

National PBM Drug Monograph
Olanzapine IM (Zyprexa IntraMuscular)

September 2004

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Olanzapine is the second atypical antipsychotic approved in an intramuscular (IM) formulation for the treatment of acute agitation associated with schizophrenia and bipolar mania. Alternative IM treatments include haloperidol and lorazepam.

Olanzapine IM's pharmacology and pharmacokinetics are similar to its oral form with the exception of 100% bioavailability, a peak plasma concentration that is ~5 times greater than the oral form, and a shorter time to peak. The IM formulation shares the labeling with its oral counterparts including its contraindications, warnings, precautions, drug interactions and adverse effects. One precaution of olanzapine IM specifically addressed in the product labeling is cardiovascular complications, including hypotension.

The initial dose of olanzapine IM is 10 mg; additional doses of 10 mg are recommended should agitation persist. The maximum dose is 30 mg per day. Doses as low as 2.5 mg can be used for older or debilitated patients.

Olanzapine IM requires reconstitution with Sterile Water for Injection resulting in 10 mg in 2 mL. Any unused portion is to be discarded after one hour. Olanzapine IM should not be given by any other route of administration. In clinical trials, the majority of patients required a single dose.

The efficacy and safety of olanzapine IM has been studied in two clinical trials of acute agitation in schizophrenia, one trial in acute agitation in bipolar mania and one trial in acute agitation in patients with dementia. Each trial included an active control of either IM haloperidol or IM lorazepam and an IM placebo control group. All were 24 hours in duration with patients receiving a maximum of 3 doses of study medication. Overall, all groups receiving active drug showed significant improvement over placebo in standardized scales used to assess agitation. Analysis of the scale results at individual time points found olanzapine IM to separate significantly from placebo 15 minutes after the first dose and from haloperidol and lorazepam at 30 minutes. At the two hour time point these difference were no longer significant between haloperidol and olanzapine. At 24 hours, comparisons between the haloperidol and olanzapine treatment arms did not differ, but both groups differed significantly from placebo. Similar findings were reported in comparisons between olanzapine and lorazepam and placebo at 24 hours.

Based on the adverse effects reported in clinical trials, the frequency of extrapyramidal symptoms was lower with olanzapine compared to haloperidol. Somnolence was more frequent with olanzapine than with lorazepam.

Olanzapine IM's cost is \$13.02 for a 10 mg dose. The cost of an IM 5 mg dose of haloperidol is \$1.95 and the cost of a 2 mg IM dose of lorazepam is \$4.64.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating olanzapine IM for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics^{1,2}

Olanzapine's mechanism of action remains unknown. Its proposed therapeutic effect, like the other atypical antipsychotics, involves antagonism of dopamine and serotonin type 2 inhibitors receptors in the nigrostriatal, mesocortical, tuberoinfundibular, and mesolimbic pathways in the brain.

After 5 mg doses of oral and IM olanzapine, the peak plasma concentration were ~5 times greater following the IM dose. Additional pharmacokinetics parameters are shown in the following table.

Parameter	Olanzapine IM	Olanzapine Oral	Haloperidol IM
Metabolism	1 st pass metabolism, CYP 1A2 & 2D6, and glucuronidation	1 st pass metabolism, CYP 1A2 & 2D6, and glucuronidation	CYP1A2, 2D6, 3A4
Elimination	~7% unchanged in urine	~7% unchanged in urine	Hepatic
Half-life	30 hrs (21 – 54 hrs)	30 hrs (21 – 54 hrs)	20 hrs
Protein Binding	93%	93%	90%
Bioavailability	100%	Absolute ~60%	100%
Onset of Action	≤2 hours	Not applicable	≤1 hour
Time to peak	15 – 45 minutes	~6 hours	2 – 4 hours

FDA Approved Indication(s) and Off-label Uses¹

Olanzapine is an atypical antipsychotic whose oral formulation was approved September 30, 1996 with indications for the treatment of schizophrenia and bipolar disorder. An oral disintegrating tablet was approved April 6, 2000. The intramuscular formulation was approved March 29, 2004 with an indication for the treatment of agitation associated with schizophrenia and bipolar I disorder.

It is likely that olanzapine IM will also be used off-label to treat or manage acute psychomotor agitation associated with other conditions.

Current VA National Formulary Alternatives

Conventional antipsychotics chlorpromazine, fluphenazine, and haloperidol are available in an intramuscular formulation for the treatment of acute psychosis and agitation.

Ziprasidone (Geodon) is the only other atypical antipsychotic available in IM form for acute treatment of psychosis and agitation. Ziprasidone IM is not on the VA National Formulary and non-formulary use includes criteria for use.

Benzodiazepines are alternatives to the antipsychotics for the acute treatment of agitation and bipolar I mania; lorazepam (Ativan), a benzodiazepine of intermediate duration, is frequently used for these indications.

Dosage and Administration¹

The initial recommended dose of olanzapine IM for agitated patients with schizophrenia or bipolar mania is 10 mg. Additional doses of 10 mg are recommended if agitation persists warranting continued IM treatment. Lower doses of 2.5 mg or 5 mg can be used for selected patients, including the elderly and the debilitated. The maximum recommended daily dose is 30 mg.

The manufacturer's labeling points out that the efficacy of repeated doses has not been systematically evaluated in controlled clinical trials. Furthermore, olanzapine IM's efficacy and safety profile has not been evaluated above a single 10 mg dose, given more frequently than 2 hours after the initial dose, nor 4 hours after the second dose, or beyond total daily doses of 30 mg.

Directions for Reconstitution and Administration

The contents of the vial should be dissolved in the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow, and be used immediately (within 1 hour) after reconstitution. Any unused portion should be discarded. Olanzapine IM is for intramuscular use only. Inject slowly, deep into the muscle mass. Do not administer intravenously or subcutaneously.

The following table provides injection volumes for various doses after reconstitution as described above.

Dose, mg Olanzapine	Volume of Injection, mL
10.0	Withdraw total contents of vial
7.5	1.5
5.0	1.0
2.5	0.5

Efficacy

Efficacy Measures

Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) – Often used as an entrant criteria as well as a primary efficacy measure. The PANSS-EC is derived from the Positive and Negative Syndrome Scale (PANSS) and assesses tension, uncooperativeness, hostility, poor impulse control, and excitement. Each item is rated by physician observation and scored from 1 to 7 (the greater the value, the greater the severity). This scale has been validated.

Agitated Behavior Scale (ABS) - A validated, 14-point scale for the assessment of agitation; used in emergency rooms to monitor a patient’s level of agitation. This scale has been validated.

Agitation Calmness Evaluation Scale (ACES) – Developed by Eli Lilly and Company as a single-item scale with a 1= marked agitation, 2 = moderate agitation, 3 = mild agitation, 4 = normal, 5 = mild calmness, 6 = moderate calmness, 7 = marked calmness, 8 = deep sleep, and 9 = unable to be aroused.

Cohen-Mansfield Agitation Inventory (CMAI) – A rating of the frequency of agitated behavior that consists of 30-items, rated on a 7-point scale. This scale has been validated.

Brief Psychiatric Rating Scale (BPRS) – A validated scale consisting of 18-symptom constructs, each rated on a 7-point scale ranging from 1 = “not present” to 7 = “extremely severe,” that measures major psychotic and nonpsychotic symptoms in persons with schizophrenia and other psychiatric conditions. A sub-scale measuring positive symptoms is sometimes used.

