Ziprasidone

A Review of its Use in Schizophrenia and Schizoaffective Disorder

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Data Selection

Sources: Medical literature published in any language since 1980 on 'ziprasidone', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were 'ziprasidone' and ('schizophrenia' or 'schizophrenic' or 'schizoaffective' or 'psychoses'); EMBASE and AdisBase search terms were 'ziprasidone' and ('schizophrenia' or 'schizophrenic' or 'schizoaffective'). Searches were last updated 26 October 2006.

Selection: Studies in patients with schizophrenia or schizoaffective disorder who received ziprasidone. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Ziprasidone, schizophrenia, schizoaffective disorder, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Ziprasidone (Geodon®, Zeldox®) is an atypical antipsychotic agent with a unique neurotransmitter receptor-binding profile. The oral formulation is indicated for the treatment of adult patients with schizophrenia and the intramuscular formulation for the control of acute agitation in these patients.

In adult patients with schizophrenia or schizoaffective disorder, oral ziprasidone was effective at a dosage of 40–80mg twice daily in patients experiencing a phase of acute illness, and at a dosage of 20–80mg twice daily in those with chronic schizophrenia or schizoaffective disorder, including those who were symptomatically stable. Ziprasidone offers the advantage over most other atypical antipsychotic agents of being available in a fast-acting intramuscular formulation for control of acute agitation, thus providing clinicians with the option to safely and effectively transition to longer-term treatment with the oral formulation. Although careful consideration should be given to the propensity for ziprasidone to cause corrected QT (QTc) interval prolongation, albeit at a relatively low incidence, the drug generally has a favourable tolerability profile of low extrapyramidal syndrome (EPS) liability, neutral bodyweight gain, and potentially low propensity for metabolic complications. Thus, ziprasidone is an effective option for the management of patients with schizophrenia or schizoaffective disorder, with the intramuscular formulation providing a useful option for the treatment of acute agitation in these patients.

Pharmacological Properties

Ziprasidone is a potent serotonin 5-HT_{2A} and dopamine D₂ receptor antagonist. It has a higher binding affinity for the 5-HT_{2A} receptor than the D₂ receptor, which may, in part, explain the beneficial effects the drug has against the negative symptoms of schizophrenia and the low risk for EPS. The pharmacological profile of ziprasidone suggests a low potential for bodyweight gain, which was confirmed in clinical trials in patients with schizophrenia or schizoaffective disorder. In addition, ziprasidone was not associated with dyslipidaemia.

The oral formulation of ziprasidone 20–60mg twice daily is well absorbed, with a maximum plasma drug concentration of 45–139 ng/mL. Systemic exposure was greater in the fed state than in the fasted state; thus oral ziprasidone should be taken with food. Ziprasidone is extensively metabolised in the liver, with <5% of the unchanged drug excreted in the urine or faeces. The terminal elimination half-life ($t_{1/2}$) of oral ziprasidone was 5–10 hours. Peak plasma concentrations were achieved within 1 hour of a dose of intramuscular ziprasidone 10 or 20mg. The $t_{1/2}$ of the intramuscular formulation is 2–3 hours. Currently available data suggest there are no pharmacokinetic drug interactions that necessitate dosage adjustment of ziprasidone.

Therapeutic Efficacy

Oral ziprasidone 40–80mg twice daily was shown to be as effective as oral risperidone, haloperidol and olanzapine in the treatment of acute exacerbations of schizophrenia or schizoaffective disorder in short-term (6- or 8-week) trials. With longer-term treatment (≥ 12 weeks) in patients with chronic schizophrenia, the efficacy of oral ziprasidone was not significantly different from that of haloperidol and was equivalent to that of amisulpride; however, oral olanzapine showed superior efficacy to ziprasidone. In the clinical practice setting in patients with chronic schizophrenia in the CATIE study, which evaluated the time to discontinuation from treatment for any reason, the efficacy of oral olanzapine or risperidone was superior to that of oral ziprasidone. Nevertheless, in well controlled extension studies, the antipsychotic efficacy of ziprasidone was not significantly different from that of olanzapine or risperidone over the longer term in patients with an acute exacerbation of symptoms.

The intramuscular formulation of ziprasidone (5–20mg) rapidly reduced acute agitation in adult patients with psychotic disorders.

Tolerability

Ziprasidone is well tolerated; the most frequent treatment-emergent adverse events were CNS- or gastrointestinal system-related, the majority of which were of mild to moderate severity. Treatment-related serious adverse events were infrequent. The tolerability profile of oral ziprasidone was similar to that of placebo over 52 weeks; however, asthenia occurred more frequently with ziprasidone. In other longer-term trials, ziprasidone was associated with more treatment-emergent insomnia, vomiting, psychosis and 'decreased appetite' than olanzapine but less 'weight increase' and 'appetite increase' than olanzapine.

The drug was associated with a low propensity to cause EPS or EPS-related adverse events. Oral and intramuscular ziprasidone was associated with less severe EPS than haloperidol. Although there is potential for clinically significant QTc prolongation, in clinical trials, the drug was infrequently associated with this event when administered at recommended dosages.

1. Introduction

Schizophrenia is a chronic, debilitating illness associated (in the majority of patients) with recurrent episodes of acute exacerbation of schizophrenic symptoms that punctuate the stable phase, where patients are asymptomatic or where symptoms are less severe than in the acute phase.^[1] Schizoaffective disorder shares some prominent symptoms both with schizophrenia and mood disorder,^[2] but a widely accepted clinical definition of this disorder is not currently available.^[3] Worldwide, schizophrenia affects roughly 24 million people;^[4] epidemiological data for schizoaffective disorder are lacking.

Pharmacological management is the cornerstone of treatment of schizophrenia.^[1] Antipsychotic agents are used to target the psychotic symptoms of

schizoaffective disorder^[2] (discussion of the treatment of the other symptoms of this disorder are beyond the scope of this review). In addition, patients with mental disorders, including schizophrenia or schizoaffective disorder, may experience acute agitation, which is broadly defined as mental tension accompanied by motor restlessness, and can lead to behavioural dyscontrol.^[5] Antipsychotics and benzodiazepines are used to reduce the patient's level of agitation.^[1] Where a patient refuses oral medication, rapidly-acting parenteral formulations may be administered.^[1] Atypical antipsychotic agents (second-generation antipsychotics; e.g. risperidone, olanzapine, quetiapine, aripiprazole) appear to offer the advantage over the conventional antipsychotic drugs (first-generation antipsychotics;

Table I. Overview of the pharmacodynamic properties of oral ziprasidone (ZIP)***In vitro* neurotransmitter receptor binding**

High affinity for serotonin 5-HT_{1A}, 5-HT_{1B/1D}, 5-HT_{2A}, 5-HT_{2C} and dopamine D₂ receptors,^[21] moderate affinity for α_1 -adrenergic and histamine H₁ receptors, and very low affinity for α_2 -adrenergic and muscarinic receptors^[10]

Agonist at 5-HT_{1A} receptors^[10,21,22]

Antagonist at D₂,^[10] 5-HT_{2A} and 5-HT_{2C}^[10] and α_1 -^[10] or α_2 C^[23]-adrenergic receptors

***In vivo* receptor occupancy in patients with schizophrenia or schizoaffective disorder**

Minimum dose of oral ZIP 60mg twice daily (mean plasma ziprasidone concentration of 50 ng/mL) required for 60% D₂ receptor occupancy (i.e. for antipsychotic efficacy)^[24]

High ratio of 5-HT₂ : D₂ striatal receptor occupancy with oral ZIP 40–160 mg/day^[24]

Pharmacodynamic effects predicted by receptor binding profile or receptor occupancy

Improved cognitive deficits and mood symptoms via high 5-HT_{2C}/D₂ receptor affinity ratio and agonist action at 5-HT_{1A} receptors^[11]

Antidepressant and/or anxiolytic efficacy due to agonism at 5HT_{1A} receptors, 5-HT_{1B/1D} antagonism and inhibition of serotonin and noradrenaline (norepinephrine) uptake^[21]

Orthostatic hypotension and sedation less likely because of lower α_1 -adrenergic than D₂ receptor affinity^[21]

Reduced anticholinergic adverse effects via lower affinity for M₁ receptors relative to D₂ receptors^[11]

Minimal bodyweight gain via agonism at 5-HT_{1A} receptors and general activation of serotonin and adrenoreceptors that counteract high affinity for 5-HT_{2C} receptors, which are associated with bodyweight gain (reviewed by Casey and Zorn^[25]) and lower affinity for M₁ receptors relative to affinity for D₂ receptors^[21] (see section 2.1 for effect of ZIP on bodyweight in patients)

Lower propensity for extrapyramidal syndrome than haloperidol because striatal D₂ receptor occupancy of ZIP was lower than that of haloperidol (60% vs 75%; $p = 0.002$)^[26]

Pharmacodynamic effects in animal models

Dose-dependently inhibited amphetamine-induced hyperactivity, apomorphine-induced stereotypy and quipazine-induced head twitches (indicative of antagonism at 5-HT_{2A} receptors)^[10]

Inhibited conditioned avoidance behaviour (indicative of antipsychotic efficacy via D₂ receptor blockade)^[10]

Six-fold higher dose required for blocking head twitch than for inhibition of amphetamine-induced hyperactivity (indicative of high 5-HT_{2A} : D₂ affinity ratio)^[10]

Equivocal effects on neurocognition;^[27,28] no effect on phencyclidine-induced social interaction deficits (model of negative symptoms, e.g. social withdrawal);^[29] and suppressed olanzapine-induced hyperphagia^[30]

e.g. haloperidol, perphenazine) of greater efficacy against the negative symptoms of schizophrenia and a lower likelihood of causing extrapyramidal syndrome (EPS).^[6] However, atypical antipsychotic agents are associated with varying degrees of adverse effects, such as bodyweight gain, metabolic changes and hyperprolactinaemia,^[6] and may be selected between based on these differences.^[11]

Ziprasidone (Geodon®, Zeldox®)¹ is an atypical antipsychotic with a receptor binding profile distinct from other atypical antipsychotic agents (reviewed previously^[7]) that is approved for the treatment of the symptoms of bipolar mania and schizophrenia in the US^[8] and numerous EU countries.^[9] This review focuses on the efficacy and tolerability of ziprasidone in patients with schizophrenia or schizoaffective disorder.

