

National PBM Drug Monograph
Ziprasidone (Geodon® for injection)
VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel

Ziprasidone IM was FDA approved on 6/21/02. Ziprasidone IM is not a depot parenteral product.

INDICATIONS

For the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need IM antipsychotic medication for rapid control of the agitation.

Since there is no experience regarding the safety of administering ziprasidone IM to patients already taking oral ziprasidone, the practice of co-administration is not recommended.

PHARMACOKINETICS

Bioavailability	100%
Tmax (single-dose)	~ 60 minutes or earlier
T1/2	2-5 hours
Metabolism	CYP 3A4 ++, aldehyde oxidase ++, CYP 1A2 +

++=major pathway +=minor pathway

DOSING

10-20mg administered PRN up to a maximum dose of 40mg per day. Doses of 10mg can be administered every 2 hours; doses of 20mg may be administered every 4 hours. IM administration for more than 3 consecutive days has not been studied.

Ziprasidone IM has not been systematically evaluated in patients \geq 65 years old or in patients with hepatic or renal impairment. Cyclodextrin, an excipient in the IM formulation is cleared by renal filtration; therefore, administer cautiously in patients with impaired renal function.

AVAILABILITY

Ziprasidone injection is available as a single use vial of 20mg/ml, which requires reconstitution with 1.2ml of sterile water for injection. Shake vial for 30-60 seconds until solution turns pale pink and no visible particles are apparent. Ziprasidone cannot be mixed with other medications or solvents. There are no preservatives or bacteriostatic agents in the vial; therefore it is recommended that any unused portion be discarded.

Once reconstituted, the solution can be stored for up to 24 hours at 59-86°F or refrigerated for up to 7 days.

EFFICACY

Details on each study can be found in the appendix located at the end of the review.

Ziprasidone IM was studied in two similarly designed 24-hour studies in patients with agitation associated with their underlying psychotic disorder. Lesem compared ziprasidone 2mg and 10mg and Daniel compared the 2mg and 20mg doses. Baseline antipsychotic was withdrawn 4-72 hours prior to the first dose of ziprasidone. After the initial dose, up to 3 identical additional doses could be administered at the discretion of the clinician. Benztropine for EPS and propranolol for akathisia were allowed during study if needed. They were not permitted as prophylactic treatment.

In the Lesem study, lorazepam up to 8mg/day for agitation and temazepam up to 30mg HS for insomnia were allowed between screening and up to 4 hours before baseline assessment. They were permitted during the 24-hour study if needed except for immediately after administration of study drug. In the Daniel study, lorazepam and temazepam were allowed during the screening period, but not during the treatment period.

In Lesem et al., the primary endpoint was the Behavioral Activity Rating Scale (BARS) score at 2 hours. The BARS was developed by Pfizer for the IM ziprasidone program to assess the level of behavioral activity of patients with psychosis. The BARS describes 7 levels of activity 1= difficult or unable to arouse; 2=asleep but responses normally to verbal or physical contact; 3=drowsy, appears sedated; 4=quiet and awake (normal level of activity); 5= signs of overt (physical or verbal) activity, calms down with instructions; 6=extremely or continuously active, not requiring restraint; 7=violent, requires restraint.

Secondary endpoints included % who were BARS responders at 2 hours, defined as a ≥ 2 point reduction in the BARS score, mean area under the curve of the BARS from 0-2 hours and 0-4 hours after the first injection, the mean change from baseline at 4 hours for the PANSS (Positive and Negative Syndrome Scale) total score, PANSS agitation items, CGI-S (Clinical Global Impression-Severity of Illness scale), and CGI-I (Clinical Global Improvement Scale). All statistical comparisons were made between groups.

The enrolled patients were considered as having moderate agitation. Decreased agitation, as measured by the BARS score, was seen as early as 15 minutes after the dose. There was a continued decrease in the BARS score with the 10mg dose over the 4-hour period, which was significantly different from the 2mg dose. The primary endpoint of the BARS score at 2 hours was 3.2 for the 10mg group and 3.7 for the 2mg group (values estimated from graph) and was considered statistically significant compared to the 2mg group. The 10mg group also had a statistically significantly lower AUC for the BARS score and had a higher responder rate based on the 2-hour BARS score (57.1% versus 29.6%). There was no significant difference between groups for the other measured endpoints.

The primary endpoint in the 20mg study by Daniel et al was the BARS score at 4 hours. All other measured parameters were the same as in the Lesem study. The BARS score at 4 hours was 2.8 for the 20mg dose and 3.8 for the 2mg dose (estimated from graph). The mean BARS score was significantly lower for the 20mg dose compared to the 2mg dose at all other time points. The 20mg dose also showed statistically significant results compared to the 2mg dose for all other measured endpoints except for the PANSS total score.

Overall, the time to response (2 point decrease in BARS score) was:

20mg dose - 50% within 1 hour

10mg dose – 50% within 2 hours

2mg dose - 50% at 6-8 hours

Comparative trials with haloperidol

There are 3 head-to-head trials comparing ziprasidone and haloperidol. Study 121 and Brook et al. were 7-day trials beginning with IM dosing followed by oral. Both were randomized, open label, and parallel in design. The third study was a 6-week randomized, blinded-assessment, parallel trial.

Study 121 was a tolerability study and included **non-agitated** patients with acute psychosis related to schizophrenia, schizoaffective, bipolar with psychotic features, schizophreniform, delusional, brief psychotic, or shared psychotic disorders. Patients were randomized to receive a fixed dose of ziprasidone IM 5mg, 10mg, or 20mg administered QID, or flexible dose haloperidol IM 2-4 times daily for 3 days, followed by oral for the remainder of the study. The mean IM haloperidol dose used was 11mg/day with the majority requiring only 2 doses. Concomitant treatment with lorazepam, temazepam, oral anticholinergics, and beta-blockers were allowed.