Simpson Angus Scale (SAS) – This validated 10 item instrument is used to measure the symptoms of Parkinsonism or drug-induced parkinsonian side effects. The clinician rates each item from 0 (normal or absence of the condition) to 4 (the condition is extreme in severity). The global score is the sum of all scores divided by the number of items.

Barnes Akathisia Scale (BAS) – Used to evaluate akathisia associated with antipsychotic medications, including an objective and a subjective component plus a global impression rating for the overall disorder. The objective and subjective items are rated from 0 (normal, no evidence) to 3 (constant, severe, intense); the global assessment is rated from 0 (absent) to 5 (severe). This scale has been validated.

Summary of Efficacy Findings

Common Study Design Components

The following were included in all or most of the efficacy studies:

- All studies used a double-blind, placebo-controlled, randomized design.
- Subjects were 18 years of age or older and provided informed consent prior to enrollment.
- A screening period preceded the treatment period.

- Each treatment period lasted 24 hours during which the subject could receive up to 3 doses of study medication, rescue medication (usually a benzodiazepine) was permitted following the second dose of study medication, and anticholinergic medications were only permitted for the treatment of newly emergent extrapyramidal side effects.
- Subjects were randomly assigned to olanzapine 2.5, 5, 7.5 or 10 mg per IM injection (not all studies used every dose). Comparator arms included placebo, and haloperidol 7.5 mg per IM injection or lorazepam 2 mg per IM injection. A second dose equal to the amount of the first dose was permitted at the clinician's discretion, but no sooner than 2 hours and no later than 20 hours after the first dose. A third dose of study medication was permitted no sooner than 4 hours after the second dose, but within 20 hours of the initial dose.
- Assessments for efficacy were conducted at screening, immediately prior to the first dose, then at 0.25, 0.5, 1, 1.5, 2, 4, 6, 12 and 24 hours after the first dose. Not all studies collected data at each time point.
- Response was considered a $\geq 40\%$ reduction in PANSS-EC from baseline at 2 hours.

Treatment of Acute Agitation in Schizophrenia^{3,4,5}

The efficacy and safety of IM olanzapine was evaluated for the management of acute agitation in schizophrenics in two trials using placebo and haloperidol as comparison arms. The first trial's primary hypothesis was the existence of a dose-response relationship in agitation reduction on the PANSS-EC within 2 hours after an initial dose of 2.5, 5, 7.5 and 10 mg doses of olanzapine IM. Secondary hypotheses included 1) at 2 hours after the initial dose there would not be a difference in between IM olanzapine and IM haloperidol 7.5 mg in the reduction of agitation and that olanzapine would be superior to placebo; 2) IM olanzapine's efficacy would be confirmed by response rates, the use of benzodiazepines, injection frequency, and additional measures of agitation; 3) IM olanzapine's efficacy would last for 24 hours; and 4) the overall safety profile of IM olanzapine would be superior to IM haloperidol. (See Breier et al, 2002, Appendix for study details)

All doses of olanzapine and haloperidol produced significant mean changes in PANSS-EC score 2 hours after the first dose compared to placebo ($p < 0.01$ vs. $O_{2.5 \text{ mg}}$ and $p < 0.001$ vs. all others. Haloperidol and $O_{5, 7.5 \text{ \& } 10 \text{ mg}}$ also produced a change significant from $O_{2.5 \text{ mg}}$ ($p < 0.01$ vs. $O_{5 \text{ mg}}$; $p \leq 0.001$ $O_{7.5 \text{ \& } 10 \text{ mg}}$; $p = 0.04$ vs. H). No significant differences were found between the three higher doses of olanzapine compared to haloperidol.

The response rates for all four doses of olanzapine and haloperidol were significantly greater than placebo; demonstrating a response-relationship with olanzapine. Olanzapine $_{7.5 \text{ \& } 10 \text{ mg}}$ produced greater response rates than olanzapine $_{2.5 \text{ mg}}$. There were no significant differences between any of the olanzapine groups and haloperidol. On the other efficacy measures, the $O_{5, 7.5, \text{ \& } 10 \text{ mg}}$ groups all differed significantly from placebo. Subjects receiving haloperidol 7.5 mg differed significantly from placebo on all measures except the BPRS-Positive scale.

At 24 hours after the first dose, all doses of olanzapine were significantly different from placebo on the PANSS-EC, ABS, ACES, BPRS, and BPRS-positive scales; except $O_{2.5 \text{ mg}}$ on the BPRS-positive scale. Haloperidol differed significantly from placebo on the BPRS-positive scale and ABS. Olanzapine $_{7.5 \text{ \& } 10 \text{ mg}}$ showed significantly greater mean improvement in the ABS compared to haloperidol.

Over the 24-hour study period, two-thirds of subjects treated with placebo received 2 or 3 doses of study medication, compared to $\leq 35\%$ subjects in the $O_{5, 7.5 \text{ \& } 10 \text{ mg}}$ and haloperidol groups. Benzodiazepines were given to 36% of subjects assigned to placebo compared to 4% – 10% of those receiving olanzapine; no subject assigned to haloperidol received a benzodiazepine. Anticholinergic use was limited to the $O_{2.5 \text{ mg}}$ and haloperidol groups.

Hypotension was unique to olanzapine and experienced by $\sim 4\%$ of subjects. Extrapyramidal symptoms were more common in the haloperidol group. The percent of subjects with Parkinsonian symptoms was significantly greater with haloperidol compared to placebo and $O_{2.5, 5, \text{ \& } 7.5 \text{ mg}}$. No other between group differences were significant. The frequency of ECG QTc changes did not differ among the treatment groups.

The investigators concluded that IM olanzapine demonstrated a dose-response relationship in the treatment of acute agitation in schizophrenics and was well tolerated. They recommended that 10 mg be the initial dose for most patients.

The second study in acutely agitated schizophrenics, Wright et al randomized 270 subjects to IM olanzapine 10 mg, haloperidol 7.5 mg, or placebo in a 2:2:1 ratio. The study hypotheses were noninferiority between olanzapine and haloperidol, and that olanzapine would be superior to placebo in decreasing agitation. Enrollment criteria, study design and assessment measures were essentially the same as those in the previous trial; the PANSS-EC was measured at baseline, 15, 30, 45, 60, 90, and 120 minutes, and 24 hours after the initial dose of study medication.

In the first 2 hours after the initial dose, significant differences in PANSS-EC scores were noted at 15, 30, and 45 minutes between olanzapine and haloperidol, from 30 minutes onward with haloperidol vs. placebo, and at all points for olanzapine compared to placebo. At 24 hours after the last dose IM olanzapine and IM haloperidol were both superior to placebo for reducing on the BPRS-total, BPRS-positive and the Clinical Global Impressions – Improvement of Illness scales. Olanzapine and haloperidol were deemed comparable at the 24 hour time point. Overall, the percent responding was 73% for olanzapine, 69% for haloperidol, and 33% for placebo ($p < 0.001$ for both active groups vs. placebo). Benzodiazepine use was also significantly more frequent in the placebo group (39%) than both olanzapine (16%, $p = 0.002$) and haloperidol (20%, $p = 0.009$)

Treatment emergent parkinsonism occurred less frequently in subjects treated with olanzapine than haloperidol (4.3% vs. 13.3%, $p = 0.036$). The incidence of akathisia did not differ between the two groups. The change mean change in SAS and BAS scores did favor olanzapine in comparison to haloperidol. There were no significant QTc changes from baseline noted within or between groups.