2. Pharmacodynamic Properties

Ziprasidone is a potent serotonin 5-HT_{2A} and dopamine D₂ receptor antagonist, with a 6-fold higher binding affinity for the 5-HT_{2A} receptor than the D₂ receptor (table I).^[10] As with most other atypical antipsychotic drugs, the therapeutic efficacy of ziprasidone against the negative symptoms of schizophrenia and low liability for EPS (compared with conventional antipsychotic drugs) may in part be explained by the high *in vivo* serotonin 5-HT_{2A} to dopamine D₂ receptor occupancy ratio,^[11] although the exact mechanism of action of ziprasidone is unclear. The pharmacodynamic properties of ziprasidone have been reviewed previously,^[7,11] thus only an overview is provided in this section and in table I.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Although transient increases in serum prolactin levels were observed in healthy volunteers^[12] and in patients with schizophrenia,^[13] ziprasidone was generally not associated with marked, sustained elevations in prolactin levels in clinical trials (see section 4 for trial design details).^[14-19] Serum prolactin levels >110% of the upper limit of normal were reported in 25% of ziprasidone and 65% of haloperidol recipients at any timepoint.^[14] Clinically significant elevations of prolactin (>35 ng/mL in men and >50 ng/mL in women) were reported in 14% of men and 22% of women receiving ziprasidone compared with 59% of men and 77% of women receiving risperidone.^[19] Between-group differences in the incidence of elevated prolactin levels were not significant in a trial versus olanzapine.^[20] The incidence of hyperprolactinaemia-associated adverse events is reviewed in section 5.

Ziprasidone is likely to prolong the corrected QT (QTc) interval to a greater extent than other second-generation antipsychotic agents.^[8,31] In a study examining the effects of thioridazine and second-generation antipsychotic agents on the QTc interval in patients with psychotic disorders,^[31] the increase in QTc interval from baseline with ziprasidone 160 mg/day was 15.9ms, while that with thioridazine 300 mg/day was 30.1ms. Increases in QTc interval with quetiapine 750 mg/day, risperidone 6–8 mg/day, olanzapine 20 mg/day or haloperidol 15 mg/day were 1.7–7.1ms. In patients receiving intramuscular ziprasidone 20mg then 30mg (the latter dosage is 50% higher than the maximum recommended) or haloperidol 7.5mg then 10mg, changes in QTc interval at peak plasma concentrations of the drug after each injection were 4.6 and 12.8ms for ziprasidone, and 6.0 and 14.7ms for haloperidol.^[8] No subjects in either of these studies experienced QTc interval prolongation of ≥500ms; the clinical significance of increases in the QTc interval with ziprasidone is not clear. Consequently, the advantages of treatment with the drug should be weighed against the potential to cause QTc interval prolongation.^[8]

2.1 Effect on Bodyweight and Metabolic Profile

Ziprasidone was generally associated with a minimal increase (<1kg)^[8,14,16,32,33] or reduction^[15,18,20,34-37] in bodyweight in trials of short-term^[8,14,32,34] or longer-term^[15,16,18,20,33,35-37] duration (some data available as an abstract plus poster^[16,35]). For example, the mean changes in bodyweight from baseline in patients receiving ziprasidone were not significantly different from those observed in patients receiving haloperidol,^[14] but were significantly different from those observed in olanzapine recipients (−1.12 vs +3.06kg^[36] and −1.65 vs +2.53;^[20] $p < 0.001$).

The frequency of weight gain reported as an adverse event was similar with ziprasidone and placebo (0.4%).^[8] However, the incidence of clinically significant bodyweight gain (≥7% of bodyweight) with ziprasidone was significantly greater than with placebo in an analysis of pooled data (10% vs 4%; p -value not reported).^[8] In individual trials, clinically significant bodyweight gain was reported in 9% of ziprasidone and 18% of amisulpride recipients^[38] and in significantly fewer ziprasidone than olanzapine recipients (3% vs 16%; $p < 0.001$).^[20] Overall between-group differences for clinically important bodyweight gain were significant ($p < 0.01$) in two phases of the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial, occurring in 7%^[18] and 6%^[37] of ziprasidone recipients compared with 12–30% of patients receiving olanzapine, risperidone, quetiapine or perphenazine (see section 4.2.3 for trial design details).^[18,37]

Ziprasidone appears to have a low propensity to cause dyslipidaemia^[18,20,32,36,37] or adverse effects on glucose metabolism^[20,32,36,39] and had a generally more favourable effect on lipid levels than olanzapine (table II).^[20,32,36] In the CATIE study,^[18,37] cholesterol and triglyceride levels decreased numerically from baseline in ziprasidone and risperidone recipients but increased numerically in patients receiving olanzapine, quetiapine or perphenazine (the latter in phase 1 only^[18]) [statistical analyses vs baseline were not reported]. Between-group differences in cholesterol and triglyc-

Table II. Effect of oral ziprasidone (ZIP) compared with oral olanzapine (OLZ) on lipid levels in patients (pts) with schizophrenia or schizoaffective disorder. In these randomised, double-blind, multicentre, 6-,^[32] 24-,^[20] or 28-week^[36] flexible-^[32,36] or fixed-^[20] dose trials, changes from baseline at study-end were reported as mean^[20,36] or median^[32] values

Study	Regimen (mg/day)	Evaluable pts ^a	Triglyceride (mmol/L)		Total cholesterol (mmol/L)		HDL-cholesterol (mmol/L)		LDL-cholesterol (mmol/L)	
			baseline	change	baseline	change	baseline	change	baseline	change
Breier et al. ^[36]	ZIP 80–160	196–203	1.68	−0.24††	4.92	−0.33†	1.19	+0.02††	2.98	−0.27†
	OLZ 10–20	204–215	1.62	+0.39	4.97	+0.08	1.24	−0.06	3.00	+0.02
Kinon et al. ^{[20]b}	ZIP 80–160	129–146	2.19	−0.11†	5.16	−0.30	1.25	−0.01	2.95	−0.19
	OLZ 10–20	156–172	2.33	+0.15	5.24	−0.06	1.24	−0.05	3.04	−0.11
Simpson et al. ^{[32]b}	ZIP 80–160	106–113	1.39	−0.02†	4.78	−0.03††			2.95	−0.03††
	OLZ 5–15	105–120	1.40	+0.29*	4.75	+0.50*			2.79	+0.34*

a Analyses were modified intent-to-treat last observation carried forward;^[20,32,36] pt numbers were different for different lipid parameters.

b Values originally reported as mg/dL. To convert units from mmol/L to mg/dL, divide by 0.02586 for total cholesterol, HDL- and LDL-cholesterol, and by 0.01129 for triglycerides.

HDL = high-density lipoprotein; **LDL** = low-density lipoprotein; * $p < 0.001$ vs baseline; † $p < 0.05$, †† $p \leq 0.001$ vs OLZ.

eride levels favoured ziprasidone (and risperidone) over olanzapine, quetiapine and perphenazine ($p < 0.001$ for all comparisons).^[18,37] Additionally, changes from baseline in fasting insulin^[32,39] or glucose^[20,36] levels were not significantly different between patients receiving ziprasidone and those receiving olanzapine. However, the between-group difference in the mean change from baseline to study end in glycosylated haemoglobin levels was significantly different in a 24-week trial (−0.06% vs +0.06%; $p = 0.01$).^[20]

3. Pharmacokinetic Properties

This section provides an overview of the pharmacokinetics of oral and intramuscular ziprasidone. Pharmacokinetic parameters for oral ziprasidone 20–60mg twice daily and intramuscular ziprasidone 10 or 20mg are shown in table III.

Oral ziprasidone is well absorbed.^[8] Steady-state concentrations were achieved within 1–3 days of administration.^[8] Systemic exposure to ziprasidone after oral administration (measured by the area under the plasma concentration-time curve [AUC]) was dose-proportional (table III) and resulted in accumulation of the drug after multiple doses.^[12] The absolute mean oral bioavailability of a single 20mg dose in the fed state was about 60% in healthy volunteers.^[40] Systemic exposure to ziprasidone is

greater in the fed than fasted state;^[8,41] thus, oral ziprasidone should be taken with food (section 6).^[8]

Ziprasidone is >99% bound to plasma proteins, mainly albumin and α_1 -acid glycoprotein.^[8] After a single 5mg intravenous infusion, the volume of dis-

Table III. Summary of multiple-dose pharmacokinetics of oral ziprasidone (ZIP)^[12] and single-dose pharmacokinetics of intramuscular ZIP^[40] in adult healthy volunteers (vols) in randomised, double-^[12] or single-^[40] blind studies. Only recommended dosages are included. Mean values are presented

Regimen (no. of vols)	C _{max} (ng/mL)	AUC ₁₂ ^[12] or AUC _∞ ^[40] (ng • h/mL)	t _{max} (h)	t _{1/2} (h)
Oral ZIP^{a,b}				
20mg bid (6)	44.6	259.2	3.8	4.8
40mg bid ^c (6)	118.6	658.0	3.7	8.8
60mg bid ^d (6)	139.4	1027.9	4.7	10.0
Intramuscular ZIP^b				
10mg (6)	156	463	0.65	2.24
20mg (6)	244	846	0.71	2.97

a Multiple-dose pharmacokinetic parameters were assessed after 18 days' treatment.

b Oral ZIP administered immediately after a meal;^[12] intramuscular ZIP administered in fasted state.^[40]

c Vols received a single 20mg dose on d1, 20mg bid d4–d6, 40mg bid d7–d17 and a single 40mg dose on d18.

d Vols received a single 20mg dose on d1, 20mg bid d4–d6, 40mg bid d7–d9, 60mg bid d10–d17 and a single 60mg dose on d18.

AUC₁₂ = area under the plasma concentration-time curve (AUC) from time zero to 12h; **AUC**_∞ = AUC from time zero to infinity; **bid** = twice daily; **C**_{max} = maximum plasma drug concentration; **t**_{1/2} = terminal elimination half-life; **t**_{max} = time to reach C_{max}.

tribution at steady state was 1.03 L/kg in healthy volunteers.^[40]

Ziprasidone is extensively metabolised in the liver, predominantly via reduction by aldehyde oxidase and to a lesser extent via cytochrome P450 (CYP) 3A4 and CYP1A2.^[8] Approximately 66% of a dose is eliminated in the faeces and 20% in the urine; <4% and <1% of unchanged drug is excreted via these routes.^[8] Most of the pharmacological activity of ziprasidone is attributable to the parent drug.^[8] The terminal elimination half-life ($t_{1/2}$) of ziprasidone following multiple doses of oral ziprasidone 20–60mg twice daily was 4.8–10 hours (table III).^[12] The mean apparent systemic clearance was 5.08 mL/min/kg after a single 5mg intravenous infusion (healthy volunteers).^[40]

Single-dose pharmacokinetics of intramuscular ziprasidone 10 or 20mg in healthy volunteers indicated that although the maximum plasma drug concentration ($C_{\max}$) increased in a less than dose-proportional manner; systemic exposure (based on AUC values) increased in a dose-proportional manner.^[40] $C_{\max}$ occurred within 1 hour of administration (table III), and the drug exhibited a high bioavailability (100%) [5mg dose].^[40] The $t_{1/2}$ of intramuscular ziprasidone was 2–3 hours (table III).^[40]

Age, sex, race, renal or hepatic impairment or smoking status had no clinically significant effects (i.e. those requiring dosage adjustment) on the pharmacokinetic properties of oral ziprasidone.^[8] Intramuscular ziprasidone has not been formally evaluated in elderly patients or patients with hepatic or renal impairment.^[8] Nevertheless, in a population pharmacokinetic modelling study (available as an abstract),^[42] there were no significant correlations between the pharmacokinetics of intramuscular ziprasidone and age, sex or race and no correlation was seen between renal or liver function at baseline and ziprasidone clearance.^[42] However, since the cyclodextrin excipient of intramuscular ziprasidone is cleared renally, this formulation should be administered with caution in patients with impaired renal function.^[8]

Pharmacokinetic drug interactions with ziprasidone have been reviewed extensively elsewhere,^[7] thus a brief overview is presented (data were obtained from the manufacturer's US prescribing information^[8]). There were no clinically significant effects of cimetidine, an antacid (Maalox[®]), benztropine, propranolol or lorazepam on the pharmacokinetics of ziprasidone, or of ziprasidone on the pharmacokinetics of lithium, oral contraceptives or dextromethorphan.^[8] Although coadministration of ziprasidone with carbamazepine (a CYP3A4 inducer) reduced the AUC of ziprasidone by about 35% and coadministration with ketoconazole increased the AUC and $C_{\max}$ values of ziprasidone by approximately 35–40%, dosage adjustment is not required when these agents are coadministered with ziprasidone, because the drug is primarily metabolised by pathways other than CYP.^[8] Ziprasidone is not expected to interact with drugs metabolised by CYP enzymes, and little potential exists for drug interactions with other highly protein-bound drugs (e.g. warfarin or propranolol), according to *in vitro* studies.