The Brief Psychiatric Rating Scale (BPRS) and the CGI-S were the primary outcomes. At the end of the IM phase, The BPRS score decreased by a mean of 5.6 for ziprasidone and 6.3 for haloperidol. Decreases at the end of the oral phase were 6.2 and 7.5 for ziprasidone and haloperidol respectively. At the end of the IM phase, the CGI-S score decreased by 0.2 with ziprasidone and by 0.3 with haloperidol. At the end of the oral phase, the changes were 0.3 and 0.4 respectively,. These data were obtained from a poster presentation where statistical evaluation was not provided.

In the study by Brook et al. patients had to be experiencing agitation, in addition to acute psychosis as described for study 121. At baseline, 66% of patients were taking an antipsychotic agent, which was discontinued for the purpose of the study. Flexible dosing of IM ziprasidone (initial dose 10mg; additional doses 5-20mg PRN, max 80mg/d) and IM haloperidol (2.5-10mg; max. 40mg/d) was administered for up to 3 days followed by oral for remainder of study. The mean IM dose of ziprasidone for days 1, 2, and 3 were 23.3mg, 27.6mg, and 27.6mg respectively and for

haloperidol were 7.6mg, 10.1mg, and 11mg. Seventy percent of patients received IM for ≤ 2 days. Concomitant treatment with lorazepam, temazepam, oral anticholinergics, and beta-blockers were allowed.

Efficacy assessments included the 18-item BPRS, BPRS agitation items, CGI-S, CGI-I. At the end of the IM phase, the BPRS total (ZIP -6.24 vs. HAL -3.18) and BPRS agitation (ZIP -1.93 vs. HAL -0.8) cores decreased significantly more with ziprasidone than haloperidol. The changes from baseline at the end of the 7 days were not significantly different between groups. There was a significantly greater decrease in CGI-S after both the IM phase (ZIP -0.49 vs. HAL -0.15) and the oral phase (ZIP -0.89 vs. HAL -0.38) for the ziprasidone group versus the haloperidol group. After both the IM phase and the oral phase, the CGI-I was similar for both groups.

The 6-week trial was conducted in patients who were hospitalized or transferred to a high dependency unit for acute exacerbation. It is not clear from the poster, if patients were experiencing agitation; however, the need for IM medication was left to the judgment of the investigator. In the ziprasidone arm, patients initially received 10 or 20mg IM, which may be repeated up to 40mg/day for up to 3 days. Those randomized to haloperidol received 2.5 or 5mg initially which, may be repeated up to 10mg/day for up to 3 days. Intramuscular administration was then followed by oral therapy for the remainder of the study. Oral dosing for ziprasidone began at 40mg BID and could be adjusted to 40-80mg BID. Oral dosing for haloperidol began at 5mg BID and could be adjusted to 5-20mg BID. Concomitant treatment with lorazepam, temazepam, oral anticholinergics, and beta-blockers were allowed.

The median duration of IM therapy was 2 days (range 1-4 days) for both drugs. Approximately 75% of patients received 2 injections per day. The mean IM ziprasidone dose for days 1, 2, and 3 were 22.7mg, 23.7mg, and 21.8mg respectively. For IM haloperidol, the mean doses were 7.3mg, 8.1mg, and 6.2mg respectively. The mean oral dose of ziprasidone was 115.8mg and for haloperidol was 11.5mg daily. Efficacy assessments included the change from baseline in the BPRS score and the CGI-S score and the final CGI-I score. Secondary endpoints included the BPRS anxiety subscale and the Covi Anxiety Scale. The only significant finding was the change in the BPRS score after the IM phase of the study favoring ziprasidone (ZIP -6.15 vs. HAL -4.13). There was no significant difference between ziprasidone and haloperidol for BPRS at study end and for the CGI-S, and CGI-I. Greater improvement in the Covi Anxiety Scale was seen with IM ziprasidone ($p < 0.01$) (data not shown in article).

A post-hoc analysis in a subset of severely ill patients, defined as CGI-S ≥ 5 , was conducted. The mean change in the BPRS score for ziprasidone IM was -6.51 and for haloperidol was -4.9, which was found to be significant. The difference in change in BPRS scores at last visit was not significantly different between the 2 groups (-15.78 vs. -17.69).

In summary, the change from baseline for the BPRS score was statistically significantly greater with ziprasidone IM than haloperidol. At study end, the change in BPRS score was not significantly different between ziprasidone and haloperidol. Changes in the CGI-S varied from study to study. In the 7-day trial by Brook, the change from baseline in the CGI-S score was considered significant for ziprasidone both after the IM phase and at end of study. In the 6-week study, the change at either time point was not significantly different between the 2 agents. Comments on study 121 cannot be made since a statistical analysis was not provided. However, numerically, the change in BPRS and CGI-S scores were greater for haloperidol after the IM phase and at end of study.

SAFETY AND TOLERABILITY

The most common adverse events with ziprasidone were headache, nausea and somnolence. The incidence of side effects reported is listed for each study in the table below. The effects on QTc interval will be addressed separately.

Table 1. Incidence of adverse events

	Study 125 ZIP2mg/10mg	Study 126 ZIP2mg/20mg	Study 121 (IM phase) ZIP 5mg/ 10mg/ 20mg/HAL	Study 306 (IM phase) ZIP/HAL	6 week study ZIP/HAL
Headache	5.6%/ 12.7%	0/ 4.9%	17.4/ 14.1/ 19.7/ 8.0%		8.6%/ 1.5%
Inj. Site pain	13%/ 7.9%	2.6%/ 7.3%	5.8/ 9.9/ 16.7/ 2.0%		
Nausea/vomiting	1.9%/ 7.9%	7.9%/ 12.2%	21.7/ 31/ 33.3 / 8.0%	3.3%/ 0	
Somnolence	3.7%/ 7.9%	13.2%/ 19.5%	7.2/ 9.9/ 16.7/ 2%		12.9%/ 5.3%
Insomnia		5.3%/ 0%	10.1/ 15.5/ 21.2/ 12%		21.3%/ 15.8%
Akathisia	0/ n=1	0/ 0	5.8/ 5.6/ 12.1/ 21%	2.2%/0	8.2%/ 23.3%
Dystonia		0/ 0	7.2/ 2.8/ 3.0/ 10%	1.1%/7.1%	3.1%/ 10.5%