The authors concluded that in the initial 24 hours, olanzapine IM is comparable to IM haloperidol in decreasing the symptoms of acute agitation in patients with schizophrenia. The onset of efficacy for both drugs was seen within 2 hours of the first dose.

Treatment of Acute Agitation in Bipolar Mania⁶

One study has evaluated the efficacy and safety of 10 mg olanzapine IM in acutely agitated bipolar mania compared to placebo with lorazepam 2 mg IM as an active control group (See Meehan, et al., 2001 in the Appendix). The Young-Mania Rating Scale (YMRS), BPRS-Mania, PANSS-Hostility, and PANSS-Depression scale were used to measure efficacy, in addition to the previously mentioned assessments used in the schizophrenic trials. Efficacy was assessed at 2 and 24 hours after the initial dose and safety was assessed over the entire 24-hour treatment period.

Two hundred and one subjects were randomized. In the two hours after the initial dose of study medication, subjects treated with olanzapine had a significantly greater mean improvement in the PANSS-EC than those treated with lorazepam or placebo. This difference was significant from both groups at 30, 60, 90, and 120 minutes after the dose. There was a trend towards significance in favor of lorazepam when compared to placebo ($p = 0.053$) at 2 hours. Comparisons for earlier times were not provided. At 2 hours, olanzapine differed significantly from lorazepam and placebo in change in ABS, ACES, PANSS-total, and PANSS-positive (except PANSS-positive vs. lorazepam, $p = 0.056$). Lorazepam differed from placebo in all assessments as well.

After 24 hours, there were no differences between the olanzapine and lorazepam treatment groups. Olanzapine was significantly different from placebo on the PANSS-EC, ABS, ACES, PANSS-total, and PANSS-positive scales. Lorazepam differed from placebo on the ABS and ACES scales only.

No cases of treatment emergent EPS were reported, nor were there significant differences among the treatment groups for the QTc interval at the 2 hour point. At 2 hours after the initial dose, supine systolic blood pressure changed on average by -7.26 mm Hg for olanzapine, -8.64 mm Hg for lorazepam and +1.2 mmHg for placebo ($p < 0.001$). Standing systolic blood pressure changed on average by -5.09 mm Hg, -7.10 mm Hg and 0 mmHg for olanzapine, lorazepam and placebo, respectively ($p < 0.02$). Upon pairwise comparisons, only standing SBP differed between olanzapine and placebo ($p = 0.027$). Mean orthostatic pulse rate at 2 hours changed +6.9 bpm for olanzapine, +0.96 bpm for lorazepam and +0.35 for placebo ($p < 0.009$). Pairwise comparison found these changes significant between olanzapine and lorazepam ($p = 0.015$), and olanzapine and placebo ($p = 0.009$). There was one case of syncope associated with olanzapine.

The studies authors concluded that IM olanzapine was safe and effective in acutely agitated patients with bipolar mania.

Treatment of Acute Agitation in Dementia⁷

A multicenter, double-blind, placebo controlled parallel trial, conducted in nursing homes and hospitals, randomized agitated patients with Alzheimer's disease, vascular dementia or a mixed dementia to IM olanzapine 2.5 mg or 5 mg, IM lorazepam 1 mg, or IM placebo in a 1:1:1:1 ratio. A second or third dose were available, with the third dose being half the first dose, although patients in the placebo would receive 5 mg of olanzapine IM. Efficacy assessments were made using the PANSS-EC, the Cohen-Mansfield Agitation Inventory (CMAI), and the ACES. The CMAI is a 30-item, 7-point rating scale for rating the frequency of agitated behavior. The change in the PANSS-EC score was the primary outcome variable. The Neuropsychiatric Inventory/Nursing Home (NPI/NH) scale was used to measure baseline severity of a patient's psychopathology.

A total of 272 patients were randomized. The severity of cognitive impairment was moderate based on a mean Mini Mental Status Exam score of 11.8, with severity being significantly greater in the NH patients. At the 2 hour study point, both the olanzapine 5 mg and lorazepam 1 mg groups showed significantly greater improvement on the PANSS-EC, CMAI, and ACES scales compared to placebo. The olanzapine 2.5 mg group differed from placebo on the PANSS-EC and ACES scales. There were no differences on the three measures of agitation between the olanzapine and lorazepam groups. Interestingly, compared to baseline, all four treatment groups' agitation had decreased significantly on all three measures after 2 hours. Clinical response rates at 2 hours were significantly greater for all three active treatment arms compared to placebo: 62% olanzapine 2.5mg, 66.7% olanzapine 5 mg, 72.1% lorazepam, and 37.3% placebo.

At 24 hours after the first injection, the differences from baseline were not as great compared to the 2 hour time point, yet they were still significant from placebo on the PANSS-EC for both olanzapine groups, and the ACES for the olanzapine 5 mg and lorazepam groups.

At the 2 and 24 hour time points, no differences between any of the four treatment groups were seen in the frequency of extrapyramidal symptoms or corrected QTc interval, nor were there significant differences in vital signs.

The authors concluded that IM olanzapine may be beneficial in the rapid treatment of patients with dementia who are acutely agitated.

For further details on the efficacy results of the clinical trials, refer to *Clinical Trials Tables Appendix, page 11*.

Adverse Events (Safety Data)^{1,3,4,5}

The information on the adverse events reported with olanzapine IM are limited due to the small number of patients studied, the limited number of doses administered, and the 24 hour study duration in the pivotal trials. The adverse events reported have been consistent with those reported with its oral formulation. Clinical trials have focused on treatment emergent EPS which are less frequent than with IM haloperidol. Based upon an open-label clinical pharmacology study described in olanzapine's package insert, approximately one-third of non-agitated schizophrenic patients experienced significant orthostatic decrease in systolic blood pressure after receiving three 10 mg doses administered 4 hours apart. The frequency of hypotension in clinical trials was lower, which might be explained by the fact that most patients did not receive a second or third dose of study medication.

Treatment-emergent Adverse Events Reported by $\geq 1\%$ of Agitated Patients with Either Schizophrenia or Bipolar Mania: IM olanzapine vs. placebo¹

Percentage of Patients Reporting

Body System/Adverse Event	Olanzapine (N=415)	Placebo (N=150)
Body as a Whole		
Asthenia	2	1
Cardiovascular		
Hypotension	2	0
Postural hypotension	1	0
Nervous System		
Somnolence	6	3
Dizziness	4	2
Tremor	1	0

Composite Frequency (%) of Treatment Emergent Extrapyrimal Symptoms (EPS) from the Acute Agitation in Schizophrenia^{Trials3,4,5,a}

EPS	Olanzapine (all doses)	Haloperidol	Placebo ^b
Acute Dystonia	0/316	11/166 (6.6%)	0/45
Akathisia	3/302 (1%)	11/164 (6.7%)	0/42
Parkinsonism	7/273 (2.6%)	23/162 (14.2%)	0/42

^aBased on data available in two published trials

^bPlacebo data only reported in one of two published trials

Common Adverse Events

Agitation, anxiety, dry mouth, headache, hypertension, insomnia, and nervousness were reported by at least 1% of patients receiving either olanzapine IM or placebo IM. The incidence of these events with olanzapine was either equal to or less than placebo,

Additional adverse events were reported in clinical trials. These findings are included in the Appendix.