4. Therapeutic Efficacy

The efficacy of ziprasidone in adults was evaluated in trials in patients experiencing acute exacerbation of schizophrenia or schizoaffective disorder (section 4.1) or in patients with chronic schizophrenia or schizoaffective disorder (including trials in patients who were symptomatically stable) [section 4.2], and in adult patients with acute agitation associated with psychosis (section 4.3). Although a trial in patients with treatment-resistant schizophrenia has been conducted, neither ziprasidone nor the comparator agent (chlorpromazine) are approved for this indication, and for this reason these data are not reviewed here.^[43] Only trials in ≥ 100 patients are discussed, except where available data are more limited. All studies, which were fixed- or flexible-dose trials, are published in full, with the exception of studies 115 and 104 (section 4.1) that are available only in a FDA review document,^[44] several extension studies^[16,45] and a study with the intramuscular formulation.^[46] Although two trials in-

cluded dosages other than those approved (studies 104 and 115),^[44] only recommended dosages of ziprasidone are discussed in this section.

Eligible patients, the majority of whom were male, had a mean age of 30–50 years and were diagnosed according to the DSM-III^[47] or DSM-IV^[48] criteria with schizophrenia, or in some trials,^[14,19,20,32,34,44,49–53] with either schizophrenia or schizoaffective disorder. However, patients with other psychotic disorders were included in most of the trials reviewed in section 4.3.^[51–53] The majority of patients had previously received antipsychotic treatment (where reported).^[15,18–20,33,34,37,50–53]

Some trials excluded patients who had previously not responded to treatment or had discontinued because of intolerable adverse events,^[14,15,18,20,32,33,36,37,44,49,50] or had received clozapine within the previous 7 days^[36] or 12 weeks.^[14,51,53] Most trials allowed concomitant medication (where reported); for example, lorazepam for sedation^[19] or benztropine for EPS.^[32] Efficacy analyses were for the intent-to-treat (ITT) population using last-observation-carried-forward (LOCF), unless specified otherwise.

4.1 In Patients in the Acute Phase of Schizophrenia or Schizoaffective Disorder

Seven trials have assessed the efficacy of ziprasidone in the treatment of the acute phase of schizophrenia or schizoaffective disorder; four are versus placebo,^[44,49,50] and three versus an active comparator.^[14,19,32] Inclusion criteria in trials evaluating the antipsychotic efficacy of ziprasidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder were a Positive and Negative Syndrome Scale (PANSS) total score of ≥ 59 ^[44] or ≥ 60 ;^[19,50] a Brief Psychiatric Rating Scale (BPRS) total score of ≥ 37 ^[44,49] or ≥ 40 ;^[14] a score of ≥ 4 on either a minimum of two core PANSS^[19,50] or BPRS^[44,49] items; a score of ≥ 3 on the Clinical Global Impressions Global Improvement (CGI-I);^[50] or a score of ≥ 4 on the CGI Severity of Illness (CGI-S) scale and a score of ≥ 4 on one of the PANSS positive items.^[32] Patient baseline characteristics were generally similar between treatment

groups.^[14,19,32,44,49,50] Symptom severity at baseline is shown in tables IV and V.

Where reported, primary efficacy endpoints included: the mean change from baseline in the PANSS total score^[19] or PANSS-derived BPRS (BPRSd)/BPRS total score;^[14,32,44,49] the BPRSd/BPRS core items score;^[44,49] the CGI-S score;^[14,19,44,49] or the CGI-I score at study end.^[14] Studies comparing ziprasidone with active comparators were equivalence trials. The basis for establishing equivalence is shown in table V.^[14,19,32]

4.1.1 Versus Placebo

Recipients of oral ziprasidone 60 or 80mg twice daily experienced significantly better antipsychotic efficacy than placebo recipients, according to reductions from baseline in BPRS/BPRSd total and core scores and CGI-S scores (table IV)^[44,49,50] [primary efficacy endpoints where specified^[44,49]]. Data were less consistent with lower dosages of ziprasidone (table IV). Nevertheless, the recommended initial dosage for acute treatment is 20^[8] or 40mg^[54] twice daily (section 6). In study 115, there was no evidence for a ziprasidone dose-response relationship (primary statistical analysis).^[44] Discontinuation rates were 36–58%,^[44,49,50] 46–68%^[44,49,50] and 44%^[44] in ziprasidone, placebo and haloperidol recipients, respectively.

4.1.2 Versus Active Comparators

The antipsychotic efficacy of ziprasidone treatment was equivalent to that of risperidone,^[19] olanzapine^[32] or haloperidol^[14] in patients experiencing an acute exacerbation of schizophrenic symptoms. Ziprasidone improved the PANSS total and negative symptom scores (table V). Criteria for equivalence were met for primary efficacy endpoints versus risperidone^[19] and olanzapine^[32] and for the mean change in the BPRS total score versus haloperidol (table V).^[14] In this latter trial, between-group differences in the mean change from baseline in CGI-S scores (table V) and study-end responder rates based on CGI-I scores (74% of ziprasidone vs 75% of haloperidol recipients) were not significant (also primary efficacy endpoints, but not designed to test for equivalence).^[14] Patients received the intramuscular formulation of zipra-

Table IV. The efficacy of oral ziprasidone (ZIP) in adult patients (pts) with acute exacerbation of schizophrenia or schizoaffective disorder in randomised, double-blind, placebo (PL)-controlled, multicentre, fixed-dose trials.^a Mean baseline (b/line) and changes from b/line scores are presented, and only recommended dosages are shown

Study [treatment duration (wk)]	Regimen (mg)	No. of evaluable pts ^c	BPRS/BPRSd total score ^b		BPRS/BPRSd core items score		PANSS total score		PANSS negative symptom subscale score		CGI-S score	
			b/line	change ^d	b/line	change ^d	b/line	change	b/line	change	b/line	change ^d
Study 115 ^[44] [6]	ZIP 20 bid	86	53.8	-4.9*	16.1	-2.3*	93.2	-7.5*	22.9	-1.5	4.9	-0.4*
	ZIP 60 bid	76	51.8	-5.2*	16.0	-2.2*	90.4	-8.6*	23.4	-2.1	4.9	-0.4*
	HAL 15 od	82	53.9	-8.8**	16.2	-4.1**	94.1	-15.2**	24.1	-3.1*	5.0	-0.8**f
	PL	80	54.3	-1.2	16.6	-0.9	93.3	-0.4	22.4	+0.2	4.9	-0.1
Study 104 ^[44] [4]	ZIP 20 bid	55	34.5	-5.4	13.0	-2.3					4.8	-0.3
	ZIP 40 bid	47	36.2	-2.6	12.8	-1.2					4.9	-0.2
	PL	47	33.4	-3.5	13.7	-2.2					5.0	-0.4
Daniel et al. ^[50]	ZIP 40 bid	104	56.5	-7.7* ^g	16.9	-3.4* ^g	98.2	-12.4* ^g	25.4	-3.1* ^g	4.8	-0.5* ^g
(study 114) [6]	ZIP 80 bid	103	55.0	-10.3** ^g	16.6	-4.5** ^g	95.8	-17.1** ^g	24.3	-3.9** ^g	4.8	-0.8** ^g
	PL	91	55.1	-3.4 ^g	16.4	-2.0 ^g	97.3	-5.4 ^g	24.9	-0.9 ^g	4.8	-0.2 ^g
Keck et al. ^[49]	ZIP 20 bid	43	36.5	-5.2	13.4	-2.6					4.7	-0.4
(study 106) [4]	ZIP 60 bid	41	36.6	-10.1*	13.6	-4.1					4.7	-0.6*
	PL	47	37.0	-4.1	13.9	-2.3					4.7	-0.2

a Although not permitted per protocol, a small number of pts in studies 104 and 115 received additional antipsychotic agents (n = 2–4 [ZIP]; n = 5 [HAL]; n = 4 or 9 [PL]).^[44]

b Study 115^[44] and Daniel et al.^[50] used the BPRSd scale; all others used the BPRS.

c Intent-to-treat last observation carried forward analyses were modified to include any pt who had a b/line assessment and at least one post-b/line assessment.^[44,49,50]

d Primary efficacy endpoints (where specified).^[44,49]

e In study 115, the primary statistical analysis was the ZIP dose-response relationship, and the efficacy of ZIP and HAL were not compared. A higher-than-recommended dosage (100mg bid) was investigated in study 115 and a lower-than-recommended dosage (5mg bid) in study 104; these data are not reviewed.

f 83 pts included in the intent-to-treat last observation carried forward analysis of this endpoint.

g Values estimated from graphs.

bid = twice daily; **BPRS** = Brief Psychiatric Rating Scale; **BPRSd** = PANSS derived BPRS; **CGI-S** = Clinical Global Impression of Severity Illness Scale; **HAL** = haloperidol; **od** = once daily; **PANSS** = Positive and Negative Syndrome Scale; * p < 0.05, ** p < 0.001 vs PL.

