, 34.6 and 35.8 *vs* 70.8%).[42]

In the second long-term (28-week) study, patients were randomised to receive flexible-dose ziprasidone 80 to 160 mg/day or haloperidol 5 to 15 mg/day. Improvements from baseline in psychopathology scores were seen in both treatment groups, although the improvements tended to be greater in ziprasidone, compared with haloperidol, recipients. Significantly more ziprasidone, compared with haloperidol, recipients experienced a PANSS negative symptom response (48 *vs* 32%).[43]

3.3 Intramuscular Use

Intramuscular ziprasidone is effective in patients with acute agitation associated with an underlying psychotic disorder. Reductions from baseline in Behavioural Activity Rating Scale scores were seen in two 24-hour studies comparing the use of intramuscular ziprasidone 2mg with ziprasidone 10 or 20mg. In both studies, the higher dose of ziprasidone was significantly more effective than the lower dose. In each study, PANSS total, PANSS agitation items and CGI severity scores were reduced from baseline in both treatment groups.[44,45]

Intramuscular ziprasidone was associated with significantly greater reductions in BPRS total, BPRS agitation items and CGI severity scores than intramuscular haloperidol in a nonblind, randomised study involving patients with acute agitation associated with psychosis.[46] Patients received intramuscular treatment for 3 days followed by 4 days of oral therapy. Further reductions in BPRS total, BPRS agitation items and CGI severity scores were seen after the switch to oral therapy in both treatment groups.

4. Tolerability

The overall incidence of adverse events was similar in oral ziprasidone 40 to 160 mg/day recipients and placebo recipients in two short-term, double-blind, randomised, multicentre studies involving patients with an acute exacerbation of schizophrenia or schizoaffective disorder (75 to

89% *vs* 75 and 86%).[35,36] Adverse events reported more frequently in ziprasidone 80 or 160 mg/day recipients, compared with placebo recipients, included dyspepsia (9 and 14 *vs* 9%), nausea (14 and 7 *vs* 9%), dizziness (9 and 17 *vs* 9%) and somnolence (19 and 19 *vs* 5%) in one study;[36] in the other study, ziprasidone 40 or 120 mg/day recipients, compared with placebo recipients, were more likely to experience abdominal pain (11 and 2 *vs* 8%), dyspepsia (11 and 6 *vs* 6%), nausea (7 and 6 *vs* 4%), constipation (7 and 11 *vs* 4%), coryzal symptoms (7 and 4 *vs* 2%) and rash (7 and 2 *vs* 0%).[35] Oral ziprasidone was associated with a low incidence of movement disorders in both studies; extrapyramidal syndrome occurred in 2 to 7% of ziprasidone 40 to 160 mg/day recipients, compared with 1 and 2% of placebo recipients.[35,36] In addition, oral ziprasidone had negligible effect on bodyweight.[35,36] Elevations in cholesterol, triglyceride and random glucose levels were the most commonly reported laboratory test abnormalities.[35,36]

In a 6-week study, median bodyweight (+3.3 *vs* +0.5kg)[47] and body mass index (+1.17 *vs* +0.24)[48] increased from baseline by a significantly greater extent in olanzapine than in ziprasidone recipients. Olanzapine, compared with ziprasidone, was also associated with significantly greater increases from baseline in fasting total cholesterol (+20 *vs* –1 mg/dl), low density lipoprotein cholesterol (+13 *vs* –1 mg/dl) and fasting triglyceride (+26 *vs* –2 mg/dl) levels.[47] In addition, median fasting plasma insulin levels and insulin resistance increased from baseline by a smaller extent in ziprasidone, compared with olanzapine, recipients.[47]

In a 1-year placebo-controlled study involving stable patients with chronic schizophrenia, adverse events were reported in 71.8 to 73.7% of oral ziprasidone 40 to 160 mg/day recipients and in 77.3% of placebo recipients.[41] The most commonly reported adverse events included anxiety, agitation and insomnia. Clinically significant bodyweight gain (increase in bodyweight of ≥7%) occurred in 5 to 11% of ziprasidone recipients, although the median bodyweight change was –1, –2 and –3kg in recipients of ziprasidone 40, 80 and 160 mg/day, respectively.[41]