Other Adverse Events

The oral and IM forms of olanzapine share a common package insert. Many other adverse effects have been reported with oral olanzapine and are conceivably possible with IM olanzapine. This additional information can be attained via the package insert or another drug information source.

Tolerability

Over 90% of patients assigned to olanzapine completed treatment in the clinical trials. Reasons cited for discontinuing participation included a lack of efficacy or the physician's decision to withdraw the patient. Pain at the injection site was not mentioned.

For further details on the safety results of the clinical trials, refer to *Clinical Trials Tables Appendix, page 11*.

Precautions/Contraindications¹

The same precautions and contraindications that accompany the oral forms of olanzapine apply to IM olanzapine.

Precautions

Cardiovascular complications including orthostatic hypotension, bradycardia, tachycardia, and syncope have been reported with IM olanzapine. Patients' experiencing symptoms after receiving IM olanzapine should assume a

supine position until examination has indicated that they are no longer experiencing postural hypotension and/or bradycardia.

Olanzapine should be used with caution in patients with a seizure disorder or another condition that lowers their seizure threshold.

In studies involving oral olanzapine, elevated prolactin and liver transaminases concentrations have been reported.

Due to its sedating effects, patients should not drive or operate machinery after receiving IM olanzapine as their thinking, reaction time and alertness may be impaired.

Alterations in body temperature and dysphagia have been associated with olanzapine. Olanzapine's anticholinergic effects may aggravate or worsen certain medical conditions, particularly when taken with other drugs with anticholinergic effects.

Warnings

Olanzapine's labeling includes warnings about an increase risk for hyperglycemia and diabetes, mellitus, cerebral vascular adverse events in elderly patients with dementia, neuroleptic malignant syndrome, and tardive dyskinesia. Clinicians are advised to be watchful for these complications and make the appropriate adjustments in treatment.

Contraindications

Olanzapine is contraindicated in patients with a known hypersensitivity to the product.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

This analysis is pending.

Drug Interactions^{1,2}

Drug-Drug Interactions

Drug interactions that have been reported with oral olanzapine could potentially occur with olanzapine IM. Specific concerns would include medications with duplicative (e.g., anticholinergic, sedative, hypotension) or with opposing pharmacologic effects (e.g., dopamine agonists).

Drugs that induce CYP1A2 or glucuronyl transferase enzymes (e.g., carbamazepine, omeprazole and rifampin) may increase olanzapine's clearance, whereas inhibitors (e.g., fluvoxamine) of this enzyme could potentially inhibit olanzapine's clearance.

According to olanzapine's package insert, administration of 2 mg of IM lorazepam 1 hour after a 5 mg IM dose of olanzapine did not significantly alter the pharmacokinetic profile of either drug. Somnolence, greater than observed by either drug, was observed.

Patients taking olanzapine should avoid consuming alcoholic beverages as this may increase CNS depression.

Herb/Nutraceutical: Avoid dong quai, St John's wort, kava kava, gotu kola, valerian (may increase CNS depression and/or cause photosensitization).

Drug-Lab Interactions

Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

Acquisition Costs

The following table provides the cost per dose for IM olanzapine, haloperidol, and lorazepam in the doses usually ordered for agitated patients. Larger or smaller doses may be appropriate depending on the clinical parameters.

Drug	Dose	Cost/Dose (\$)
Olanzapine	10 mg IM	13.02
Haloperidol	5 mg IM	1.95
Lorazepam	2 mg IM	4.64

Pharmacoeconomic Analysis

There have been no pharmacoeconomic studies or forecasts with olanzapine IM.

Conclusions

Olanzapine IM offers a safe and effective alternative to existing IM treatments for acute agitation due to schizophrenia and bipolar mania. Its primary advantage is in its safety profile, particularly its lower frequency of extrapyramidal symptoms compared to IM haloperidol. There is concern that hypotension following olanzapine IM may be more problematic than with other treatments. Changes in the QTc interval do not appear to differ between olanzapine, alternative treatments and placebo.

In controlled clinical trials, olanzapine IM's efficacy is comparable to that of IM haloperidol and lorazepam. Its onset of action appears to be faster than IM haloperidol and IM lorazepam; how clinically and economically important this is can be debated. A limitation cited in the trials conducted in schizophrenia and bipolar mania was that subjects had to provide written informed consent; however, if they were capable of providing consent, their agitation might have been able to have been managed by other methods, including oral medication. Thus, olanzapine's efficacy in the true patient population for which it is indicated as not been studied, nor for ethical reasons is it possible. Efficacy was also assessed via rating scales which are often difficult to translate into a clinical meaning. Data on the need for restraints, time in restraints or seclusion, or time spent in one-to-one observation for safety were either not collected or reported. Such data would provide insight into whether the faster onset of action justifies olanzapine IM's greater purchase price.

Olanzapine IM is considerably more expensive than IM haloperidol and IM lorazepam. Furthermore, it must be used within 1 hour of reconstitution. Thus, the remainders left from doses less than 10 mg will most likely need to be discarded.

Formulary Decision

Olanzapine IM was added to the VA National Formulary as monotherapy for the treatment of acute agitation associated with schizophrenia or bipolar I mania.

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Appendix: Clinical Trials Table