EPS	N=1/ 0	N=1/0	0/ 1.4/ 4.5/ 15%	0/ 21.4%	5.3%/ 22.6%
Agitation	N=2/ n=1		8.7/ 7.0/ 9.1/ 9.0%		5.3%/6.8%
Hypertonia		0/ 0	1.4/ 1.4/ 3.0/ 11%	0/ 7.1%	5.8%/14.3%
Asthenia		5.3%/ 0	2.9/ 2.8/ 6.1/ 3.0%		7.7%/3.0%
Tremor		0/ 0	2.9/ 5.6/ 3.0/ 3.0%		5%/10.5%
Dizziness	N=2/ 3.2%	2.6%/ 9.8%	15.9/ 19.7/ 15.2/ 0%		8.6%/ 4.5%
Tachycardia	0/ 0	0/ 0	2.9%/11.3%/7.6%/6%	2.2%/ 0	
HTN			4.3%/7.0%/6.1%/1%	6.7%/ 0	
Postural HOTN	0/ 0	0/ 5%	1.4 – 4.5%/ 0	1.1%/ 0	<1%/ <1%
Ataxia	0/ 0	0/ 0		0/ 0	
Confusion	0/ 0	0/ 0		0/ 0	

Discontinuations

When combining the two 24-hour ziprasidone studies, only 2 patients discontinued treatment due to a treatment-emergent adverse event. In the 7-day fixed-dose trial, the percent of patients discontinuing IM treatment secondary to an adverse event was 3.6% for ziprasidone and 1% for haloperidol. In the 2 flexible dose studies, the percent discontinuing treatment during the IM phase due to an adverse event was 1.1 % for ziprasidone and 0% for haloperidol (7-day study) and 0.2% for ziprasidone and 0.7% for haloperidol (6-week study).

Table 2. Discontinuations due to treatment-emergent adverse events

24-hour studies (Lesem and Daniel)	7-day fixed-dose trial at end of IM phase (Study 121)	7-day flexible dose trial – at end of IM phase (Brook)	6-week trial- at end of IM phase
N=2	3.6% ziprasidone 1% haloperidol	1.1% ziprasidone 0% haloperidol	0.2% ziprasidone 0.7% haloperidol

Movement disorders

Please refer to table 1 for the incidence of EPS, akathisia, etc. The Simpson-Angus scale and the Barnes Akathisia Scale were used for evaluating extrapyramidal side effects and akathisia respectively. In the two 24-hour studies, the Simpson Angus score, 1 hour post-dose, decreased from baseline by a mean of 0.9, and 0.25 for the 10 and 20mg doses respectively. At the end of the 24 hours, the change was 0.75 for the 10mg dose and 0.37 for the 20mg dose. The decrease in the Barnes Akathisia score, 1 hour post-dose was 0.25 for ziprasidone 10mg and 0.62 for 20mg. The decrease of 0.25 seen with the 10mg dose was similar to the change seen with the 2mg dose from both studies. At the end of 24 hours, the decrease in Barnes score was 0.19 and 0.37 for the 2 doses respectively.

The Simpson-Angus score at the end of the IM phase in the Brook study decreased by a mean of 0.61 for ziprasidone and increased by 3.8 for haloperidol. The Barnes akathisia score decreased slightly with ziprasidone and increased slightly with haloperidol (-0.03 vs. +0.44). In the 6-week trial, the Extrapyramidal Symptom Rating Scale (ESRS) scale was used instead of the Simpson Angus scale. At the end of the IM phase, the mean ESRS score decreased by 1.0 with ziprasidone and increased by 4.0 with haloperidol. The change in the Barnes Akathisia score was a mean increase of 0.1 and 1.1 with ziprasidone and haloperidol respectively.

Table 3. Change in movement disorder scales

	Lesem (10mg dose)	Daniel (20mg dose)	Study 121 (end of IM phase)	Brook (end of IM phase)	6-week study
Simpson Angus/ ESRS (6-wk trial)	1hr-post dose -0.9 24 hrs post -0.75	1hr-post dose -0.25 24 hrs post -0.37	-0.45/ -0.11/-0.18 (ZIP 5/10/20mg) +0.15 HAL	-0.61 ZIP +3.8 HAL	-1.0 ZIP +4.0 HAL
Barnes Akathisia	1hr-post dose -0.25 24 hrs post -0.19	1hr-post dose -0.62 24 hrs post -0.37	-0.09 to 0.02 ZIP +0.19 HAL	-0.03 ZIP +0.44 HAL	+0.1 ZIP +1.1 HAL

Effect on QTc interval

In a combined analysis of 5 trials (125, 125, 121, 306, 6 week), the effect of ziprasidone IM on QTc was comparable to haloperidol IM (Table 4).

Table 4. Effect on QTc interval

QTc Δ from baseline	Ziprasidone (n=476)	Haloperidol (n=149)
≥ 30msec	7.6%	9.5%
≥ 60msec	0.2%	1.5%
≥ 75msec	0.2%	0
≥ 15%	0.4%	1.5%

≥ 25%	0	0
QTc > 450 msec	1.1%	1.3%
QTc > 480msec	0.2%	0
QTc > 500msec	0	0

A separate study was done that specifically evaluated the effect of ziprasidone and haloperidol on the QTc interval at the observed peak concentration of the drug. Fifty-nine patients with psychosis requiring antipsychotics with normal ECGs were evaluated. This was a single blind parallel study comparing ziprasidone and haloperidol IM. Any existing antipsychotic was tapered over a 10-day period. Subjects were randomized to receive ziprasidone 20mg IM followed by 30mg IM 4 hours later or haloperidol 7.5mg IM followed by 10mg 4 hours later. Eighty percent of the subjects were male. The mean age of the group was 43. The mean weight of the males in the ziprasidone and haloperidol groups was 187 and 197 pounds respectively and for the females was 177 and 164. No patient had QTc ≥ 500msec at any time and no patient had a change from baseline ≥ 75msec. The results are summarized in the table 5.