Table V. Comparative efficacy of ziprasidone (ZIP) in adult patients (pts) with acute exacerbation of schizophrenia or schizoaffective disorder in randomised, double-blind^[19,32] or nonblind and rater-blinded,^[14] multicentre, 6-^[14,32] or 8-^[19] week flexible-dose equivalence trials. Least squares mean (LSM)^[14,19,32] baseline (b/line) and changes from b/line scores are presented

Study	Regimen (mg)	No. of evaluable pts ^a	BPRS ^[14,32] or BPRSd ^[19] total score		BPRS ^[14,32] or BPRSd ^[19] core score		PANSS total score		PANSS negative symptom subscale score		CGI-S score	
			b/line	change	b/line	change	b/line	change	b/line	change	b/line	change
Addington et al. ^[19]	ZIP 40–80 bid PO	123	53.2	–15.2*	15.9	–5.5*	94.0	–25.8* ^{b,c}	24.7	–6.4*	4.7	–1.1* ^{b,c}
	RIS 3–5 bid PO	132	55.6	–15.9*	16.6	–6.0*	98.2	–27.3* ^b	25.5	–6.4*	4.9	–1.2* ^b
Brook et al. ^[14]	ZIP ≤40 mg/day IM (3d) ^d then ZIP 40–80 bid PO	429	57.0	–15.0* ^e							5.3	–1.4 ^b
	HAL ≤10 mg/day IM (3d) ^d then HAL 5–20 mg/day PO	138	57.0	–15.8 ^b							5.3	–1.5 ^b
Simpson et al. ^[32]	ZIP 40–80 bid PO	125	51.5	–11.5* ^{b,f,g}							4.9	–1.2 ^f
	OLZ 5–15 mg/day PO	129	50.7	–12.0* ^{b,f}							4.9	–1.2 ^f

a In the Addington et al.^[19] trial, evaluable pts were defined as those receiving the study drug for ≥14d with no major protocol violations or deviations. In the other two trials,^[14,32] analyses were for the modified intent-to-treat last observation carried forward pt population, defined as pts who received at least one dose of study medication and who had a b/line and/or post-b/line assessment.

b Primary endpoint.

c The predefined criterion for equivalence of a lower 95% CI limit of ≥0.60 for the ZIP : RIS ratio was met for the mean change from b/line in PANSS total score (ratio = 0.95; lower 95% CI limit = 0.78) and the CGI-S score (ratio = 0.87; lower 95% CI limit = 0.70). 124 evaluable pts in ZIP group for CGI-S data.

d ZIP IM administered as 10 or 20mg dose, with 2h between each 10mg dose and 4h between each 20mg dose, and HAL IM administered as 2.5 or 5mg dose, with 2h between each dose.

e The predefined criterion for equivalence of an upper 95% CI limit of ≤4 and a 95% CI including zero was met for the difference in LSM change from b/line in BPRS total score (95% CI –1.86, 3.47).

f Value estimated from a graph.

g The predefined criterion for equivalence of an upper 95% CI limit of ≤3.5 and a 95% CI including zero was met for the difference in LSM change from b/line in BPRS total score (95% CI –2.36, 3.18). 126 evaluable pts in OLZ group for BPRS total score data.

bid = twice daily; **BPRS** = Brief Psychiatric Rating Scale; **BPRSd** = PANSS derived BPRS; **CGI-S** = Clinical Global Impression of Severity Illness Scale; **HAL** = haloperidol; **IM** = intramuscular; **OLZ** = olanzapine; **PANSS** = Positive and Negative Syndrome Scale; **PO** = per oral; **RIS** = risperidone; * $p < 0.001$ vs b/line.

done or haloperidol for the first 3 days of treatment in this trial, thus the data presented are for both the intramuscular and oral phases.

The overall mean dosages of oral ziprasidone were 114.2,^[19] 129.9^[32] and 116.0^[14] mg/day, and of oral risperidone,^[19] olanzapine^[32] and haloperidol^[14] were 7.4,^[19] 11.3^[32] and 11.5^[14] mg/day, respectively. In one trial, the maximum allowed dosage of risperidone was 5mg twice daily,^[19] which is less than the maximum recommended dosage of 6mg with twice-daily administration^[55] (see section 7 for discussion).

In general, for secondary efficacy endpoints, the efficacy of ziprasidone was equivalent to that of risperidone^[19] and was not significantly different from that of haloperidol^[14] or olanzapine.^[32] Equivalent reductions from baseline in PANSS negative symptom scores and BPRSd total and core items scores (table V) were seen with ziprasidone or risperidone.^[19] Similarly, response rates (CGI-I score of 1 or 2 at last study visit; 50% vs 60% of patients) [ziprasidone : risperidone ratio = 0.84; lower limit of 95% CI = 0.67] and the least squares mean change from baseline in Global Assessment of Functioning (GAF) scores (+16.5 vs +15.6; ziprasidone : risperidone ratio = 1.06; lower limit of 95% CI = 0.81) were similar between these treatment groups (evaluable patient population).^[19] Baseline GAF scores were 38 and 35.^[19]

The efficacy of ziprasidone did not differ from that of haloperidol for the changes from baseline in the Covi Anxiety Scale (-1.31 vs -0.68) or BPRS subscale scores, except for the BPRS negative symptom subscale, for which ziprasidone was superior to haloperidol (-2.9 vs -2.2 [values estimated from a graph]; $p < 0.05$) [secondary efficacy endpoints].^[14] Baseline BPRS negative symptom subscale scores were ≈ 12 in both treatment groups and baseline Covi anxiety scale scores were 8.1 in patients receiving ziprasidone and 8.5 in patients receiving haloperidol.^[14] Moreover, the efficacy of ziprasidone was not different from that of olanzapine for study-end response rates (a $\geq 20\%$, 30% or 40% improvement from baseline in BPRS total score), changes from baseline in the Calgary

Depression Scale for Schizophrenia (CDSS) score or PANSS positive symptoms scores (all secondary efficacy endpoints).^[32]

Rates of overall discontinuation were significantly lower with olanzapine than with ziprasidone (37% vs 49%; $p < 0.05$); however, discontinuation because of lack of efficacy was not significantly different (9% vs 8%).^[32] Completion rates in other studies were between 63% and 71% of patients receiving ziprasidone,^[14,19] risperidone^[19] or haloperidol.^[14]

In the 6-month^[39] or 44-week^[16] double-blind extension studies of the short-term comparisons with olanzapine^[32] or risperidone,^[19] patients receiving oral ziprasidone ($n = 2-49$ ^[39] and 62^[16]) experienced improvements in their schizophrenic symptoms and global severity of illness over the long term (up to 1 year) that were not significantly different from those in patients receiving olanzapine ($n = 57-66$)^[39] or risperidone ($n = 77$).^[16]

The beneficial effects of oral ziprasidone 40-80mg twice daily on attention, memory, working memory, motor speed and executive functions did not differ from those observed with olanzapine 5-15mg once daily in a short-term comparison^[32] ($n = 49-73$ and 60-89) [cognitive data reported in separate publication^[56]], and in the double-blind, 6-month extension of this trial ($n = 62$ and 71).^[57]

4.2 In Patients with Chronic Schizophrenia or Schizoaffective Disorder

4.2.1 Comparative Clinical Trials

The efficacy of ziprasidone was evaluated versus placebo in a 52-week trial,^[15] and versus haloperidol,^[33] olanzapine^[20,36] and amisulpride^[38] in shorter-term (12-,^[38] 24-^[20] or 28-^[33,36] week) trials. Trials were of randomised, double-blind, multicentre design (see tables VI and VII for additional trial design details of studies versus active comparators).

All trials enrolled inpatients and/or outpatients with chronic disease; three^[15,33,38] excluded those who had recently experienced an acute exacerbation of symptoms. Two trials only enrolled patients who were symptomatically stable,^[15,33] one trial focused on patients with predominantly negative symp-

Table VI. Select inclusion or exclusion criteria and baseline patient disease characteristics in ziprasidone comparative clinical trials in patients (pts) with chronic schizophrenia or schizoaffective disorder. See table VII for trial design details of studies vs active comparators

Study (setting)	Mean disease duration (y)	Recent/current exacerbation excluded	Psychiatric rating scale score inclusion criteria
Arato et al. ^[15] (inpt)	21–23	Yes	CGI-S score ≤ 5
Breier et al. ^[36] (inpt or outpt)	≈ 16	No	BPRS total score ≥ 42 ; one of the PANSS positive symptom subscale items ≥ 4 ; CGI-S scores ≥ 4
Hirsch et al. ^[33] (outpt)	≈ 12	Yes	GAF score > 30 ; PANSS negative symptom subscale score ≥ 10
Kinon et al. ^[20a] (inpt or outpt)			MADRS total score ≥ 16 ; MADRS item two score ≥ 4
Olie et al. ^[38a] (outpt)		Yes	PANSS negative subscale score ≥ 6 points greater than PANSS positive subscale score

a Disease history and/or duration not stated.

BPRS = Brief Psychiatric Rating Scale; **CGI-S** = Clinical Global Impression of Severity Illness Scale; **GAF** = Global Assessment of Functioning; **MADRS** = Montgomery-Asberg Depression Rating Scale; **PANSS** = Positive and Negative Syndrome Scale.

toms^[38] and another^[20] enrolled patients with prominent symptoms of depression. All patient baseline characteristics were broadly similar between treatment groups, including baseline values for efficacy endpoints,^[15,20,33,36,38] apart from one trial where ziprasidone recipients had a lower mean age than olanzapine recipients (38 vs 40 years; $p = 0.04$)^[36] and another trial where the number of patients treated with antipsychotic agents within a 30-day period prior to baseline was greater in ziprasidone than olanzapine treatment groups (82% vs 71%; $p < 0.05$).^[20]

In the trial versus placebo, the primary efficacy endpoint was the Kaplan-Meier estimate of the time to relapse.^[15] Relapse was defined as a CGI-I score of ≥ 6 , a PANSS hostility or unco-operativeness item score of ≥ 6 on two consecutive days or any patient withdrawn from the study because of exacerbation of schizophrenic symptoms requiring further treatment.^[15] Primary efficacy endpoints in trials versus active comparators were the mean change from baseline in the CDSS total score (at week 8),^[20] PANSS total^[33,36] and/or negative symptom subscale scores^[33,38] and GAF^[33] scores. One of the four trials (i.e. the trial vs amisulpride^[38]) was an equivalence study (see table VII for criteria for establishing equivalence).

Versus Placebo

The probability of relapse at 1 year was significantly lower with twice-daily ziprasidone 20mg ($n = 71$), 40mg ($n = 68$) or 80mg ($n = 67$) than with placebo ($n = 71$) in patients with chronic stable disease; respective relapse rates were 43%, 35%, 36% and 77% (all $p \leq 0.002$ vs placebo) [primary efficacy endpoint].^[15] The majority of patients who experienced relapse did so in the first 6 months of the trial (61 of 71 patients in the ziprasidone group and 35 of 43 patients in the placebo group). In addition, all dosages of ziprasidone were superior to placebo for the mean change from baseline in PANSS total ($p \leq 0.001$), negative and positive symptom subscale (both $p < 0.05$) scores, CGI-S scores and GAF scores (both $p < 0.01$) [secondary efficacy endpoints].^[15]

The overall rates of discontinuation were 86% for placebo recipients and 55–58% for ziprasidone recipients.^[15] The investigators noted that the higher rate of discontinuation in the placebo group was probably due to the higher rate of relapse.