Study Design Analysis type Setting	Eligibility Criteria	Dosing	Demographics	Results																																																																																																																																																																																					
³ Breier et al., 2002 MC, DB, PC, RCT Acutely agitated schizophrenics LOCF	Inclusion criteria: ≥18 years; PANSS-EC _{≥14} (out of 35) with ≥1 item score ≥4; warrant IM Tx. Exclusion criteria: Unable to consent; Significant medical or substance abuse disorder	Study Medications: Olanzapine (O) IM 2.5, 5, 7.5, or 10 mg; Haloperidol (H) 7.5 mg or Placebo (P) Maximum of 3 doses in 24 hrs, with the 2nd dose no sooner than 2 hrs after the 1st, and the 3rd no sooner than 4 hrs after the 2nd. Concomitant medications: Benzodiazepine (BZD) use permitted within a restricted time frame surrounding each dose of study medication. Anticholinergic medications permitted to treat new onset EPS.	Age: 36.3 ± 11 yrs. Sex: 57.4% male Race: 66% white 24% African PANSS-EC (baseline) O _{2.5} 18.3 ± 2.4 O ₅ 19.7 ± 3.4 O _{7.5} 18.9 ± 2.6 O ₁₀ 19.3 ± 2.6 H _{7.5} 19.3 ± 3.1 P 18.8 ± 2.8	N _R = 270; 99.3% completed the study. EFFICACY <table border="1"> <thead> <tr> <th>Outcome</th> <th>O_{2.5}</th> <th>O₅</th> <th>O_{7.5}</th> <th>O₁₀</th> <th>H_{7.5}</th> <th>P</th> </tr> </thead> <tbody> <tr> <td>Efficacy: Mean (SD) change at 2 hrs</td> <td>n = 48</td> <td>n = 45</td> <td>n = 46</td> <td>n = 46</td> <td>n = 40</td> <td>n = 45</td> </tr> <tr> <td>PANSS-EC</td> <td>-5.5 (4.6)</td> <td>-8.1 (5.3)</td> <td>-8.7 (5.0)</td> <td>-9.4 (4.9)</td> <td>-7.5 (5.9)</td> <td>-2.9 (4.7)⁺</td> </tr> <tr> <td>BPRS total</td> <td>-8.2 (9.1)[#]</td> <td>-10.4 (7.5)</td> <td>-12 (7)</td> <td>-12 (5.9)</td> <td>-9.2 (7.2)[§]</td> <td>-3.7 (5.5)</td> </tr> <tr> <td>BPRS positive</td> <td>-1.5 (3.1)</td> <td>-1.7 (2.8)</td> <td>-2.1 (2.9)</td> <td>-1.9 (2.3)</td> <td>-1.4 (2.2)</td> <td>-0.4 (1.3)</td> </tr> <tr> <td>Response rate</td> <td>50%</td> <td>62.6%</td> <td>73.9%</td> <td>80.4%</td> <td>60%</td> <td>20%</td> </tr> <tr> <td>ABS</td> <td>-5.8 (5.5)</td> <td>-9.0 (5.5)</td> <td>-10.5 (5.6)</td> <td>-10.4 (5.7)</td> <td>-7.7 (5.2)[§]</td> <td>-3.0 (5)</td> </tr> <tr> <td>ACES</td> <td>1.3 (1.5)</td> <td>2.3 (1.9)</td> <td>2.4 (1.7)</td> <td>2.6 (1.7)</td> <td>1.8 (1.6)[§]</td> <td>0.7 (1.2)</td> </tr> <tr> <td>Mean (SD) change at 24 hrs</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>PANSS-EC</td> <td>-4.9 (4.3)</td> <td>-5.5 (4.9)</td> <td>-5.5 (4.1)</td> <td>-5.9 (5.2)</td> <td>-4.5 (4.0)</td> <td>-3.1 (3.3)</td> </tr> <tr> <td>BPRS total</td> <td>-8.4 (7.4)</td> <td>-9.2 (7.8)</td> <td>-9.6 (7.5)</td> <td>-9.0 (7.7)</td> <td>-7.3 (7.5)</td> <td>-4.3 (5.4)</td> </tr> <tr> <td>BPRS positive</td> <td>-1.5 (2.3)</td> <td>-2.0 (2.6)</td> <td>-1.9 (2.7)</td> <td>-1.7 (2.4)</td> <td>-1.8 (3.0)[§]</td> <td>-0.6 (2.2)</td> </tr> <tr> <td>ABS</td> <td>-5.7 (4.2)</td> <td>-6.7 (5.9)</td> <td>-7.7 (5.8)[#]</td> <td>-7.4 (7.0)[#]</td> <td>-5.0 (4.1)[§]</td> <td>-2.6 (4.0)</td> </tr> <tr> <td>CGI-S</td> <td>-0.3 (0.5)</td> <td>-0.5 (0.8)[§]</td> <td>-0.6 (0.7)[§]</td> <td>-0.4 (0.5)</td> <td>-0.4 (0.6)</td> <td>-0.2 (0.6)</td> </tr> <tr> <td>ACES</td> <td>0.9 (0.8)</td> <td>1.1 (1.1)</td> <td>1.0 (1.0)</td> <td>0.9 (0.9)</td> <td>0.8 (0.7)</td> <td>0.5 (0.7)</td> </tr> <tr> <td>Mean dose in 24 hr, mg (SD)</td> <td>4.0 (1.5)</td> <td>6.9 (2.7)</td> <td>9.8 (3.8)</td> <td>12.6 (4.9)</td> <td>9.9 (4.6)</td> <td>NA</td> </tr> <tr> <td>% Receiving 2 or 3 injections</td> <td>52.1</td> <td>35.5</td> <td>28.3</td> <td>23.9</td> <td>25</td> <td>66.7</td> </tr> <tr> <td>% BZD use</td> <td>10.4</td> <td>4.4</td> <td>4.3</td> <td>8.7</td> <td>0</td> <td>35.6</td> </tr> <tr> <td>Mean mg (SD) BZD*</td> <td>3.2 (1.1)</td> <td>2.0 (0)</td> <td>3.0 (1.4)</td> <td>3.5 (1.0)</td> <td>0</td> <td>3.4 (1.1)</td> </tr> </tbody> </table> <p>[^]p=0.01 vs. O₅; p≤0.001 vs. O_{7.5} & O₁₀; p=0.04 vs. H ⁺p=0.01 vs. O_{2.5}; p<0.001 vs. O₅, O_{7.5}, O₁₀, and H [#]p<0.05 vs. P [§]Lorazepam equivalents</p> <p>ADVERSE EVENTS</p> <table border="1"> <thead> <tr> <th rowspan="2">Treatment Emergent Adverse Event</th> <th colspan="6">Percent of