In a 28-week study involving stable patients with chronic or subchronic schizophrenia, oral ziprasidone 80 to 160 mg/day recipients were more likely than haloperidol 5 to 15 mg/day recipients to experience vomiting, nausea or somnolence, and haloperidol recipients were more likely than ziprasidone recipients to experience dry mouth or dizziness.[43] Movement disorders occurred in 14.9% of ziprasidone recipients and 40.5% of haloperidol recipients.[43] Mean bodyweight increased by 0.3kg in men who received ziprasidone and by 0.8kg in women who received ziprasidone; these increases were similar to those observed in patients receiving haloperidol.[43]

With regard to cardiovascular adverse events, oral ziprasidone therapy was associated with small increases in the QTc interval in several studies.[20,35,47] Pooled data from trials involving 4571 patients who received oral ziprasidone at dosages of up to 160 mg/day indicate that mean prolongation of the QTc interval was 5.9 to 9.7 msec.[49] A QTc interval of >500 msec was seen in 0.06% of ziprasidone recipients and 0.23% of placebo recipients. In a study specifically designed to assess the effect of ziprasidone on QTc prolongation,[23] the QTc interval was prolonged by a greater extent in ziprasidone recipients than in risperidone, olanzapine, quetiapine or haloperidol recipients (although it should be noted that the 95% confidence intervals for ziprasidone, risperidone and quetiapine overlapped).[50] Importantly, the QTc prolongation associated with ziprasidone was not exacerbated by concomitant administration of the CYP3A4 inhibitor ketoconazole.[50] Ziprasidone therapy was associated with a low incidence of orthostatic hypotension.[36]

Intramuscular ziprasidone was generally well tolerated in two 24-hour studies involving patients with acute agitation associated with an underlying psychotic disorder.[44,45] The overall incidence of adverse events ranged from 35.2 to 43.9% in recipients of ziprasidone 2 to 20mg. The most com-

monly reported adverse events included headache, injection site pain, somnolence and nausea. Orthostatic hypotension was reported in two recipients of intramuscular ziprasidone 20mg. Intramuscular ziprasidone 5 to 20mg was better tolerated than intramuscular haloperidol 2.5 to 10mg in a study involving patients with acute agitation associated with an underlying psychotic disorder.[46] Adverse events occurred in 31.1% of ziprasidone recipients and in 50% of haloperidol recipients. Extrapyramidal adverse effects were reported in no ziprasidone recipients and in 21.4% of haloperidol recipients.

5. Dosage and Administration

Oral ziprasidone has been approved in the US[23] and in numerous other countries worldwide[51] for use in the treatment of schizophrenia. In the US, the initial recommended dosage of ziprasidone is 20mg twice daily; this may be titrated to a maximum dosage of 80mg twice daily.[23] Ziprasidone should be administered with food. Dosage adjustments are not needed in patients with renal or hepatic impairment or on the basis of age, gender or race. In Europe, it is recommended that ziprasidone be started at a dosage of 40mg twice daily and titrated to a maximum dosage of 80mg twice daily (if needed).[52] Maintenance therapy should comprise the lowest effective ziprasidone dosage (20mg twice daily may be sufficient).

US prescribing information states that ziprasidone is contraindicated in patients with uncompensated heart failure, recent acute myocardial infarction or a known history of QT prolongation.[23] The use of ziprasidone in combination with other drugs known to prolong the QTc interval should be avoided. In addition, clinicians should be alert to the identification of other agents that have consistently been shown to prolong the QTc interval; such drugs should not be prescribed in combination with ziprasidone. Given that ziprasidone therapy may be associated with orthostatic hypotension, caution should be exercised in administering ziprasidone to patients with cardiovascular disease, cerebrovascular disease or conditions that may predispose patients to hypotension. The effects of certain antihypertensives may be enhanced by concomitant administration of ziprasidone. In addition, caution should be used when ziprasidone is administered in combination with centrally acting drugs. Ziprasidone should be discontinued in patients who develop a rash for which an alternative aetiology cannot be found.