Table 5. Change in QTc during peak drug serum concentration

	Ziprasidone (n=25)	Haloperidol (n=24)
Δ QTc at Cmax (msec)		
Injection # 1	4.6 [0.4, 8.9]	6.0 [1.4, 10.5]
Injection #2	12.8 [6.7, 18.8]	14.7 [10.2, 19.2]
Average Δ over 24 hours	3.4msec	6.3msec
Extrapyramidal	6.5%	33.3%

Mean [95% CI]

COST

The price of each 20mg vial of ziprasidone is \$26.20. The price of generic haloperidol 5mg/ml ranges from \$2.80 – \$3.90 and the brand name product is approximately \$4.90. In case benzotropine is needed, the price of the 2mg/ml injection is between \$2.24-\$2.46 and the tablets range from 3-6 cents depending on the manufacturer and dose. The cost of a 50mg injection of diphenhydramine ranges between \$0.20 – 1.00 depending on the manufacturer and whether it is a multi-dose vial or single use injection.

Based on the 7-day study by Brook and the 6-week study, the percent of patients using concomitant anxiolytics and hypnotics were similar for both groups. The percent of patients using anticholinergic any time during IM treatment was around 14% with ziprasidone and around 49% with haloperidol. The average anticholinergic dose used and whether it was administered IM or oral was not provided.

Based on the Brook study and the 6-week study, the average daily dose was around 24.4mg for ziprasidone IM, with the majority requiring 2 days of treatment. Therefore, over a 2-day period, treatment for a single patient may require 2-4 vials at a cost of \$52.40 – \$104.80. Similarly for haloperidol, the average daily IM dose was approximately 8.4mg day, with the majority requiring 2 days of treatment. Therefore, treatment for a single patient may require 3-4 vials at a cost of \$9.00 – 12.00 for 2 days of treatment. Since dose-specific information on the anticholinergics used was not provided, one cannot calculate the additional cost. Approximately a third more (absolute difference 49%-14% =35%) of patients given haloperidol required an anticholinergic sometime during IM therapy. The additional cost of anticholinergic medication is unlikely to add substantial cost, therefore making haloperidol less costly from a drug acquisition standpoint only.

SUMMARY POINTS

- Many agitated patients with psychosis can be managed with an oral atypical agent; however, there is a subset where only a parenteral agent can be used. Oral agents should be used whenever possible.
- Neuroleptic agents, such as haloperidol have been used parenterally for agitated patients without an underlying psychiatric condition (eg. substance abuse, delirium in the medically ill, etc.). At this time, there are no data using ziprasidone in this setting.

- The studies by Lesem, Daniel, and Brook evaluated agitated patients. Study 121 was a tolerability study and did not include agitated patients. It is unclear if the 6-week trial included agitated patients, although the majority was described as being severely ill. In those trials evaluating agitated patients, the level of agitation was considered as moderate. Severely psychotic, confused, hostile, etc. patients were excluded.
- The 3 comparator studies with haloperidol were open label (the 6-week trial was assessment blinded), and may be subject to bias.
- Some of the efficacy outcomes were found to show statistically significantly greater improvement with ziprasidone versus haloperidol.
- Sometimes in practice, haloperidol is mixed in the same syringe with a benzodiazepine. Ziprasidone cannot be mixed in the same syringe with any other medication.
- Ziprasidone requires reconstitution with sterile water.
- One of the attractive features of using ziprasidone is the easy transition from IM to oral; however, this benefit is lost for those who will be resuming or continuing their previous atypical agent.
- There are considerably less extrapyramidal side effects with ziprasidone than haloperidol. This may improve patient comfort and acceptability of further treatment.
- Even though ziprasidone appears to have similar effects on the QTc interval as does haloperidol (patients with underlying cardiac disease were excluded), the same contraindications for oral ziprasidone need to be observed when using the IM formulation.
- From a drug acquisition standpoint only, ziprasidone is approximately 5-10x more costly than haloperidol. The additional cost of anticholinergic medications should not substantially contribute to the cost of haloperidol.

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APPENDIX – Summary of clinical trials

Abbreviations used: AE=adverse event, AUC=area under the curve, BARS=Behavioral Activity Rating Scale, BPRS=Brief Psychiatric Rating Scale, CGI-S=Clinical global impression-severity, CGI-I=clinical global impression-improvement, DB= double-blind, ESRS=Extrapyramidal Symptom Rating Scale, LOE=lack of efficacy, R=randomized, PANSS=Positive and negative syndrome scale, PR= parallel