Subjects</th> </tr> <tr> <th>O_{2.5}</th> <th>O₅</th> <th>O_{7.5}</th> <th>O₁₀</th> <th>H_{7.5}</th> <th>P</th> </tr> </thead> <tbody> <tr> <td>Hypotension</td> <td>4.2</td> <td>4.4</td> <td>2.2</td> <td>4.3</td> <td>0</td> <td>0</td> </tr> <tr> <td>Acute Dystonia</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> <td>5.0</td> <td>0</td> </tr> <tr> <td>Parkinsonism</td> <td>0</td> <td>0</td> <td>0</td> <td>2.9</td> <td>16.7[^]</td> <td>0</td> </tr> <tr> <td>Akathisia</td> <td>0</td> <td>4.8</td> <td>0</td> <td>0</td> <td>7.9</td> <td>0</td> </tr> <tr> <td>Anticholinergic Use</td> <td>2.1</td> <td>0</td> <td>0</td> <td>0</td> <td>7.5</td> <td>0</td> </tr> </tbody> </table> <p>[^]p<0.05 haloperidol vs. olanzapine 2.5, 5, 7.5 mg and placebo. No other between group differences were observed. [#]p<0.05</p> <p>N_R, Number randomized</p>	Outcome	O _{2.5}	O ₅	O _{7.5}	O ₁₀	H _{7.5}	P	Efficacy: Mean (SD) change at 2 hrs	n = 48	n = 45	n = 46	n = 46	n = 40	n = 45	PANSS-EC	-5.5 (4.6)	-8.1 (5.3)	-8.7 (5.0)	-9.4 (4.9)	-7.5 (5.9)	-2.9 (4.7) ⁺	BPRS total	-8.2 (9.1) [#]	-10.4 (7.5)	-12 (7)	-12 (5.9)	-9.2 (7.2) [§]	-3.7 (5.5)	BPRS positive	-1.5 (3.1)	-1.7 (2.8)	-2.1 (2.9)	-1.9 (2.3)	-1.4 (2.2)	-0.4 (1.3)	Response rate	50%	62.6%	73.9%	80.4%	60%	20%	ABS	-5.8 (5.5)	-9.0 (5.5)	-10.5 (5.6)	-10.4 (5.7)	-7.7 (5.2) [§]	-3.0 (5)	ACES	1.3 (1.5)	2.3 (1.9)	2.4 (1.7)	2.6 (1.7)	1.8 (1.6) [§]	0.7 (1.2)	Mean (SD) change at 24 hrs							PANSS-EC	-4.9 (4.3)	-5.5 (4.9)	-5.5 (4.1)	-5.9 (5.2)	-4.5 (4.0)	-3.1 (3.3)	BPRS total	-8.4 (7.4)	-9.2 (7.8)	-9.6 (7.5)	-9.0 (7.7)	-7.3 (7.5)	-4.3 (5.4)	BPRS positive	-1.5 (2.3)	-2.0 (2.6)	-1.9 (2.7)	-1.7 (2.4)	-1.8 (3.0) [§]	-0.6 (2.2)	ABS	-5.7 (4.2)	-6.7 (5.9)	-7.7 (5.8) [#]	-7.4 (7.0) [#]	-5.0 (4.1) [§]	-2.6 (4.0)	CGI-S	-0.3 (0.5)	-0.5 (0.8) [§]	-0.6 (0.7) [§]	-0.4 (0.5)	-0.4 (0.6)	-0.2 (0.6)	ACES	0.9 (0.8)	1.1 (1.1)	1.0 (1.0)	0.9 (0.9)	0.8 (0.7)	0.5 (0.7)	Mean dose in 24 hr, mg (SD)	4.0 (1.5)	6.9 (2.7)	9.8 (3.8)	12.6 (4.9)	9.9 (4.6)	NA	% Receiving 2 or 3 injections	52.1	35.5	28.3	23.9	25	66.7	% BZD use	10.4	4.4	4.3	8.7	0	35.6	Mean mg (SD) BZD*	3.2 (1.1)	2.0 (0)	3.0 (1.4)	3.5 (1.0)	0	3.4 (1.1)	Treatment Emergent Adverse Event	Percent of Subjects						O _{2.5}	O ₅	O _{7.5}	O ₁₀	H _{7.5}	P	Hypotension	4.2	4.4	2.2	4.3	0	0	Acute Dystonia	0	0	0	0	5.0	0	Parkinsonism	0	0	0	2.9	16.7 [^]	0	Akathisia	0	4.8	0	0	7.9	0	Anticholinergic Use	2.1	0	0	0	7.5	0
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				ADVERSE EVENTS <table border="1"> <thead> <tr> <th>Treatment Emergent Adverse Event</th> <th>O₁₀</th> <th>H_{7.5}</th> <th>P</th> </tr> </thead> <tbody> <tr> <td>Acute Dystonia</td> <td>0</td> <td>7.1</td> <td>NR</td> </tr> <tr> <td>EPS</td> <td>0.8</td> <td>5.6</td> <td>NR</td> </tr> <tr> <td>Anticholinergic Use</td> <td>4.6</td> <td>20.6</td> <td>3.7</td> </tr> </tbody> </table> <p>NR = not reported, assumed to be 0. EPS = Extrapyramidal Symptoms</p>	Treatment Emergent Adverse Event	O ₁₀	H _{7.5}	P	Acute Dystonia	0	7.1	NR	EPS	0.8	5.6	NR	Anticholinergic Use	4.6	20.6	3.7																																												
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⁶ Meehan, et al., 2001 DB, PC, MC, RCT Acutely agitated bipolar mania ITT, LOCF	<u>Inclusion Criteria</u> ≥18 years DSM-IV BP, mania or mixed Agitation severe enough to warrant IM route PANSS-EC ≥14, with ≥1 item scored ≥4. Able to provide informed consent.	O _{10 mg} x 2, then O _{5 mg} ; or Lorazepam L _{2 mg} x 2, then L _{1 mg} ; or Placebo x 2, then O _{10 mg} 2:1:1 2 nd dose no sooner than 2 hrs after first, 3 rd dose no sooner than 1 hr after 2 nd dose. Treatment duration: 24 hours Concurrent use of pre-existing lithium and valproate was allowed provided the dose was not changed during the trial.	