Intramuscular ziprasidone is available for use in a number of European countries[51,52] and has been deemed approvable by the US Food and Drug Administration[53] for use in agitated patients with schizophrenia or schizoaffective disorder.

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References

1. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995 Oct; 275: 101-13
2. Zorn SH, Lebel LA, Schmidt AW, et al. Pharmacological and neurochemical studies with the new antipsychotic ziprasidone. In: Palomo T, Beninger R, Archer T, editors. Interactive monoaminergic basis of brain disorders. Madrid: Fundación Cerebro y Mente, 1999: 377-93
3. Altar CA, Wasley AM, Neale RF, et al. Typical and atypical antipsychotic occupancy of D_2 and S_2 receptors: an autoradiographic analysis in rat brain. Brain Res Bull 1986; 16: 517-25
4. Bersani G, Grispini A, Marini S, et al. Neuroleptic-induced extrapyramidal side effects: clinical perspectives with ritanserin (R 55667), a new selective 5-HT_2 receptor blocking agent. Curr Ther Res 1986; 40 (3): 492-9
5. Meltzer HY, Matsubara S, Lee J-C. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1,

D-2 and serotonin$_2$ pK_i values. J Pharmacol Exp Ther 1989; 251 (1): 238-46
6. Meltzer HY, Shigehiro M, Lee J-C. The ratios of serotonin$_2$ and dopamine$_2$ affinities differentiate atypical and typical antipsychotic drugs. Psychopharmacology (Berl) 1989; 25: 390-2
7. Meltzer HY. The mechanism of action of novel antipsychotic drugs. Schizophr Bull 1991; 17 (2): 263-87
8. Leysen JE, Janssen PMF, Schotte A, et al. Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and clinical effects: role of $5HT_2$ receptors. Psychopharmacology (Berl) 1993; 112 (1 Suppl.): S40-54
9. Goldstein JM. Pre-clinical pharmacology of new atypical antipsychotics in late stage development. Expert Opin Invest Drugs 1995; 4: 291-8
10. Kapur S, Remington G. Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. Annu Rev Med 2001; 52: 503-17
11. Miceli JJ, Gunn KP, Rubin RH, et al. $5HT_2$ and D_2 receptor occupancy of ziprasidone in healthy volunteers [poster]. Presented at the 35th Annual Meeting of the American College of Neuropsychopharmacology; 1998 Dec 8-10; San Juan, Puerto Rico
12. Bench CJ, Lammertsma AA, Dolan RJ, et al. Dose dependent occupancy of central dopamine D_2 receptors by the novel neuroleptic CP-88,059-01: a study using positron emission tomography and ^{11}C-raclopride. Psychopharmacology (Berl) 1993 Sep; 112: 308-14
13. Bench CJ, Lammertsma AA, Grasby PM, et al. The time course of binding to striatal dopamine D_2 receptors by the neuroleptic ziprasidone (CP-88,059-01) determined by positron emission tomography. Psychopharmacology (Berl) 1996 Mar; 124: 141-7
14. Fischman AJ, Bonab AA, Babich JW, et al. Positron emission tomographic analysis of central 5-hydroxytryptamine$_2$ receptor occupancy in healthy volunteers treated with the novel antipsychotic agent, ziprasidone. J Pharmacol Exp Ther 1996; 279: 939-47
15. Buckley PF. Ziprasidone: pharmacology, clinical progress and therapeutic promise. Drugs Today 2000; 36 (8): 583-9
16. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. Neuropsychopharmacology 1998 Feb; 18: 63-101
17. Brooks EW, Mansbach RS. Effects of the novel antipsychotic ziprasidone on drug-disrupted prepulse inhibition in the rat [abstract]. Soc Neurosci Abstr 1997; 23 (2): 1953
18. Goff DC, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1998; 18: 296-304
19. Ananth JV, Burgoyne KS, Smith MW, et al. Prolactin levels in patients taking risperidone and ziprasidone [abstract]. American Psychiatric Association 2001 Annual Meeting; 2001 May 5-10; New Orleans (LA)