Versus Active Comparators

The antipsychotic efficacy of ziprasidone did not differ from that of haloperidol (table VII).^[33] No significant between-group difference was seen in mean change from baseline in PANSS total and negative symptom scores or GAF scores (primary endpoints). Likewise, there were no significant dif-

Table VII. Efficacy of oral ziprasidone (ZIP) compared with oral haloperidol (HAL),^[33] oral amisulpride (AMI)^[38] or oral olanzapine (OLZ)^[20,36] in adult patients (pts) with schizophrenia or schizoaffective disorder. Pts were either inpts^[20,36] and/or outpts^[20,33,36,38] with chronic disease, and in one trial,^[20] had moderate depressive symptoms (mean Montgomery-Asberg Depression Rating Scale [MADRS] score 27). Mean^[20,33,36] or least squares (LS) mean^[38] data from randomised, double-blind, multicentre trials with either a fixed^[20] or flexible^[33,36,38] drug dose

Study [duration (wk)]	Regimen (mg)	No. of evaluable pts ^a	PANSS total score		PANSS negative symptom subscale score		CGI-S		GAF	
			b/line	change	b/line	change	b/line	change	b/line	change
Breier et al. ^[36] [28]	ZIP 40–80 bid	261	101.8	–26.0 ^{b,c}	27.2	–6.3	4.8	–1.1 ^d		
	OLZ 10–20 od	268	99.5	–35.7 ^{††b}	26.4	–8.5 ^{††}	4.8	–1.6 ^{††}		
Hirsch et al. ^[33] [28]	ZIP 40–80 bid	110	73.5	–9.1 ^b	22.6	–3.6 ^b	4.2	–0.5	53.0	+3.2 ^b
	HAL 2.5–7.5 bid	117	73.7	–8.1 ^b	22.6	–3.0 ^b	4.2	–0.4	53.6	+2.5 ^b
Kinon et al. ^[20] [24] ^e	ZIP 80–160 mg/day	158	79.1	–8.3 ^f					46.0	+3.2
	OLZ 10–20 mg/day	168	79.6	–13.5 ^{†f}					45.6	+6.6 [†]
Olie et al. ^[38] [12]	ZIP 20–80 bid	50	NR	–14.1 [*]	31.0 ^g	–6.9 ^{*b,h}	NR	–0.7 [*]		
	AMI 50–100 bid	53	NR	–16.6 [*]	29.0 ^g	–8.1 ^{*b}	NR	–0.8 [*]		

a Analyses were intent-to-treat last observation carried forward. In the Hirsch et al.^[33] and Olie et al.^[38] trials, evaluable pts were those completing 14d^[33] or ≥4wk^[38] treatment with no study protocol violations^[33,38] and either ≥1 post-b/line assessment^[33] or an assessment at b/line and ≥1 post-b/line assessment.^[38] In the Kinon et al.^[20] trial, evaluable pts were those with an assessment at b/line and ≥1 post-b/line assessment, although pt numbers were not specified for PANSS data. The evaluable pt population was not described in the Breier et al.^[36] trial.

b Primary efficacy endpoint.

c The primary analysis was an MMRM, for which only the LS mean PANSS total endpoint scores (58 [OLZ] vs 67 [ZIP]) were reported (between-group difference –4.65; $p < 0.001$).

d 263 evaluable pts.

e Results from different dosage groups were reported together, and parameters reported in this table are all secondary efficacy endpoints.

f There was no significant between-group difference with a MMRM analysis.

g B/line value in randomised pts ($n = 60$ [ZIP] or 63 [AMI]).

h The predefined criterion for equivalence of 95% CI lower limit of >0.60 was met for the ratio of LS adjusted mean change from b/line in PANSS negative symptom subscale score (lower limit of 95% CI = 0.62). The between-group difference in LS adjusted mean change from b/line in this score was 1.16 (95% CI –1.09, 3.41; $p = 0.31$).

b/line = baseline; **bid** = twice daily; **CGI-S** = Clinical Global Impression Severity of Illness Scale; **GAF** = Global Assessment of Functioning; **MMRM** = mixed-effects model repeated measures; **NR** = not reported; **od** = once daily; **PANSS** = Positive and Negative Syndrome Scale; * $p < 0.001$ vs baseline; † $p < 0.05$, †† $p < 0.001$ vs ZIP.

ferences between ziprasidone and haloperidol in CGI-S scores or depressive symptoms (secondary endpoints).^[33] In this flexible-dose trial, patients received a modal dosage of ziprasidone 80 mg/day and haloperidol 5 mg/day. Less than half of the patients in either treatment group completed the study (45% of ziprasidone and 42% of haloperidol recipients) and 18% of patients in either treatment group discontinued therapy because of an insufficient clinical response.^[33]

Comparisons of ziprasidone with olanzapine therapy for up to 28 weeks in patients with schizophrenia generally showed that olanzapine had greater antipsychotic activity than ziprasidone.^[20,36] Olanzapine resulted in a significantly greater improvement from baseline in PANSS total score at study end than ziprasidone in the 28-week trial (table VII) [primary efficacy endpoint].^[36] In the other, 24-week trial,^[20] there was no significant difference in improvements from baseline in CDSS total scores between ziprasidone and olanzapine in the primary endpoint, which was assessed at 8 weeks (-6.1 vs -6.4) [baseline values not reported]. In general, secondary efficacy endpoint results, including those shown in table VII, and the study-end response rate (59% vs 43%; $p < 0.001$) in one trial^[36] and the mean change from baseline in Montgomery-Asberg Depression Rating Scale total score at 24 weeks in the other trial (-12.1 vs -9.15; $p = 0.003$)^[20] confirmed the superiority of olanzapine over ziprasidone. The 28-week trial was a flexible-dose trial,^[36] and patients received a mean modal dosage of ziprasidone 116 mg/day or olanzapine 15.3 mg/day. The 24-week trial was a fixed-dose trial in which patients received ziprasidone 80, 120 or 160 mg/day or olanzapine 10, 15 or 20 mg/day.^[20] Significantly more olanzapine than ziprasidone recipients completed treatment (60% vs 42%^[36] and 45% vs 30%;^[20] both $p < 0.01$ vs ziprasidone) and in one trial,^[36] the rate of therapy discontinuation because of an insufficient clinical response with olanzapine was half that with ziprasidone (7% vs 14%; $p = 0.02$).

The improvement in negative symptoms of schizophrenia with ziprasidone was equivalent to

that with amisulpride (assessed using mean change from baseline in PANSS negative symptom subscale scores in the evaluable population [primary endpoint; table VII]).^[38] Although significant improvements from baseline with either treatment were seen for secondary endpoints (PANSS total, CGI-S and BPRSd total scores; all $p < 0.001$ vs baseline) equivalence in the evaluable population was not established. The mean dose of ziprasidone was 118.0 mg/day and of amisulpride was 144.7 mg/day.^[38] A clinical response (>20% reduction from baseline in PANSS negative symptom subscale score at last assessment) was seen in 62% of ziprasidone and 74% of amisulpride recipients ($n = 50$ and 53) and overall completion rates were 70% and 79%.^[38]

4.2.2 Switching Trials

In three 6-week, noncomparative, multicentre, flexible-dose studies in stable symptomatic outpatients, switching from a prior antipsychotic agent to oral ziprasidone 20–80mg twice daily was effective regardless of the switching strategy used, with no significant difference between any two strategies in the overall rates for discontinuation from treatment or on any measures of antipsychotic efficacy (e.g. the mean change from baseline in PANSS total scores or CGI-S scores) [all three studies reported together].^[34] Treatment switching strategies were discontinuation of the previous antipsychotic agent the day before switching to ziprasidone; a 50% dose reduction of the prior antipsychotic in the first week of treatment with ziprasidone, followed by discontinuation of the prior treatment at the start of the second week of therapy with ziprasidone; and dose reduction of the prior antipsychotic 4 days after initiation of treatment with ziprasidone, followed by complete discontinuation at the start of the second week of therapy with ziprasidone.^[34] Prior antipsychotic treatments differed in each study, and were risperidone ($n = 58$), olanzapine ($n = 104$) or conventional antipsychotic agents ($n = 108$).^[34]

Significant (all $p < 0.05$ vs baseline) improvements in PANSS scores were observed in all three trials after 6 weeks,^[34] and the improvement was maintained for up to 1 year (median treatment dura-

tion 215 days) in an extension study (data pooled from the three studies [$n = 122$]).^[45] In addition, patients experienced small to modest improvements in cognitive function over 6 weeks (as reported in a separate publication^[58]).

4.2.3 In the Clinical Practice Setting

In the ≥ 18 -month, 3-phase CATIE trial, which was designed to assess the relative efficacy of several antipsychotics in the treatment of schizophrenia in a clinical practice setting, adult patients with chronic or recurrent schizophrenia, including those with acute exacerbation of symptoms or with medical or psychiatric comorbidities, were enrolled.^[59] At phase 1 baseline, the average duration since first treatment with an antipsychotic agent was 14 years, and 28% of patients had experienced exacerbation of symptoms in the previous 3 months.^[18] Phases 1 and 2 were randomised, multicentre trials;^[18,37] phase 1 assessed the comparative effectiveness of a first-generation antipsychotic (perphenazine) with numerous second-generation antipsychotics (olanzapine, risperidone, quetiapine or ziprasidone) in a double-blind manner,^[18,59] whereas phase 2 compared the effectiveness of ziprasidone with other second-generation antipsychotics.^[37] Those patients who discontinued phase 1 study drug ($n = 1052$) then selected between the 'efficacy' and the double-blind 'tolerability' pathways of the second phase of the trial;^[60] the 'efficacy' pathway ($n = 99$) is not discussed as ziprasidone was not included as a treatment option.^[60] The 'tolerability' pathway ($n = 444$) [hereafter simply referred to as phase 2 of the trial], was recommended to patients who discontinued their prior antipsychotic treatment because of poor tolerability. In this pathway, patients received an atypical antipsychotic not previously received, until completion either of 18 months' treatment in total across phases 1 and 2 or of 6 months of phase 2 treatment (which may have given ≥ 18 months' total duration across both phases).^[37] Phase 1 data are not discussed because primary comparative analyses with ziprasidone were conducted in phase 2.^[37] Although ziprasidone was approved for use in the US only after the trial began,^[18,37] addition of a ziprasidone treatment arm was per protocol; thus the ITT

'ziprasidone cohort' were those patients randomised after ziprasidone was added to the trial and included 889 of 1493 randomised patients in phase 1^[18] and 333 of 444 patients in phase 2.^[37] Phase 3 results are not currently available.