Mean age 40 year (11.3) Male: 53% Origin: White: 73% Black: 16% Psychotic features: 53%	N _R = 201; 96.1% completed; 99% O, 94.1% L, 90% P EFFICACY <table border="1"> <thead> <tr> <th>Outcome</th> <th>O_{10 mg}</th> <th>L_{2 mg}</th> <th>P</th> <th></th> </tr> <tr> <th>Baseline (SD)</th> <th>n = 99</th> <th>n = 51</th> <th>n = 51</th> <th></th> </tr> </thead> <tbody> <tr> <td>PANSS-EC</td> <td>12.96 (3.18)</td> <td>12.39 (2.97)</td> <td>12.72 (3.10)</td> <td></td> </tr> <tr> <td>BPRS total</td> <td>30.48 (10.36)</td> <td>29.24 (9.71)</td> <td>29.02 (9.10)</td> <td></td> </tr> <tr> <td>BPRS positive</td> <td>6.87 (4.41)</td> <td>6.43 (4.57)</td> <td>6.20 (3.90)</td> <td></td> </tr> <tr> <td>ABS</td> <td>28.79 (5.84)</td> <td>28.14 (5.43)</td> <td>27.66 (4.74)</td> <td></td> </tr> <tr> <td>ACES</td> <td>2.24 (0.50)</td> <td>2.33 (0.55)</td> <td>2.26 (0.56)</td> <td></td> </tr> <tr> <td>YMRS</td> <td>26.17 (7.55)</td> <td>25.14 (8.96)</td> <td>26.59 (6.94)</td> <td></td> </tr> <tr> <td>CGI-S</td> <td>4.58 (0.80)</td> <td>4.37 (0.70)</td> <td>4.55 (0.69)</td> <td></td> </tr> <tr> <td colspan="4">Efficacy: Mean (SD) change at 2 hrs</td> <td>Overall p-value</td> </tr> <tr> <td>PANSS-EC</td> <td>-9.60 (4.74)^{**†}</td> <td>-6.75 (5.20)</td> <td>-4.84 (4.66)</td> <td><0.001</td> </tr> <tr> <td>BPRS total</td> <td>-17.29 (10.78)^{**†}</td> <td>-11.65 (9.72)</td> <td>-9.08 (8.85)</td> <td><0.001</td> </tr> <tr> <td>BPRS positive</td> <td>-3.48 (3.90) §</td> <td>-2.41 (3.31)</td> <td>-1.60 (2.73)</td> <td>0.006</td> </tr> <tr> <td>ABS</td> <td>-11.30 (6.09)[‡]</td> <td>-8.39 (6.32) §</td> <td>-4.78 (5.49)</td> <td><0.001</td> </tr> <tr> <td>ACES</td> <td>2.90 (1.80)^{**†}</td> <td>1.88 (1.77) §</td> <td>0.82 (1.40)</td> <td><0.001</td> </tr> <tr> <td>BPRS-Mania</td> <td>-8.40 (4.27) †[*]</td> <td>-5.82 (4.62)</td> <td>-4.31 (3.90)</td> <td><0.001</td> </tr> <tr> <td>PANSS-Hostility</td> <td>-7.26 (3.73) †[*]</td> <td>-5.02 (4.11)</td> <td>-3.52 (3.54)</td> <td><0.001</td> </tr> <tr> <td>PANNS-Depression</td> <td>-4.45 (3.54) †[‡]</td> <td>-3.04 (2.87)</td> <td>-2.25 (3.44)</td> <td><0.001</td> </tr> <tr> <td>Response Rate</td> <td>80.6%^{††}</td> <td>64.7%</td> <td>44%</td> <td></td> </tr> <tr> <td colspan="4">Mean (SD) change at 24 hrs</td> <td></td> </tr> <tr> <td>PANSS-EC</td> <td>-5.78 (4.72) §</td> <td>5.65 (5.20)</td> <td>-3.94 (4.32)</td> <td>0.069</td> </tr> <tr> <td>BPRS total</td> <td>-13.13 (11.41) §</td> <td>-11.71 (10.48)</td> <td>-8.20 (9.48)</td> <td>0.028</td> </tr> <tr> <td>BPRS positive</td> <td>-2.67 (3.86) ^</td> <td>-2.37 (3.62)</td> <td>-1.10 (2.81)</td> <td>0.039</td> </tr> <tr> <td>ABS</td> <td>-7.04 (6.07) §</td> <td>-6.92 (5.86) §</td> <td>-3.88 (5.15)</td> <td>0.005</td> </tr> <tr> <td>ACES</td> <td>1.04 (0.85) §</td> <td>1.06 (0.79) §</td> <td>0.56 (0.99)</td> <td><0.003</td> </tr> <tr> <td>YMRS</td> <td>-9.69 (8.97)</td> <td>-9.16 (8.19)</td> <td>-8.15 (8.87)</td> <td>0.623</td> </tr> <tr> <td>CGI-S</td> <td>-0.77 (0.93)</td> <td>-0.63 (0.81)</td> <td>-0.70 (1.27)</td> <td>0.722</td> </tr> </tbody> </table>	Outcome	O _{10 mg}	L _{2 mg}	P		Baseline (SD)	n = 99	n = 51	n = 51		PANSS-EC	12.96 (3.18)	12.39 (2.97)	12.72 (3.10)		BPRS total	30.48 (10.36)	29.24 (9.71)	29.02 (9.10)		BPRS positive	6.87 (4.41)	6.43 (4.57)	6.20 (3.90)		ABS	28.79 (5.84)	28.14 (5.43)	27.66 (4.74)		ACES	2.24 (0.50)	2.33 (0.55)	2.26 (0.56)		YMRS	26.17 (7.55)	25.14 (8.96)	26.59 (6.94)		CGI-S	4.58 (0.80)	4.37 (0.70)	4.55 (0.69)		Efficacy: Mean (SD) change at 2 hrs				Overall p-value	PANSS-EC	-9.60 (4.74) ^{**†}	-6.75 (5.20)	-4.84 (4.66)	<0.001	BPRS total	-17.29 (10.78) ^{**†}	-11.65 (9.72)	-9.08 (8.85)	<0.001	BPRS positive	-3.48 (3.90) §	-2.41 (3.31)	-1.60 (2.73)	0.006	ABS	-11.30 (6.09) [‡]	-8.39 (6.32) §	-4.78 (5.49)	<0.001	ACES	2.90 (1.80) ^{**†}	1.88 (1.77) §	0.82 (1.40)	<0.001	BPRS-Mania	-8.40 (4.27) † [*]	-5.82 (4.62)	-4.31 (3.90)	<0.001	PANSS-Hostility	-7.26 (3.73) † [*]	-5.02 (4.11)	-3.52 (3.54)	<0.001	PANNS-Depression	-4.45 (3.54) † [‡]	-3.04 (2.87)	-2.25 (3.44)	<0.001	Response Rate	80.6% ^{††}	64.7%	44%		Mean (SD) change at 24 hrs					PANSS-EC	-5.78 (4.72) §	5.65 (5.20)	-3.94 (4.32)	0.069	BPRS total	-13.13 (11.41) §	-11.71 (10.48)	-8.20 (9.48)	0.028	BPRS positive	-2.67 (3.86) ^	-2.37 (3.62)	-1.10 (2.81)	0.039	ABS	-7.04 (6.07) §	-6.92 (5.86) §	-3.88 (5.15)	0.005	ACES	1.04 (0.85) §	1.06 (0.79) §	0.56 (0.99)	<0.003	YMRS	-9.69 (8.97)	-9.16 (8.19)	-8.15 (8.87)	0.623	CGI-S	-0.77 (0.93)	-0.63 (0.81)	-0.70 (1.27)	0.722
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Treatment Emergent Adverse Event	Percent of Subjects			p-value
	O _{10 mg}	L _{2 mg}	P	
≥ 1 ADE	34.3%	51%	25.5%	L vs. .P, 0.014
Somnolence	13.1%	9.8%	5.9%	NS
Dizziness	9.1%	13.7%	2.0%	NS
Nausea	1%	7.8%	0	O vs. L, <0.05
Vomiting	0	5.9%	2%	O vs. L, <0.05