Ziprasidone IM

	Inclusion	Dosing	Demographics	Results		
					ZIP2 (n=54)	ZIP10 (n=63)
Study 125 Lesem 2001 R, DB, PR Ziprasidone IM 2mg vs. 10mg 24 hours n=157	<p>≥ 18 years old Recently admitted to hospital for schizophrenia, schizoaffective, bipolar with psychotic features, delusional, or psychotic disorder not-specified (DSM-IV) Score ≥ 3 on at least 3 PANSS items: anxiety, tension, hostility, or excitement at screening and at baseline</p> <p>Acute agitation associated with underlying disorder</p>	<p>Ziprasidone IM 2mg versus 10mg</p> <p>After initial dose, up to 3 identical additional doses (a minimum of 2 hours apart) could be administered at the discretion of the clinician</p> <p>Baseline antipsychotic withdrawn 4-72hrs prior to the first dose of ziprasidone</p> <p><i>Lorazepam up to 8mg/day for agitation and temazepam up to 30mg HS for insomnia were allowed between screening and up to 4 hours before baseline assessment. They were permitted during the 24-hour study if needed except for immediately after administration. of study drug</i></p> <p><i>Benztropine for EPS and propranolol for akathisia were allowed during study if needed. They were not permitted as prophylactic treatment</i></p>	<p>BARS- ZIP2mg 4.65 ± 0.65; ZIP10mg 4.79 ± 0.57 PANSS total – ZIP2mg 89.4 ± 18.8; ZIP10mg 90 ± 20.2 PANSS agitation – ZIP2 mg 14.9 ± 2.7; ZIP10mg 15 ± 3.3 CGI-S – ZIP2mg 4.2 ± 0.9; ZIP10mg 4.4 ± 0.9 Diagnosis 47.9% schizophrenia and 33.3% schizoaffective Benztropine use – ZIP2mg 22.2%; ZIP10mg 17.5% Lorazepam use – ZIP2mg 20.3%; ZIP10mg 19%</p> <p>~ 2/3 of patients received antipsychotic tx in the 48 hours prior to screening</p>			
				Completed study	96.3%	96.8%
				% receiving 1, 2, 3, or 4 injections	24.1/33.3/18.5/24.1	36.5/33.3/15.9/14.3
				BARS score at 2hrs	3.7	3.2*
				BARS % responders at 2hrs	29.6%	57.1%*
				BARS score AUC _{0-2hrs}	8.3 ± 1.18	7.57 ± 1.41*
				BARS score AUC _{0-4hrs}	15.88 ± 2.72	13.47 ± 3.03*
				CGI-S at 4hrs/endpoint	-0.74 ± 1.01 -0.5 ± 0.8	-0.76 ± 1.07 -0.71 ± 1.01
				PANSS total at 4hrs/endpoint	-13.3 ± 12.55 -12.3 ± 15.23 (15%)	-12.68 ± 13.7 -13.55 ± 17.29 (14%)
				PANSS agitation at 4hrs/endpoint	-4.44 ± 4.36 -4.02 ± 4.03 (29%)	-4.27 ± 3.77 -3.35 ± 3.89 (30%)
				CGI-I score at 4hrs/endpoint	3.02 ± 0.9 3.09 ± 0.83	2.78 ± 0.96 2.89 ± 0.99
				Simpson-Angus (1hr post dose/ last observation)	-0.4/-0.55	-0.9/-0.75
				Barnes akathisia Angus (1hr post dose/ last observation)	-0.28/-0.2	-0.25/-0.19
				Lorazepam/temazepam use	13% 5.5%	9.5% 4.7%
				% using benzotropine	14.8%	9.5%
				QTc	-3.7msec	-1.8msec
				Other AEs	See table	
				Mean ± SD *significant versus ZIP2mg		

National PBM Drug Monograph - Ziprasidone (Geodon® for injection)