In CATIE phase 2,^[37] the median time to treatment discontinuation for any reason (primary efficacy endpoint) with ziprasidone 20–80mg twice daily ($n = 135$) was significantly shorter than that with olanzapine 7.5–30 mg/day ($n = 66$) or risperidone 1.5–6.0 mg/day ($n = 69$) [2.8 vs 6.3 and 7.0 months], but did not differ from that with quetiapine 200–800 mg/day ($n = 63$) [2.8 vs 4.0 months]. The overall between-group difference was significant ($p = 0.004$) [primary efficacy endpoint],^[37] as was the time to treatment discontinuation for any reason with ziprasidone in pairwise comparisons with olanzapine (Cox model hazard ratio of 0.61; 95% CI 0.43, 0.87; $p < 0.01$) and risperidone (0.60; 95% CI 0.42, 0.85; $p < 0.01$), but not with quetiapine (0.94; 95% CI 0.67, 1.31).^[37]

Although there was no significant between-group difference for the median time to discontinuation because of poor tolerability, the time to discontinuation because of lack of efficacy in the ziprasidone and quetiapine groups (4 months in each group) was shorter than in risperidone and olanzapine groups (8 and 9 months) [overall treatment difference of $p < 0.05$; secondary efficacy endpoint].^[37]

For other secondary efficacy endpoints, the antipsychotic efficacy of olanzapine and/or risperidone was superior to that of ziprasidone in terms of PANSS total and positive symptom subscale scores ($p < 0.05$ vs ziprasidone), but there were no significant differences between ziprasidone and these agents or quetiapine for changes from baseline in PANSS negative symptom or CGI-S scores (observed cases [OC] analyses, where reported).^[37]

The overall rate of discontinuation from treatment in both phases of CATIE was high (74%) and median treatment duration was only 6 months in phase 1^[18] and 4 months in phase 2.^[37] Mean modal dosages during phase 1^[18]/2^[37] were 112.8/115.9 mg/day (ziprasidone), 543.4/565.2 mg/day (quetiapine), 3.9/4.1 mg/day (risperidone), 20.1/20.5

mg/day (olanzapine) and 20.8 mg/day for perphenazine in phase 1.^[18] Dosages used for ziprasidone, quetiapine and risperidone were lower than optimal and may have confounded study results (see section 7).^[37]

4.2.4 Pharmacoeconomic Considerations

Treatment of schizophrenia is a considerable economic burden;^[1,61] despite a relatively low prevalence, the chronic nature of this disease means that treatment constitutes a relatively large proportion of the healthcare budgets of developed countries.^[62] Pharmacoeconomic data for ziprasidone are very limited.

A retrospective Spanish cost-effectiveness analysis (year of costing 2002) indicated that oral ziprasidone was dominant over oral haloperidol, risperidone and olanzapine in a modelled population of 1000 patients with chronic schizophrenia receiving treatment for 12 months; ziprasidone, the reference treatment, was associated with the lowest costs and the highest number of months where patients experienced controlled psychotic symptoms.^[62] The cost-effectiveness ratios, expressed as cost (€) per year per additional month with controlled psychotic symptoms, were €1035 for ziprasidone, €1084 for haloperidol, €1090 for olanzapine and €1087 for risperidone. Univariate sensitivity analyses generally confirmed ziprasidone as the dominant option. In this Markov model, which was conducted from a third party payer perspective and incorporated only direct medical costs, equivalent efficacy between treatment groups was assumed because the objective of the study was to evaluate the impact of adverse effects on costs (psychotic symptoms were not considered to be controlled if patients were hospitalised or were experiencing adverse events).^[62]

Another retrospective Spanish cost-effectiveness analysis indicated that ziprasidone may be cost-effective in preventing relapse in adult patients with chronic stable schizophrenia ($n = 218$) at a dosage of 80 mg/day, but not at dosages of 40 or 160 mg/day, compared with no treatment (placebo) over 1 year.^[63] The respective cost (€) per year per relapse avoided with ziprasidone was -€556.63, €124.74 and €1014.70. Relapse data were obtained from a

1-year placebo-controlled study discussed in section 4.2.1.^[15] Only direct costs (year of costing 2005) were included in this deterministic model conducted from the Spanish National Health System's perspective.^[63]

4.3 In Patients with Acute Agitation Associated with Psychosis

The efficacy of intramuscular ziprasidone in the management of acute agitation associated with psychosis has been investigated in two 24-hour, fixed-dose, randomised, double-blind, multicentre trials^[51,53] and has been compared with that of intramuscular haloperidol^[52] and intramuscular olanzapine^[46] in two 3-day fixed-^[46] or flexible^[52]-dose nonblind trials. In the latter trials, patients received the oral formulation of the study drugs for 4 days following 3 days' treatment with the intramuscular formulations; however, only data for the intramuscular formulations are reviewed in this section. All trials enrolled inpatients with acute agitation associated with their underlying psychotic disorder (e.g. schizophrenia,^[46,51-53] schizoaffective disorder,^[51-53] bipolar disorder with psychotic features,^[51,53] delusional disorder,^[51,52] schizophreniform disorder^[52] or psychotic disorder not otherwise specified^[51-53]). Study inclusion criteria in the 24-hour trials were a score of ≥ 3 on the PANSS agitation items (anxiety, tension, hostility and excitement) at screening and baseline.^[51,53] Patients were excluded if their current acute psychosis was related to substance abuse.^[51-53] Baseline patient characteristics and psychopathology scores were broadly similar between treatment groups.^[51-53]

In the fixed-dose trials, patients received intramuscular ziprasidone 2mg ($n = 38$)^[53] and $n = 54$ ^[51], 10mg ($n = 63$)^[51] or 20mg ($n = 41$)^[53] and $n = 20$ ^[46] or intramuscular olanzapine 10mg ($n = 23$).^[46] In the flexible-dose study,^[52] the initial and final doses of intramuscular ziprasidone were 10mg and 5–20mg ($n = 90$), and both the initial and final doses of intramuscular haloperidol were between 2.5 and 10mg ($n = 42$). Patients received a maximum of three^[46] or four^[51-53] doses per 24 hours. Maximum daily doses were ziprasidone 80mg^[52,53] or haloper-

idol 40mg.^[52] Each dose was administered at least 2–6 hours apart.^[51–53]

The primary efficacy endpoint was the mean Behavioural Activity Rating Scale (BARS) score 2 hours after the first dose in one 24-hour trial^[51] and at every 30-minute interval up to and including 4 hours after the first dose in the other 24-hour trial.^[53] The BARS is a seven-point scale, which assesses the level of activity of patients with acute agitation associated with psychosis, ranging in score from one to seven (1 = 'difficult to rouse', 2 = 'asleep but responds normally to verbal or physical contact', 3 = 'drowsy, appears sedated', 4 = 'quiet and awake [normal level of activity]', 5 = 'signs of overt activity, calms down with instruction', 6 = 'extremely or continuously active, not requiring restraint' and 7 = 'violent, requiring restraint').^[53] Baseline BARS scores were ≈ 5 in all patient groups in both 24-hour trials.^[51,53] No distinction was made between primary and secondary efficacy endpoints in the 3-day trials.^[46,52]

Intramuscular ziprasidone 10 or 20mg effectively and rapidly reduced acute agitation compared with intramuscular ziprasidone 2mg in patients with psychotic disorders in two fixed-dose, 24-hour trials.^[51,53] Patients receiving intramuscular ziprasidone 10^[51] or 20mg^[53] had significantly lower mean BARS scores than those receiving ziprasidone 2mg 2 hours after the first dose in one trial (3.2 vs 3.9; $p < 0.001$),^[51] and at every assessed timepoint from 0.5–4 hours after the first dose in the other trial ($p < 0.01$ for each timepoint)^[53] [primary efficacy endpoints]. Maximum efficacy in reducing agitation of the 20mg dose compared with the 2mg dose was observed at 2 hours after the first dose (mean BARS score 2.5 vs 3.8; $p < 0.001$), and superior efficacy of the 20mg versus 2mg dose was maintained up to 4 hours after the first dose.^[53] All BARS values were estimated from graphs.^[51,53] Intramuscular ziprasidone 10 or 20mg rapidly reduced the symptoms of acute agitation (within 15^[51] or 30^[53] minutes of the first dose) [secondary efficacy endpoint]. About 2-fold more ziprasidone 10^[51] or 20mg^[53] than ziprasidone 2mg recipients were responders 2 hours after the first dose (both $p < 0.001$ vs ziprasidone

2mg). Response was defined as a ≥ 2 point reduction in the BARS score.^[51,53]

Intramuscular ziprasidone 5–20mg was superior to intramuscular haloperidol 2.5–10mg for reducing the severity of schizophrenic symptoms and agitation following 3 days' treatment in a flexible-dose, nonblind trial.^[52] Acute agitation, as assessed by the mean reduction from baseline in BPRS agitation item scores, was reduced to a greater extent in ziprasidone than in haloperidol recipients (-1.93 vs -0.80 ; $p = 0.015$) [all subjects, OC analysis].^[52] Reductions in BPRS total and CGI-S scores in patients receiving ziprasidone were approximately double those in patients receiving haloperidol ($p < 0.05$ vs haloperidol).^[52] These concomitant improvements in the symptoms of schizophrenia were maintained during the transition to the oral formulation of ziprasidone, although intramuscular ziprasidone is not indicated for reducing these symptoms, but rather for controlling acute agitation.^[52]

There was no significant difference in the reduction of symptoms of acute agitation between intramuscular ziprasidone 20mg and intramuscular olanzapine 10mg in a 3-day fixed-dose trial (data available as an abstract).^[46] Patients in ziprasidone and olanzapine treatment groups experienced significant reductions from baseline in BARS (data not reported) and PANSS agitation item scores (6.1 vs 6.4) that were not significantly different between the treatment groups (p -values were not reported). Respective CGI-I scores were 2.6 versus 2.5, and the percentage of patients with a reduction in the BARS score of ≥ 2 points was 75% versus 78%.^[46]

5. Tolerability

Tolerability data for ziprasidone are available from clinical trials of ≥ 18 months' duration in patients with schizophrenia or schizoaffective disorder or psychotic disorders discussed in section 4,^[14–19,32–34,36–39,46,49–53] the manufacturer's US prescribing information,^[8] and an FDA review document.^[44] Some data are currently available as abstracts and/or posters.^[16,46] Unless stated otherwise,

all analyses were based on the ITT LOCF population.

In general, ziprasidone was well tolerated in patients with schizophrenia or schizoaffective disorder^[8,14-19,32-34,36-39,49,50] and in patients with acute agitation associated with psychotic disorders.^[8,46,51-53] EPS data and effects on the cardiovascular system are reported separately in section 5.2 and section 5.3.