Study Design	Analysis type	Setting	Eligibility Criteria	Dosing	Demographics	Results																																																																																																															
Meehan, et al., 2002	DB, PC, PG, MC, RCT	Acutely agitated patients with dementia	ITT, LOCF	<p>Inclusion Criteria:</p> <p>1) Hospitalized or nursing home patient,</p> <p>2) Age ≥ 55 yrs,</p> <p>3)NINCDSADRDA Or DSM-IV diagnosis for AD, vascular or mixed dementia,</p> <p>4) PANSS-EC score ≥14 with at least one item ≥4,</p> <p>4) Agitation severe enough to warrant IM medication.</p> <p>5) Informed consent</p> <p>Exclusion Criteria</p> <p>1) Receipt of antipsychotic, benzodiazepine or anticholinergic med. within 4 hours of 1st dose of study drug.</p> <p>2) Other exclusionary medications, abnormal ECG & laboratory values, and other behavioral factors.</p> <p>Assessments:</p> <p>PANSS-EC, CMAI, ACES, PANSS-BPRS, PANSS-total, PANSS-positive, MMSE, CGI-S, NPI-NH</p>	<p>Olanzapine 2.5mg (O2.5)</p> <p>Olanzapine 5 mg (O5)</p> <p>Lorazepam (L)</p> <p>Placebo (P)</p> <p>1:1:1:1</p> <p>Maximum of 3 doses: 2nd dose no sooner than 2 hrs after first, 3rd dose no sooner than 1 hr after 2nd dose.</p> <p>If a 3rd dose was necessary it was ½ the dose, except in the P group which received O 5mg</p> <p>Treatment duration: 24 hours</p>	<p>Mean age: 77.6 (9.7) yrs.</p> <p>Male: 39%</p> <p>Caucasian: 92%</p> <p>Mean (SD) Baseline:</p> <p>PANSS-EC 19.75 (13.0)</p> <p>ACES 2.18 (0.71)</p> <p>MMSE 11.8 (7.1)</p> <p>BPRS-total 35.8 (10.4)</p> <p>CMAI 6.97 (6.0)</p>	<p>N_R = 272; % Completing: O2.5, 94.4%; O5, 92.4%; L, 89.7%; P, 88.9%</p> <p>EFFICACY</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>O2.5</th> <th>O5</th> <th>L</th> <th>P</th> </tr> </thead> <tbody> <tr> <td>Mean (SD) change at 2 hrs</td> <td>n = 71</td> <td>n = 66</td> <td>n = 68</td> <td>n = 67</td> </tr> <tr> <td>PANSS-EC</td> <td>-7.86 (6.05)*</td> <td>-8.67 (6.97)**</td> <td>-8.49 (6.55)**</td> <td>-5.27 (6.87)</td> </tr> <tr> <td>ACES</td> <td>1.8 (1.61)*</td> <td>1.88 (1.86)**</td> <td>2.19 (1.83)**</td> <td>1.04 (1.66)</td> </tr> <tr> <td>CMAI</td> <td>-3.77 (2.93)</td> <td>-3.97 (3.89)*</td> <td>-4.18 (3.52)*</td> <td>-2.78 (3.40)</td> </tr> <tr> <td>Response Rate</td> <td>62.0%**</td> <td>66.7%***</td> <td>72.1%***</td> <td>37.3%</td> </tr> <tr> <td>Mean (SD) change at 24 hrs</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>PANSS-EC</td> <td>-6.44 (6.00)*</td> <td>-6.29 (6.75)*</td> <td>-5.75 (5.99)</td> <td>-3.81 (6.20)</td> </tr> <tr> <td>BPRS total</td> <td>-10.51 (11.5)</td> <td>-10.59 (11.31)</td> <td>-9.12 (10.27)</td> <td>-10.29 (11.72)</td> </tr> <tr> <td>BPRS positive</td> <td>-1.72 (3.5)</td> <td>-1.86 (3.39)</td> <td>-1.32 (3.32)</td> <td>-2.09 (3.8)</td> </tr> <tr> <td>ACES</td> <td>0.9 (1.19)</td> <td>1.29 (1.49)**</td> <td>1.07 (1.12)*</td> <td>0.63 (1.14)</td> </tr> <tr> <td>CMAI</td> <td>-2.82 (3.21)</td> <td>-3.36 (3.92)</td> <td>-2.82 (3.08)</td> <td>-2.21 (3.57)</td> </tr> <tr> <td>CGI-S</td> <td>-0.38 (0.80)</td> <td>-0.47 (0.89)</td> <td>-0.46 (0.80)</td> <td>-0.59 (0.92)</td> </tr> <tr> <td>MMSE Total</td> <td>0.31 (2.29)</td> <td>0.10 (3.01)</td> <td>0.08 (3.04)</td> <td>0.37 (3.62)</td> </tr> </tbody> </table> <p>MMSE – Mini Mental Status Exam CMAI – Cohen-Mansfield Agitation Inventory</p> <p>*p<0.05 relative to placebo</p> <p>**p<0.01 relative to placebo</p> <p>***p<0.001 relative to placebo</p> <p>Treatment Emergent Adverse Events With An Incidence ≥3% in Any Treatment Group Over 24 Hours^a</p> <table border="1"> <thead> <tr> <th>ADE</th> <th>O 2.5</th> <th>O5</th> <th>L</th> <th>P^b</th> </tr> </thead> <tbody> <tr> <td>Accidental injury</td> <td>1.4%</td> <td>3%</td> <td>4.4%</td> <td>0</td> </tr> <tr> <td>ECG abnormality</td> <td>1.4 %</td> <td>3%</td> <td>0</td> <td>0</td> </tr> <tr> <td>Headache</td> <td>2.8%</td> <td>3%</td> <td>1.5%</td> <td>0</td> </tr> <tr> <td>Hypertension</td> <td>0</td> <td>3%</td> <td>2.9%</td> <td>1.5%</td> </tr> <tr> <td>Somnolence</td> <td>4.2%</td> <td>3%</td> <td>10.3%</td> <td>3%</td> </tr> <tr> <td>Vasodilatation</td> <td>0</td> <td>3%</td> <td>0</td> <td>0</td> </tr> <tr> <td>Sinus bradycardia</td> <td>0</td> <td>0</td> <td>0</td> <td>3%</td> </tr> </tbody> </table> <p>^aNo statistically significant differences were seen among treatment groups</p> <p>^bExcludes data subsequent to 3rd injection</p>	Outcome	O2.5	O5	L	P	Mean (SD) change at 2 hrs	n = 71	n = 66	n = 68	n = 67	PANSS-EC	-7.86 (6.05)*	-8.67 (6.97)**	-8.49 (6.55)**	-5.27 (6.87)	ACES	1.8 (1.61)*	1.88 (1.86)**	2.19 (1.83)**	1.04 (1.66)	CMAI	-3.77 (2.93)	-3.97 (3.89)*	-4.18 (3.52)*	-2.78 (3.40)	Response Rate	62.0%**	66.7%***	72.1%***	37.3%	Mean (SD) change at 24 hrs					PANSS-EC	-6.44 (6.00)*	-6.29 (6.75)*	-5.75 (5.99)	-3.81 (6.20)	BPRS total	-10.51 (11.5)	-10.59 (11.31)	-9.12 (10.27)	-10.29 (11.72)	BPRS positive	-1.72 (3.5)	-1.86 (3.39)	-1.32 (3.32)	-2.09 (3.8)	ACES	0.9 (1.19)	1.29 (1.49)**	1.07 (1.12)*	0.63 (1.14)	CMAI	-2.82 (3.21)	-3.36 (3.92)	-2.82 (3.08)	-2.21 (3.57)	CGI-S	-0.38 (0.80)	-0.47 (0.89)	-0.46 (0.80)	-0.59 (0.92)	MMSE Total	0.31 (2.29)	0.10 (3.01)	0.08 (3.04)	0.37 (3.62)	ADE	O 2.5	O5	L	P ^b	Accidental injury	1.4%	3%	4.4%	0	ECG abnormality	1.4 %	3%	0	0	Headache	2.8%	3%	1.5%	0	Hypertension	0	3%	2.9%	1.5%	Somnolence	4.2%	3%	10.3%	3%	Vasodilatation	0	3%	0	0	Sinus bradycardia	0	0	0	3%
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PANSS-EC	-6.44 (6.00)*	-6.29 (6.75)*	-5.75 (5.99)	-3.81 (6.20)																																																																																																																	
BPRS total	-10.51 (11.5)	-10.59 (11.31)	-9.12 (10.27)	-10.29 (11.72)																																																																																																																	
BPRS positive	-1.72 (3.5)	-1.86 (3.39)	-1.32 (3.32)	-2.09 (3.8)																																																																																																																	
ACES	0.9 (1.19)	1.29 (1.49)**	1.07 (1.12)*	0.63 (1.14)																																																																																																																	
CMAI	-2.82 (3.21)	-3.36 (3.92)	-2.82 (3.08)	-2.21 (3.57)																																																																																																																	
CGI-S	-0.38 (0.80)	-0.47 (0.89)	-0.46 (0.80)	-0.59 (0.92)																																																																																																																	
MMSE Total	0.31 (2.29)	0.10 (3.01)	0.08 (3.04)	0.37 (3.62)																																																																																																																	
ADE	O 2.5	O5	L	P ^b																																																																																																																	
Accidental injury	1.4%	3%	4.4%	0																																																																																																																	
ECG abnormality	1.4 %	3%	0	0																																																																																																																	
Headache	2.8%	3%	1.5%	0																																																																																																																	
Hypertension	0	3%	2.9%	1.5%																																																																																																																	
Somnolence	4.2%	3%	10.3%	3%																																																																																																																	
Vasodilatation	0	3%	0	0																																																																																																																	
Sinus bradycardia	0	0	0	3%																																																																																																																	