<p>Study 126 Daniel 2001 R, DB, PR Ziprasidone IM 2mg vs. 20mg 24 hours n=79</p>	<p>Same inclusion criteria as in study 125</p>	<p>Ziprasidone IM 2mg versus 20mg</p> <p>After initial dose, up to 3 identical additional doses (a minimum of 4 hours apart) could be administered at the discretion of the clinician</p> <p>Other antipsychotic agents were discontinued</p> <p><i>Lorazepam up to 8mg/day for agitation and temazepam up to 30mg HS for insomnia were allowed between screening and up to 4 hours before baseline assessment. They were not allowed during the 24-hr study period</i></p> <p><i>Benztropine for EPS and propranolol for akathisia were discontinued during randomization, but were allowed during study to treat symptoms</i></p>	<p>BARS- ZIP2mg 5.00; ZIP20 mg 4.98</p> <p>PANSS total – ZIP2mg 84 ± 17.9; ZIP10mg 86.7 ± 17.9</p> <p>PANSS agitation – ZIP2 mg 14.3 ± 2.6; ZIP10mg 14.9 ± 2.6</p> <p>CGI-S – ZIP2mg 4.7 ± 0.8; ZIP10mg 4.6 ± 0.9</p> <p>Diagnosis 54.4% schizophrenia and 26.6% schizoaffective</p> <p>Antipsychotic tx within 48h of screening – ZIP2mg 65.8%; ZIP10mg 73.2%</p> <p>~ 1/3 of patients used an anticholinergic and ~1/3 used anxiolytics within 48h prior to screening</p>	<table border="1"> <thead> <tr> <th></th> <th>ZIP2 (n=38)</th> <th>ZIP20 (n=41)</th> </tr> </thead> <tbody> <tr> <td>Completed study</td> <td>94.7%</td> <td>92.7%</td> </tr> <tr> <td>% receiving 1, 2, 3, or 4 injections</td> <td>26.3/ 42.1/ 21.1/ 10.5</td> <td>41.5/ 36.6/ 14.6/ 7.3</td> </tr> <tr> <td>BARS score at 4hrs</td> <td>3.8</td> <td>2.8</td> </tr> <tr> <td>BARS score AUC_{0-4hrs}</td> <td>15.73 ± 3.06</td> <td>12.23 ± 3.17*</td> </tr> <tr> <td>BARS score AUC_{0-2hrs}</td> <td>8.48 ± 1.2</td> <td>6.95 ± 1.57*</td> </tr> <tr> <td>BARS responder rate</td> <td>26.3%</td> <td>65%*</td> </tr> <tr> <td>CGI-S at 4hrs/endpoint</td> <td>-1.16 ± 1.28 -0.92 ± 1.22</td> <td>-1.88 ± 1.45* -1.58 ± 1.3*</td> </tr> <tr> <td>CGI-I at 4hrs/endpoint</td> <td>3.05 ± 1.11 3.32 ± 1.16</td> <td>2.15 ± 0.83* 2.38 ± 0.93*</td> </tr> <tr> <td>PANSS total at 4hrs/ endpoint</td> <td>-10.1 ± 9.44 -12.08 ± 13.57</td> <td>-17.72 ± 16.62 -18.3 ± 14.63</td> </tr> <tr> <td>PANSS agitation at 4hrs/endpoint</td> <td>-4.03 ± 3.48 -4.03 ± 4.09</td> <td>-6.64 ± 3.93* -5.7 ± 3.95</td> </tr> <tr> <td>Simpson-Angus at 1hr/ endpoint</td> <td>-0.32 ± 1.19 -0.37 ± 1.26</td> <td>-0.25 ± 1.05 -0.37 ± 1.13</td> </tr> <tr> <td>Barnes akathisia scores at 1hr/ endpoint</td> <td>-0.26 ± 0.76 -0.29 ± 0.9</td> <td>-0.62 ± 0.86 -0.37 ± 0.8</td> </tr> <tr> <td>Benzotropine required</td> <td>7.9%</td> <td>7.3%</td> </tr> <tr> <td>QTc</td> <td>+3.6msec</td> <td>-1.3msec</td> </tr> </tbody> </table> <p>Mean ± SD *significant versus ZIP2mg</p>		ZIP2 (n=38)	ZIP20 (n=41)	Completed study	94.7%	92.7%	% receiving 1, 2, 3, or 4 injections	26.3/ 42.1/ 21.1/ 10.5	41.5/ 36.6/ 14.6/ 7.3	BARS score at 4hrs	3.8	2.8	BARS score AUC _{0-4hrs}	15.73 ± 3.06	12.23 ± 3.17*	BARS score AUC _{0-2hrs}	8.48 ± 1.2	6.95 ± 1.57*	BARS responder rate	26.3%	65%*	CGI-S at 4hrs/endpoint	-1.16 ± 1.28 -0.92 ± 1.22	-1.88 ± 1.45* -1.58 ± 1.3*	CGI-I at 4hrs/endpoint	3.05 ± 1.11 3.32 ± 1.16	2.15 ± 0.83* 2.38 ± 0.93*	PANSS total at 4hrs/ endpoint	-10.1 ± 9.44 -12.08 ± 13.57	-17.72 ± 16.62 -18.3 ± 14.63	PANSS agitation at 4hrs/endpoint	-4.03 ± 3.48 -4.03 ± 4.09	-6.64 ± 3.93* -5.7 ± 3.95	Simpson-Angus at 1hr/ endpoint	-0.32 ± 1.19 -0.37 ± 1.26	-0.25 ± 1.05 -0.37 ± 1.13	Barnes akathisia scores at 1hr/ endpoint	-0.26 ± 0.76 -0.29 ± 0.9	-0.62 ± 0.86 -0.37 ± 0.8	Benzotropine required	7.9%	7.3%	QTc	+3.6msec	-1.3msec
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<p>Study 121 Poster presentation and FDA transcripts R, open label, PR Ziprasidone vs. haloperidol 7 days n=306</p>	<p>Acute psychosis related to schizophrenia, schizoaffective, bipolar with psychotic features, schizophreniform, delusional, brief psychotic, and shared psychotic disorders</p> <p>Clinically stable; non-agitated</p>	<p>Received IM dosing days 1-3 then oral on days 4-7 Fixed dose IM ziprasidone QID 5, 10 (given at least 2 hrs apart), or 20mg (given at least 4 hrs apart)</p> <p>Flexible dose haloperidol IM 2 to 4 times daily</p> <ul style="list-style-type: none"> Mean IM haloperidol dose 11mg/day Most used only 2 IM doses of haloperidol per day <p>Oral ziprasidone initiated at either 2x the last daily IM dose or 80mg, whichever was higher. Dose may then be adjusted 80-200mg /day according to clinical response.