5.1 General Profile

Ziprasidone was generally as well tolerated as placebo.^[8] In a combined analysis of placebo-controlled, short-term trials, the most common treatment-emergent adverse events other than EPS or EPS-related adverse events that occurred in $\geq 5\%$ of patients receiving ziprasidone were somnolence, nausea, constipation, respiratory tract infection, dizziness, dyspepsia, asthenia and diarrhoea (figure 1).^[8] In a 52-week trial, asthenia was the only non-EPS-related adverse event occurring significantly more frequently with ziprasidone than placebo (9% vs 0%; $p < 0.05$).^[15]

The most frequent treatment-emergent adverse events with ziprasidone (oral or intramuscular formulations) were CNS- or gastrointestinal-related,

Fig. 1. Tolerability of oral ziprasidone (ZIP). Treatment-emergent adverse events that occurred in $\geq 5\%$ of patients (pts) receiving ZIP in short-term placebo (PL)-controlled trials. Data obtained from the manufacturer's US prescribing information (dosages and statistical analysis not reported).^[8]

the majority of which were of mild to moderate severity in short- and longer-term trials.^[14,16,18,33,37,39,49,50,52]

In comparative trials of 6–28 weeks' duration,^[14,19,33,38] the most frequent treatment-emergent adverse events other than EPS or EPS-related events occurring in at least 10% of patients in any treatment group with ziprasidone,^[14,19,33,38] haloperidol,^[14,33] risperidone^[19] or amisulpride^[38] were insomnia (16–25% with ziprasidone, 15%^[14] and 18%^[33] with haloperidol, 12% with risperidone,^[19] 14% with amisulpride^[38]), somnolence (3–21% with ziprasidone, 6%^[14] and 9%^[33] with haloperidol, 18% with risperidone^[19] and 10% with amisulpride^[38]) and headache (6–15% with ziprasidone, 11% with haloperidol,^[33] 18% with risperidone^[19] and 5% with amisulpride^[38]). Agitation was reported in 16% of ziprasidone and 14% of risperidone recipients,^[19] vomiting and nausea in 11% and 10% of ziprasidone and 6% and 4% of haloperidol recipients in one trial,^[33] and anxiety in 11% of ziprasidone and 9% of haloperidol recipients in another trial.^[14]

In longer-term trials versus olanzapine,^[20,36] treatment-emergent adverse events that occurred in at least 5% of patients in either treatment group and in significantly ($p < 0.05$) more ziprasidone than olanzapine recipients were insomnia (22% vs 7%),^[36] vomiting (9% vs 4%),^[36] psychosis (8% vs 3%)^[20] and 'decreased appetite' (5% vs 1%).^[20] Treatment-emergent adverse events that occurred in at least 5% of patients in either treatment group and in significantly ($p < 0.05$) fewer ziprasidone than olanzapine recipients were 'weight increase' (2% vs 13%)^[36] and 6% vs 20%^[20]) and 'appetite increase' (3% vs 7%)^[36] and 4% vs 10%^[20]).

Rates of discontinuation because of treatment-related adverse events were 2–8% in ziprasidone groups^[14,19,32,33,38] compared with 2–16% in haloperidol,^[14,33] risperidone,^[19] olanzapine^[32] or amisulpride^[38] treatment groups.

Treatment-related adverse events (severity not reported) occurred in 5%,^[38] 46%^[32] and 58%^[19] of ziprasidone recipients compared with 3%^[38] and 40%^[32] of olanzapine and 63% of risperidone^[19] recipients. Treatment-related serious adverse events

were infrequent, occurring in no more than four patients receiving oral ziprasidone 20–80mg twice daily in each trial^[15,19,33,38] and in no more than two patients receiving placebo,^[15] haloperidol,^[33] risperidone^[19] or amisulpride^[38] in each trial.

In CATIE phase 2,^[37] serious adverse events were reported in 15% of ziprasidone recipients and in 6–11% of patients receiving risperidone, olanzapine or quetiapine (overall treatment difference of $p = 0.01$), and there were two deaths in the ziprasidone and one in the risperidone treatment groups (whether these deaths or adverse events were treatment-related was not reported). Between-group differences during phase 1 of this trial for serious adverse events were not significant.^[18]

The propensity for ziprasidone to cause adverse events potentially associated with elevated serum prolactin levels (section 2) remains to be fully determined. Although reported rarely in clinical trials (in two patients receiving ziprasidone 80mg twice daily^[50]), in CATIE phase 1 and 2 the incidence of sexual dysfunction was up to 19%^[18,37] while that of galactorrhoea/gynaecomastia was up to 3%^[18,37] in patients receiving ziprasidone. Corresponding incidences in patients receiving risperidone, olanzapine, quetiapine or perphenazine were 11–29% and 0–5%.^[18,37] Menstrual irregularities occurred in 14% (of 56 female patients) of ziprasidone, 12% (92) of olanzapine, 6% (82) of quetiapine, 18% (88) of risperidone and 11% (62) of perphenazine recipients.^[18]

Intramuscular ziprasidone was generally well tolerated.^[8,14,46,52] Injection site pain was experienced by 8 of 63 patients in the 10mg dose group and in 7 of 41 patients in the 20mg dose group (maximum ziprasidone dosage of ≤ 80 mg/day) [pooled data from two 24-hour studies^[51,53]],^[8] was of mild or moderate severity, and did not lead to treatment discontinuation.^[51,53] In addition, the transition from the intramuscular to the oral formulation of ziprasidone was well tolerated.^[14,52]

The incidence of treatment-emergent adverse events (except EPS, see section 5.2) were broadly similar between intramuscular ziprasidone and intramuscular haloperidol.^[14] Insomnia occurred in

7% of ziprasidone and 5% of haloperidol recipients, with the remaining treatment-emergent adverse events occurring in $\geq 5\%$ of patients being EPS or EPS-related adverse events.^[14]

Discontinuation because of an adverse event was generally infrequent in patients receiving intramuscular ziprasidone (4 of 429 patients^[14] and 1 of 90 patients^[52]) or intramuscular haloperidol (4 of 138 patients^[14] and 0 of 42 patients^[52]). In one trial, discontinuation by one patient in each treatment group was treatment related.^[14]

5.2 Extrapyrimalidal Syndrome and Related Adverse Events

Ziprasidone was generally associated with a low incidence of EPS and EPS-related movement disorders (e.g. akathisia, dystonia, hypertonia, tremor) and changes from baseline in their severity were generally favourable in comparison with haloperidol. Severity was assessed in clinical trials via rating scales where a decrease in score indicates a lessening of severity.

In short-term, placebo-controlled trials, the incidence of EPS or EPS-related adverse events with ziprasidone was 14% compared with 8% with placebo, although akathisia occurred in a similar proportion of patients (8% vs 7%) [analysis of pooled data].^[8] The incidence of dystonia, hypertonia and tremor appear to be dose-related.^[8] In individual trials, changes in EPS severity were usually minimal in both ziprasidone and placebo groups, as assessed via the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BAS) or Simpson-Angus Rating Scale (SARS) scores.^[49,50] In a 52-week trial, EPS and EPS-related adverse events occurred in a similar proportion of oral ziprasidone 20–80mg twice daily and placebo recipients (1–12% vs 3–7%), and changes from baseline in the severity of these adverse events were minimal.^[15]

The incidence of EPS and EPS-related adverse events was up to 13% in ziprasidone,^[14,19,33,36,38] 23% in haloperidol,^[14,33] 3% in amisulpride^[38] and 20% in risperidone recipients,^[19] and 0% in patients receiving olanzapine.^[36] After 3 days' treatment with the intramuscular formulations, the incidences

of these adverse events were <5% in patients receiving ziprasidone versus 8–11% of those receiving haloperidol^[14] and 13% of those receiving olanzapine.^[46]

At the end of a 6-week rater-blinded trial, the changes from baseline in EPS severity with ziprasidone were significantly different from those observed with haloperidol for all measures (figure 2).^[14] At study end, the study-defined Movement Disorder Burden Score was significantly higher in haloperidol than ziprasidone recipients, indicating a greater burden of movement disorders in patients receiving haloperidol (0.94 vs 0.26; $p < 0.0001$).^[14] Results of an analysis of data for intramuscular ziprasidone versus haloperidol, which was administered in the first 3 days of the trial, were consistent with these outcomes (all between-group differences $p < 0.0001$).^[14]

Fig. 2. Effect of ziprasidone (ZIP) compared with haloperidol (HAL) on the severity of akathisia and extrapyramidal syndrome. Symptoms were assessed via BAS and ESRS rating scales.^[14] Adult patients with schizophrenia or schizoaffective disorder enrolled in a 6-week, randomised, nonblind and rater-blinded, multicentre trial received intramuscular ZIP ≤ 40 mg/day or HAL ≤ 10 mg/day for the first 3 days of the trial, then switched to the respective oral formulation (ZIP 40–80mg twice daily or HAL 5–20 mg/day).^[14] **BAS** = Barnes Akathisia Scale; **ESRS** = Extrapyramidal Symptom Rating Scale; **ESRS-BS** = ESRS - Behavioural Scale; **ESRS-DS** = ESRS - Dizziness Score; **ESRS-PE** = ESRS - Physician's Examination; **ESRS-PS** = ESRS - Severity of Parkinsonism; **ESRS-SP** = ESRS - Stage of Parkinsonism. * $p < 0.001$, ** $p < 0.0001$ vs HAL.

In comparisons between oral ziprasidone and olanzapine, between-group differences in the mean change from baseline in Extrapyramidal Symptom Rating Scale,^[32] BAS,^[20,32,36] AIMS^[20,32,36] and SARS^[20,36] scores were of mixed statistical significance and no firm conclusions can be drawn.

In a 4-week extension study^[16] of a short-term trial,^[19] the incidence of EPS and/or EPS-related adverse events was 50% in 62 patients receiving ziprasidone compared with 52% in 77 patients receiving risperidone, with no significant between-group differences in severity of these movement disorders. In the long-term CATIE trial,^[18,37] the proportion of patients with severe EPS and/or related adverse events was not significantly different between patients receiving ziprasidone and those receiving olanzapine, risperidone, quetiapine, or in phase 1 of the trial, perphenazine.

5.3 Cardiovascular Effects

Although ziprasidone has the potential to cause dose-related QTc interval prolongation (section 2) and is considered more likely to do so than several other antipsychotics,^[8] clinically significant prolongation of the QTc interval (generally defined as >500ms) with recommended dosages of ziprasidone was uncommon. Of the clinical trials reviewed in section 4, the incidence of this adverse event was reported in only two trials,^[18,20] occurring in <2% of ziprasidone recipients^[18,20] compared with 1% of perphenazine recipients, 3% each of quetiapine and risperidone recipients, and 0% of olanzapine recipients in one trial,^[18] and in 3% of olanzapine recipients in the other trial (defined as >450ms [men] or >470ms [women]).^[20] According to pooled data from almost 3000 ziprasidone recipients, clinically significant QTc interval prolongation occurred in 0.06% of patients, compared with 0.23% of placebo recipients (of 440 patients).^[8]

The risk of torsade des pointes and/or sudden death may increase with the use of drugs that prolong the QTc interval.^[8] Rare occurrences of torsade des pointes have been observed only with intramuscular ziprasidone during postmarketing surveillance (no details reported).^[8] Although there was a lack of

consistency in the definition of sudden death, there were 9.1 sudden deaths per 1000 subject-years with ziprasidone treatment compared with 10.5 with serindole, 3.5 with olanzapine, 1.9 with risperidone and 1.1 with quetiapine (data from an FDA review).^[44] The manufacturer's local prescribing information should be consulted for further specific information for the contraindications and warnings relating to QT interval prolongation (including in cases of overdose) and risk of sudden death.