20. Simpson G, Potkin S, Weiden P, et al. Benefits of ziprasidone in stable outpatients with schizophrenia switched from conventional antipsychotics, olanzapine or risperidone [poster]. 13th Congress of the European College of Neuropsychopharmacology; 2000 Sep 9-13; Munich
21. Miceli JJ, Wilner KD, Hansen RA, et al. Single- and multiple-dose pharmacokinetics of ziprasidone under non-fasting conditions in healthy male volunteers. Br J Clin Pharmacol 2000; 49 Suppl. 1: 5S-13S
22. Hamelin BA, Allard S, Laplante L, et al. The effect of timing of a standard meal on the pharmacokinetics and pharmacodynamics of the novel atypical antipsychotic agent ziprasidone. Pharmacotherapy 1998; 18: 9-15
23. Pfizer. GEODON™ (ziprasidone HCl) prescribing information [online]. Available from URL: http://www.pfizer.com [Accessed 2002 Mar 26]
24. Prakash C, Kamel A, Cui D, et al. Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. Br J Clin Pharmacol 2000; 49 Suppl. 1: 35S-42S
25. Everson G, Lasseter KC, Anderson KE, et al. The pharmacokinetics of ziprasidone in subjects with normal and impaired hepatic function. Br J Clin Pharmacol 2000; 49 Suppl. 1: 21S-6S
26. Aweeka F, Jayesekara D, Horton M, et al. The pharmacokinetics of ziprasidone in subjects with normal and impaired renal function. Br J Clin Pharmacol 2000; 49 Suppl. 1: 27S-33S
27. Wilner KD, Tensfeldt TG, Baris B, et al. Single- and multiple-dose pharmacokinetics of ziprasidone in healthy young and elderly volunteers. Br J Clin Pharmacol 2000; 49 Suppl. 1: 15S-20S
28. Wilner KD, Demattos SB, Anziano RJ, et al. Ziprasidone and the activity of cytochrome P450 2D6 in healthy extensive metabolizers. Br J Clin Pharmacol 2000; 49 Suppl. 1: 43S-7S
29. Muirhead GJ, Harness J, Holt PR, et al. Ziprasidone and the pharmacokinetics of a combined oral contraceptive. Br J Clin Pharmacol 2000; 49 Suppl. 1: 49S-56S
30. Apelsoff G, Mullet D, Wilner KD, et al. The effects of ziprasidone on steady-state lithium levels and renal clearance of lithium. Br J Clin Pharmacol 2000; 49 Suppl. 1: 61S-4S
31. Wilner KD, Hansen RA, Folger CJ, et al. The pharmacokinetics of ziprasidone in healthy volunteers treated with cimetidine or antacid. Br J Clin Pharmacol 2000; 49 Suppl. 1: 57S-60S
32. Miceli JJ, Smith M, Robarge L, et al. The effects of ketoconazole on ziprasidone pharmacokinetics – a placebo-controlled crossover study in healthy volunteers. Br J Clin Pharmacol 2000; 49 Suppl. 1: 71S-6S
33. Miceli JJ, Anziano RJ, Robarge L, et al. The effect of carbamazepine on the steady-state pharmacokinetics of ziprasidone in healthy volunteers. Br J Clin Pharmacol 2000; 49 Suppl. 1: 65S-70S
34. Miceli JJ, Wilner KD, Tensfeldt TG. Pharmacokinetics of intramuscular ziprasidone in healthy volunteers [abstract]. American Psychiatric Association 2001 Annual Meeting; 2001 May 5-10; New Orleans (LA)
35. Keck Jr P, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology (Berl) 1998; 140: 173-84
36. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Neuropsychopharmacology 1999 May; 20: 491-505
37. Simpson GM, O'Sullivan RL, Siu C. Zipasidone versus olanzapine in schizophrenia: results of a double-blind trial [abstract]. American Psychiatric Association 2001 Annual Meeting; 2001 May 5-10; New Orleans (LA)
38. Simpson GM, Potkin SG, Weiden PJ, et al. Benefits of ziprasidone in stable outpatient schizophrenics switched from conventional antipsychotics, olanzapine, or risperidone [abstract]. Int J Neuropsychopharmacol 2000 Jul; 3: S157-8