</p> <p>Oral haloperidol was initiated at either the total last daily IM dose or 10mg/day, whichever was higher. Dose may then be adjusted 10-80mg/day according to clinical response.</p> <p>Mean oral haloperidol dose 13mg/day</p> <p><i>Concomitant treatment with lorazepam, temazepam, oral anticholinergics, and beta-blockers were allowed PRN</i></p>	<p>Dx of schizophrenia – ZIP 68%; HAL 66%</p> <p>BPRS - ZIP 36.5 ± 12.2; HAL 38 ± 13.8</p> <p>CGI-S – ZIP 3.7± 1.2; HAL 3.8 ± 1.0</p>	<table border="1"> <thead> <tr> <th></th> <th>Ziprasidone</th> <th>Haloperidol</th> </tr> </thead> <tbody> <tr> <td>% pts. d/c IM phase (LOE/ AE/ total)</td> <td>0/3.6/12.4 (data for 10 and 20mg doses)</td> <td>0/1/7</td> </tr> <tr> <td>BPRS (IM/oral)</td> <td>-5.6 ± 7.6 -6.2 ± 8.2</td> <td>-6.3 ± 10.5 -7.5 ± 10.5</td> </tr> <tr> <td>CGI-S (IM/oral)</td> <td>-0.2 ± 0.6 -0.3 ± 0.8</td> <td>-0.3 ± 0.7 -0.4 ± 0.8</td> </tr> <tr> <td>CGI-I score (IM/oral)</td> <td>3.6 ± 0.9 3.3 ± 1.0</td> <td>3.7 ± 0.9 3.5 ± 0.9</td> </tr> <tr> <td>Simpson-Angus/Barnes akathisia scores during IM phase</td> <td>-0.11 to -0.45 -0.09 to 0.02</td> <td>+0.15 +0.19</td> </tr> </tbody> </table> <p>Mean ± SD Statistical analysis was not provided</p>		Ziprasidone	Haloperidol	% pts. d/c IM phase (LOE/ AE/ total)	0/3.6/12.4 (data for 10 and 20mg doses)	0/1/7	BPRS (IM/oral)	-5.6 ± 7.6 -6.2 ± 8.2	-6.3 ± 10.5 -7.5 ± 10.5	CGI-S (IM/oral)	-0.2 ± 0.6 -0.3 ± 0.8	-0.3 ± 0.7 -0.4 ± 0.8	CGI-I score (IM/oral)	3.6 ± 0.9 3.3 ± 1.0	3.7 ± 0.9 3.5 ± 0.9	Simpson-Angus/Barnes akathisia scores during IM phase	-0.11 to -0.45 -0.09 to 0.02	+0.15 +0.19																											
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<p>Brook 2000 Study 306 R, open label, PR Ziprasidone vs. haloperidol 7 days n=132</p>	<p>Acute psychosis requiring hospitalization related to schizophrenia, schizoaffective, bipolar with psychotic features, schizophreniform, delusional, brief psychotic, and shared psychotic disorders</p> <p>Experiencing agitation</p>	<p>Flexible dosing of IM ziprasidone (initial dose 10mg; additional doses 5-20mg PRN, max 80mg/d) and haloperidol (2.5-10mg; max. 40mg/d) for up to 3 days followed by oral for remainder of study</p> <ul style="list-style-type: none"> • Mean IM dose (day 1, 2, 3) - ZIP 23.3mg/27.6mg/27.6mg; HAL 7.6mg/10.1mg/11mg • 70% received IM for ≤ 2 days <p>Oral ziprasidone initiated at either 2x the last daily IM dose or 80mg, whichever was higher. Dose may then be adjusted 80-200mg /day according to clinical response. Oral haloperidol was initiated at either the total last daily IM dose or 10mg/day, whichever was higher. Dose may then be adjusted 10-80mg/day according to clinical response.</p> <p>Mean oral dose ZIP 90.5 ± 44.9mg; HAL 14 ± 10.1mg</p> <p><i>Concomitant treatment with lorazepam, temazepam, oral anticholinergics, and beta-blockers were allowed PRN</i></p>	<p>Dx schizophrenia – ZIP 74%; HAL 60%</p> <p>BPRS – ZIP 45.9 ± 10.5; HAL 47.5 ± 9.3</p> <p>BPRS agitation items- ZIP 9.9± 3.3; HAL 10.5 ± 3.4</p> <p>CGI-S – ZIP 5.1 ± 0.8; HAL 4.9 ± 1.1</p> <p>% CGI-S ≥5 – ZIP 70; HAL 64.3</p> <p>% using an antipsychotic 48hrs prescreen – ZIP 65.6%; HAL 66.7</p> <p>Simpson-Angus – ZIP 2.62 ± 4.64; HAL 2.49 ± 4.71</p> <p>Barnes Akathisia – ZIP 0.38 ± 0.79; HAL 0.34 ± 0.69</p> <p>% using anxiolytics prestudy - ZIP 63.3%; HAL 66.7%</p>	<table border="1"> <thead> <tr> <th></th> <th>Ziprasidone (n=90)</th> <th>Haloperidol (n=42)</th> </tr> </thead> <tbody> <tr> <td>Completed study</td> <td>91.1%</td> <td>80.9%</td> </tr> <tr> <td>% pts. d/c due to AE (IM/IM+oral)</td> <td>1.1/ 4.4</td> <td>0/ 2.4</td> </tr> <tr> <td>BPRS (IM/oral)</td> <td>-6.24 ± 8.3* -8.76 ± 11.62</td> <td>-3.18 ± 6.55 -5.83 ± 9.5</td> </tr> <tr> <td>BPRS agitation (IM/oral)</td> <td>-1.93 ± 3.41* -2.09 ± 4.41</td> <td>-0.8 ± 2.81 -1.59 ± 3.61</td> </tr> <tr> <td>CGI-S (IM/oral)</td> <td>-0.49 ± 0.62* -0.89 ± 1.23*</td> <td>-0.15 ± 0.53 -0.38 ± 1.17</td> </tr> <tr> <td>CGI-I (IM/oral)</td> <td>3.38 ± 0.98 3.07 ± 1.33</td> <td>3.49 ± 0.81 3.14 ± 1.0</td> </tr> <tr> <td>% dystonia/EPS/hypertonia/akathisia during IM tx</td> <td>1.1/ 0 / 0 / 2.2</td> <td>7.1/ 21.4 / 7.1/ 0</td> </tr> <tr> <td>% dystonia/EPS/hypertonia/akathisia during IM+ oral tx</td> <td>4.4/ 1.1 / 3.3/ 3.3</td> <td>11.9/ 38.1 / 11.9 / 9.5</td> </tr> <tr> <td>Simpson-Angus (IM/endpoint)</td> <td>-0.61 ± 3.11 -1.09 ± 4.33</td> <td>+3.8 ± 5.22 +6.0 ± 7.12</td> </tr> <tr> <td>Barnes akathisia (IM/endpoint)</td> <td>-0.03 ± 0.57 -0.1 ± 0.79</td> <td>+0.44 ± 0.87 +0.8 ± 1.14</td> </tr> <tr> <td>QTc at end of IM tx</td> <td>+2.14msec</td> <td>+2.22msec</td> </tr> </tbody> </table> <p>Mean ± SD *significant versus haloperidol</p>		Ziprasidone (n=90)	Haloperidol (n=42)	Completed study	91.1%	80.9%	% pts. d/c due to AE (IM/IM+oral)	1.1/ 4.4	0/ 2.4	BPRS (IM/oral)	-6.24 ± 8.3* -8.76 ± 11.62	-3.18 ± 6.55 -5.83 ± 9.5	BPRS agitation (IM/oral)	-1.93 ± 3.41* -2.09 ± 4.41	-0.8 ± 2.81 -1.59 ± 3.61	CGI-S (IM/oral)	-0.49 ± 0.62* -0.89 ± 1.23*	-0.15 ± 0.53 -0.38 ± 1.17	CGI-I (IM/oral)	3.38 ± 0.98 3.07 ± 1.33	3.49 ± 0.81 3.14 ± 1.0	% dystonia/EPS/hypertonia/akathisia during IM tx	1.1/ 0 / 0 / 2.2	7.1/ 21.4 / 7.1/ 0	% dystonia/EPS/hypertonia/akathisia during IM+ oral tx	4.4/ 1.1 / 3.3/ 3.3	11.9/ 38.1 / 11.9 / 9.5	Simpson-Angus (IM/endpoint)	-0.61 ± 3.11 -1.09 ± 4.33	+3.8 ± 5.22 +6.0 ± 7.12	Barnes akathisia (IM/endpoint)	-0.03 ± 0.57 -0.1 ± 0.79	+0.44 ± 0.87 +0.8 ± 1.14	QTc at end of IM tx	+2.14msec	+2.22msec						
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<p>Poster presentation R, blinded-assessment, PR Ziprasidone vs. haloperidol 6 weeks n=550</p>	<p>Schizophrenia or schizoaffective DSM-IV with acute exacerbation within 7 days of study startup</p> <p>Hospitalized or transferred to a high-dependency unit for acute exacerbation</p> <p>BPRS ≥ 40</p> <p>IM treatment considered appropriate in clinicians judgment</p>	<p><u>IM dosing</u> ZIP 10 or 20mg initially. May repeat up to 40mg/d for up to 3 days</p> <p>HAL 2.5 or 5mg initially. May repeat up to 10mg/d for up to 3 days</p> <p><u>PO dosing after minimum of 2 IM doses</u> ZIP 40mg BID initially. May be adjusted to 40-80mg BID</p> <p>HAL 5mg BID initially. May be adjusted to 5-20mg BID</p> <p><u>Doses used during study</u> Median duration of IM tx (range) ZIP 2 (1-4) days; HAL 2 (1-4) days</p> <p>Patients with 2 injections/day ZIP 76.3%; HAL 78.2%</p> <p>Mean IM dose (est. from graph) ZIP 23mg; HAL 7.25mg</p> <p>Mean oral dose ZIP 115.8mg; HAL 11.5mg</p> <p><i>Concomitant treatment with lorazepam, temazepam, oral anticholinergics, and beta-blockers were allowed PRN</i></p>	<p>Dx of schizophrenia- ZIP 89%; HAL 82%</p> <p>Mean age (yrs.) 34.5 ± 10.6 67% male</p> <p>BPRS – ZIP 57 ± 10.5; HAL 57 ± 9.6</p> <p>CGI-S- ZIP 5.3 ± 0.82; HAL 5.3 ± 0.76</p> <p>Approx. 85% of patients were considered severely ill (CGI-S ≥ 5)</p>	<table border="1"> <thead> <tr> <th></th> <th>Ziprasidone (n=417)</th> <th>Haloperidol (n=133)</th> </tr> </thead> <tbody> <tr> <td>% d/c due to LOE/AE / total (IM phase)</td> <td>0 / 0.2 / 0.9</td> <td>0 / 0.7 / 2.2</td> </tr> <tr> <td>% d/c IM + oral phases (LOE/AE/total)</td> <td>10.7/ 4.2 / 31.3</td> <td>6.5/ 9.4 / 32.6</td> </tr> <tr> <td>BPRS (IM/oral)</td> <td>-6.15 ± 0.45* -14.99 ± 0.93</td> <td>-4.13 ± 0.64 -15.79 ± 1.36</td> </tr> <tr> <td>CGI-S (IM/oral)</td> <td>-0.45 ± 0.04/ -1.35 ± 0.09</td> <td>-0.36 ± 0.04/ -1.54 ± 0.13</td> </tr> <tr> <td>% with improvement in CGI-I score at end of oral phase</td> <td>73.9%</td> <td>75.4%</td> </tr> <tr> <td>ESRS (IM/oral)</td> <td>-1/-2</td> <td>+4/+4</td> </tr> <tr> <td>Barnes akathisia (IM/oral)</td> <td>+0.1/+0.05</td> <td>+1.1/+1.3</td> </tr> <tr> <td>Akathisia</td> <td>8.2%</td> <td>23.3%</td> </tr> <tr> <td>Dystonia</td> <td>3.1%</td> <td>10.5%</td> </tr> <tr> <td>EPS</td> <td>5.3%</td> <td>22.6%</td> </tr> <tr> <td>Insomnia</td> <td>21.3%</td> <td>15.8%</td> </tr> <tr> <td>Somnolence</td> <td>12.9%</td> <td>5.3%</td> </tr> <tr> <td>Anticholinergic used during IM phase</td> <td>13.7%</td> <td>49.6%</td> </tr> </tbody> </table> <p>Mean ± SD *Significant versus haloperidol</p>		Ziprasidone (n=417)	Haloperidol (n=133)	% d/c due to LOE/AE / total (IM phase)	0 / 0.2 / 0.9	0 / 0.7 / 2.2	% d/c IM + oral phases (LOE/AE/total)	10.7/ 4.2 / 31.3	6.5/ 9.4 / 32.6	BPRS (IM/oral)	-6.15 ± 0.45* -14.99 ± 0.93	-4.13 ± 0.64 -15.79 ± 1.36	CGI-S (IM/oral)	-0.45 ± 0.04/ -1.35 ± 0.09	-0.36 ± 0.04/ -1.54 ± 0.13	% with improvement in CGI-I score at end of oral phase	73.9%	75.4%	ESRS (IM/oral)	-1/-2	+4/+4	Barnes akathisia (IM/oral)	+0.1/+0.05	+1.1/+1.3	Akathisia	8.2%	23.3%	Dystonia	3.1%	10.5%	EPS	5.3%	22.6%	Insomnia	21.3%	15.8%	Somnolence	12.9%	5.3%	Anticholinergic used during IM phase	13.7%	49.6%
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