Ziprasidone may result in orthostatic hypotension, which may be associated with tachycardia, dizziness or syncope.^[8] Orthostatic/postural hypotension or orthostatic faintness occurred in $\leq 13\%$ of oral ziprasidone recipients in clinical trials,^[18,33,37] and in 5 of 41 patients receiving the intramuscular formulation (pooled data in prescribing information).^[8] In comparison, none of the patients receiving haloperidol^[33] and 6–13% of recipients of olanzapine, risperidone, quetiapine or perphenazine experienced these adverse events.^[18,37] Tachycardia was infrequent and occurred with a similar incidence in patients receiving oral ziprasidone or placebo ($\leq 3\%$ of patients).^[8,15] Two patients receiving intramuscular ziprasidone but none of those receiving intramuscular haloperidol experienced this adverse event.^[52] Syncope occurred in 0.6% of patients receiving ziprasidone (formulation and dosage not reported).^[8]

6. Dosage and Administration

Ziprasidone is indicated for the treatment of adult patients with schizophrenia, as an oral formulation for initial or maintenance treatment^[8,54] or as an intramuscular formulation for control of acute agitation.^[8,64]

The recommended initial dosage of oral ziprasidone is 20mg twice daily in the US^[8] and 40mg twice daily in the EU (where approved),^[54] with at least 2 days between dosage adjustments (in the US^[8]). For maintenance treatment, the minimum effective dosage of 20mg twice daily may be acceptable.^[54] The maximum recommended dosage is 80mg twice daily.^[8,54] Oral ziprasidone should be taken with food.^[8,54]

The recommended dose of intramuscular ziprasidone is 10 or 20mg (US)^[8] or 10mg (Spain)^[64] as required up to a maximum daily dose of 40mg.^[8,64] In the latter country, an initial dose of 20mg may be administered if necessary, followed by a 10mg dose 4 hours later, and then the usual dose of 10mg.^[64] Doses of 10mg should be given 2 hours apart;^[8,64] however, this interval should be 4 hours with a 20mg dose (in the US).^[8] The intramuscular formulation is for short-term treatment only; use of this formulation for more than 3 days has not been studied.^[8,64] If a patient requires long-term therapy, initiation of treatment with oral ziprasidone should begin as soon as possible.

Specific dosage recommendations in special patient populations and information relating to warnings, precautions and drug interactions are contained in the manufacturer's local prescribing information.

7. Place of Ziprasidone in the Management of Schizophrenia and Schizoaffective Disorder

Only about 10–15% of patients with schizophrenia achieve a reasonable recovery after their first episode of the disease, thus the majority require life-long treatment.^[1] Although the outcome of patients with schizoaffective disorder is generally better than that of those with schizophrenia, it too is a chronic disease, and requires complex psychopharmacological management.^[2] No specific antipsychotic agents or group of agents are recommended, with the possible exception of clozapine as a second-line therapy,^[3] in the treatment of the psychotic symptoms of patients with schizoaffective disorder because data regarding the pharmacological management of patients with this psychiatric disorder are limited.^[2,3] Current treatment guidelines for schizophrenia do not recommend one atypical antipsychotic agent over another, but suggest that selecting an appropriate agent involves consideration of the patient's prior experience with antipsychotics (including efficacy and tolerability) and their preference for a given treatment.^[1] Nevertheless, ziprasidone is included amongst the atypical antipsychotic agents as a first-line treatment choice over conventional antip-

psychotic agents for the management of patients with schizophrenia.^[1,65,66] The receptor binding profile of ziprasidone (section 2) is suggestive of therapeutic efficacy in a broad range of schizophrenic symptoms and a favourable tolerability profile.

The oral formulation of ziprasidone is well absorbed and steady state is achieved within 1–3 days (section 3). The requirement to take ziprasidone with food twice a day (systemic absorption is better with food) may be perceived negatively,^[65] although whether this results in lower patient adherence to treatment has not been addressed in any clinical trials to date. The intramuscular formulation of ziprasidone was the first atypical antipsychotic available in a parenteral formulation for the control of acute agitation;^[5] other parenteral formulations currently used in this indication include benzodiazepines (e.g. lorazepam), conventional antipsychotics (e.g. haloperidol, droperidol) and olanzapine.^[5] The aim of pharmacological management of patients experiencing acute agitation is to rapidly tranquillise the patient, so reducing the immediate risk of damage to self or others.^[5] Rapid tranquillisation requires a fast onset of action, which can be achieved by administering the drug intramuscularly.^[5]

Intramuscular ziprasidone 5–20mg rapidly and effectively reduced the symptoms of agitation in well-controlled trials in patients with acute agitation associated with psychosis (section 4.3). In nonblind trials, the drug had superior efficacy compared with intramuscular haloperidol and similar efficacy to intramuscular olanzapine. As with other clinical trials with drugs indicated for the control of agitation, patients in these intramuscular ziprasidone trials had only moderate levels of agitation, because only patients who were non-intoxicated and able to consent to treatment and adhere to the trial protocol were enrolled.^[5] Well controlled trials in patients with schizophrenia experiencing acute agitation comparing the efficacy of intramuscular ziprasidone with intramuscular haloperidol, intramuscular olanzapine, and with the commonly used (at least in the US) combination of intramuscular haloperidol coadmin-

istered with intramuscular lorazepam,^[5] would be of interest.

Once a patient has been calmed, ongoing treatment with an antipsychotic may be necessary; switching from the intramuscular to the oral formulation of ziprasidone did not appear to compromise efficacy (section 4.3) and was well tolerated (section 5). A less favourable alternative to control agitation would be the use of a parenterally administered conventional antipsychotic, followed by a switch to an oral atypical antipsychotic for continuing treatment, as efficacy and tolerability may be compromised.^[5]

Ziprasidone was as effective as risperidone or haloperidol in patients experiencing acute exacerbation of their symptoms (section 4.1). Although the trial versus haloperidol was rater-blinded,^[14] the relative efficacy of these two agents would be better confirmed in a double-blind trial. The antipsychotic efficacy of ziprasidone was maintained for up to 52 weeks and was not significantly different from that of risperidone over this time period in these patients. In patients with chronic schizophrenia, the antipsychotic efficacy of ziprasidone was not significantly different from that of the conventional antipsychotic agents haloperidol or perphenazine or the atypical antipsychotic agents quetiapine or amisulpride (section 4.2). The comparative efficacy of ziprasidone versus risperidone remains to be confirmed in a head-to-head trial because ziprasidone was inferior to risperidone in CATIE phase 2, but not in phase 1; the CATIE study is the only study to date comparing these agents in patients with chronic schizophrenia (section 4.2.3).

In patients with acute exacerbation of symptoms (section 4.1), ziprasidone had equivalent antipsychotic efficacy to olanzapine over the short term, with no significant difference in efficacy between these treatment groups in an extension study of 6 month's duration. In contrast, in patients with chronic schizophrenia, the efficacy of olanzapine was generally superior to that of ziprasidone (section 4.2). These equivocal results across different studies may result from the different disease state of

patients at baseline and different maximum dosages of olanzapine used in different trials.

Differences between manufacturer-recommended dosages of antipsychotic agents, effective therapeutic dosages,^[67] expert opinion on dosages used in clinical practice,^[66] dosages recommended in treatment guidelines^[1] and choices of maximum dosages in clinical trials of these agents, appear to be an area of intense debate. Although the approved dosage range of ziprasidone is 40–160 mg/day,^[8] this may be below the optimal therapeutic dosage;^[18] treatment guidelines recommend a dosage range of 120–200 mg/day.^[1] In the CATIE study in patients with chronic schizophrenia, investigators noted that dose may have been a factor in the comparative performance of the different antipsychotic agents studied.^[18,37] The dosages of ziprasidone, and also quetiapine and risperidone, may not have been optimal;^[37] whereas the mean modal dosage of olanzapine was as high as the maximum recommended dosage of 20 mg/day^[68] (section 4.2.3). Since one to four capsules of assigned treatment were allowed daily,^[18,37] those patients randomised to olanzapine or quetiapine would have received higher than the maximum recommended (olanzapine)^[68] or the target (quetiapine)^[69] dosages if they were titrated up to four capsules per day. In contrast, four capsules per day of ziprasidone or risperidone gave a total daily dose within the recommended range of 40–160mg for ziprasidone^[8] or 2–8mg for risperidone.^[55]

The efficacy and tolerability of ziprasidone have yet to be compared with newer atypical antipsychotic agents such as aripiprazole. A head-to-head trial versus aripiprazole would be of particular interest because they appear to share numerous properties such as a broad range of efficacy against the symptoms of schizophrenia and a low potential to cause EPS, hyperprolactinaemia, bodyweight gain and dyslipidaemia.^[70] Although ziprasidone may improve the cognitive deficits of schizophrenia, including over the longer-term (section 4.1.2), trials assessing the effect of ziprasidone on neurocognition as a primary efficacy endpoint have yet to be conducted. Health-related quality-of-life data and

robust pharmacoeconomic analyses would also be of value.

The differing adverse event profiles of antipsychotic agents should be carefully considered when selecting between agents for treatment of a patient, since adverse effects are the primary reason for discontinuation from treatment.^[1] Ziprasidone was well tolerated in studies of ≥ 18 months duration (section 5). Ziprasidone was associated with a relatively low incidence of EPS and EPS-related adverse events (section 5.2); like other atypical antipsychotic agents^[1] the incidence of these adverse events was less than that observed with haloperidol. The drug appears to have a lower potential than haloperidol or risperidone to produce clinically relevant elevated prolactin levels (section 2); however, further investigation is required to clarify whether this correlates with a low propensity for adverse events related to hyperprolactinaemia. Ziprasidone offers the advantage over olanzapine and, to a lesser extent, risperidone and quetiapine,^[1] of minimal bodyweight gain (which may reduce the likelihood of noncompliance^[71]) and less potential to cause metabolic abnormalities (dyslipidaemia, glucose metabolism disturbances) [section 2.1].

The advantages of ziprasidone should be balanced against its potential to cause QTc interval prolongation (section 2) and the concomitant risk for sudden cardiac death (reviewed by Taylor^[72]). Compared with adverse effects that are readily observable over the course of time (e.g. weight gain, dyslipidaemia), and can therefore be treated and/or the antipsychotic treatment regimen altered, the first sign of QTc interval prolongation may be sudden death.^[72] Thus, the recommendations contained in the manufacturer's prescribing information for ziprasidone to reduce the risk of these adverse events should be followed. Adhering to these recommendations may limit the usefulness of the intramuscular formulation used in emergency situations to control an acutely agitated patient, since there may not be sufficient time to obtain the necessary information about the patient. Nonetheless, intramuscular ziprasidone appears to be widely used, at least in the US.^[5]

In conclusion, oral ziprasidone is effective and well tolerated in adult patients with schizophrenia or schizoaffective disorder during a phase of acute exacerbation of symptoms as well as in chronic disease. Ziprasidone offers the advantage over most other atypical antipsychotic agents of being available in a fast-acting intramuscular formulation for control of acute agitation, thus providing clinicians with the option to safely and effectively transition to longer-term treatment with the oral formulation. Although careful consideration should be given to the propensity for ziprasidone to cause QTc interval prolongation, albeit at a relatively low incidence, the drug generally has a favourable tolerability profile of low EPS liability, neutral bodyweight gain, and potentially low propensity for metabolic complications. Thus, ziprasidone is an effective option for the management of patients with schizophrenia or schizoaffective disorder, with the intramuscular formulation providing a useful option for the treatment of acute agitation in these patients.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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