39. Stip E. Haloperidol to ziprasidone switching strategies in schizophrenia [abstract]. American Psychiatric Assocation 2001 Annual Meeting; 2001 May 5-10; New Orleans (LA)
40. Hirsch SR. Replacement of depot antipsychotic therapy with oral ziprasidone [abstract]. American Psychiatric Association 2001 Annual Meeting; 2001 May 5-10; New Orleans (LA)
41. Arató M, O'Connor R, Meltzer H, et al. Ziprasidone: efficacy in the prevention of relapse and in the long-term treatment of negative symptoms of chronic schizophrenia [poster]. Presented at the 10th Annual Meeting of the European College of Neuropsychopharmacology; 1997 Sep 13-17; Vienna
42. Arató M, O'Connor R, Meltzer H, et al. Ziprasidone: efficacy in the prevention of relapse and in the long-term treatment of negative symptoms of chronic schizophrenia [abstract]. Eur Neuropsychopharmacol 1997 Sep; 7 Suppl. 2: S214
43. Hirsch S, Power A, Kissling W. A 28-week comparison of flexible-dose ziprasidone with haloperidol in outpatients with stable schizophrenia [poster]. American Psychiatric 1999 Annual Meeting; 1999 May 15-20; Washington, DC
44. Lesem MD, Zajecka JM, Swift RH, et al. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. J Clin Psychiatry 2001; 62 (1): 12-8
45. Daniel DG, Potkin SG, Reeves KR, et al. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind randomized trial. Psychopharmacology (Berl) 2001; 155: 128-34
46. Brook S, Lucey JV, Gunn KP, et al. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. J Clin Psychiatry 2000 Dec; 61 (12): 933-41
47. Glick I, Romano SJ, Simpson G, et al. Insulin resistance in olanzapine- and ziprasidone-treated patients: results of a double-blind, controlled 6-week trial [poster]. American Psychiatric Association 2001 Annual Meeting; 2001 May 5-10; New Orleans (LA)
48. Simpson G, Romano S, Horne R, et al. Ziprasidone vs olanzapine in schizophrenia: results of a double-blind trial [poster]. American Psychiatric Association 2001 Annual Meeting; 2001 May 5-10; New Orleans (LA)
49. Romano SJ. Cardiovascular safety profile of ziprasidone: clinical development data [abstract]. American Psychiatric Association 2001 Annual Meeting; 2001 May 5-10; New Orleans (LA)
50. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001; 158 (11): 1774-82
51. Pfizer. Pfizer to launch Zeldox in 9 European Union countries beginning next month: new antipsychotic medicine will provide important new treatment option for patients with schizophrenia [media release] [online]. Available from URL: http://www.pfizer.com [Accessed 2002 Mar 8]
52. Pfizer. Zeldox (ziprasidone) prescribing information [in Swedish] [online]. Available from URL: http://www.pfizer.se [Accessed 2002 Feb 18]
53. Pfizer Inc. FDA advisory committee recommends approval of Pfizer's injectable schizophrenia medicine ziprasidone [media release] [online]. Available from URL: http://www.pfizer.com [Accessed 2002 Feb 22]

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