



Clinical Edit Proposal

Drug/Drug **Geodon[®] for Injection (ziprasidone mesylate) /**
Class: **Atypical Antipsychotic Agents, Injectable**

Prepared for: Missouri Medicaid
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New Criteria

Revision of Existing Criteria

Executive Summary

Purpose: The purpose of this monograph is to provide an extensive review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, or require prior authorization for use.

Dosage Forms & Manufacturer: Geodon[®] for Injection (ziprasidone mesylate) available as a single dose vial (20mg ziprasidone/mL). Pfizer US Pharmaceutical Group.

Summary of Findings: Ziprasidone mesylate (Geodon[®] for Injection) is the first atypical antipsychotic approved for intramuscular use in the United States. It is indicated for use in patients with acute exacerbations of schizophrenia. It assists in rapidly controlling the agitated behavior and psychotic symptoms, such as hallucinations and delusions, in these patients.

Status Recommendation: Prior Authorization (PA) Required Open Access
 Clinical Edit

Type of PA Criteria: Increased Risk of ADE Non-Preferred Agent
 Appropriate Indications PA Not Required

Purpose

The purpose of this monograph is to provide an extensive review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug or not (open access). While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction^{1,2}

On June 24, 2002, the US Food and Drug Administration granted approval for ziprasidone mesylate (Geodon[®] for Injection) to rapidly control agitated behavior and psychotic symptoms, such as hallucinations and delusions, in patients with acute exacerbations of schizophrenia. Ziprasidone mesylate is the first and only atypical antipsychotic agent approved in the United States for intramuscular (IM) injection.

Dosage Form(s)^{2,3}

Geodon[®] for Injection is available in a single dose vial as ziprasidone mesylate (20mg ziprasidone/mL when reconstituted according to label instructions) for intramuscular administration.

Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20mg of ziprasidone and 4.7mg of methanesulfonic acid soubulized by 294mg of sulfobutylether β -cyclodextrin sodium.

Manufacturer^{3,4}

Pfizer US Pharmaceutical Group
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New York, New York, 10017
800-438-1985
<http://www.pfizer.com>

Indication(s)^{3,4}

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



Clinical Efficacy^{3,4}

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. Antagonism at receptors other than dopamine and 5HT2 with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone.

Intramuscular Pharmacokinetics

Systemic Bioavailability: The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_{1/2}$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Metabolism and Elimination: Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

The results of the intramuscular ziprasidone trials:

(1) In a one-day, double-blind, randomized trial (n=79) involving doses of ziprasidone intramuscular of 20 mg or 2 mg, up to four times daily, ziprasidone intramuscular 20 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0-4 hours, and by CGI severity at 4 hours and study endpoint.

(2) In another one-day, double-blind, randomized trial (n=117) involving doses of ziprasidone intramuscular of 10 mg or 2 mg, up to four times daily, ziprasidone intramuscular 10 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0-2 hours, but not by CGI severity.

Contraindications^{3,4}

QT Prolongation

Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure.

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with:

- Dofetilide
- Class Ia anti-arrhythmics
- Mesoridazine
- Pimozide
- Halofantrine
- Levomethadyl acetate
- Arsenic trioxide
- Sotalol
- Class III anti-arrhythmics
- Thioridazine
- Sparfloxacin
- Mefloquine
- Dolasetron mesylate
- Tacrolimus
- Quinidine
- Droperidol
- Chlorpromazine
- Gatifloxacin
- Moxifloxacin
- Pentamidine
- Probucol



Ziprasidone is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects.

Warnings^{3,4}

QT Prolongation and Risk of Sudden Death

Ziprasidone use should be avoided in combinations with other drugs that are known to prolong the QTc interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The management of NMS should include: (1) immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological regimens for NMS.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less



harmful treatments are not available or appropriate. In patients who do not require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

Precautions^{3,4}

General

Rash – In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to the dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these events were reported to completely recover.

Orthostatic Hypotension – Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the dose-titration period.

Seizures – During clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone, although there were confounding factors that may have contributed to the occurrence of seizures. Ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, especially in the population of 65 years and older.

Hyperprolactinemia – Ziprasidone elevates prolactin levels in humans, as do other drugs that antagonize dopamine D₂ receptors. Increased prolactin levels were also observed in animal studies with this compound. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients.

Potential for Cognitive or Motor Impairment – Somnolence was a commonly reported adverse event in patients treated with ziprasidone. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely.

Priapism – One case of priapism was reported in the premarketing database. While the relationship of the event to ziprasidone use has not been established, other drugs with similar effects have been reported to induce priapism, and it is possible that ziprasidone may share this capacity.

Body Temperature Regulation - Although not reported with ziprasidone, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents.



Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions that may contribute to elevation in core body temperature.

Use in Patients with Concomitant Illness – Clinical experience with ziprasidone with certain concomitant systemic illnesses is limited.

Adverse Effects ^{3,4}

The most commonly observed adverse events associated with intramuscular ziprasidone (incidence 5% or greater) and observed at a rate on intramuscular ziprasidone (in higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were:

- Headache (13%)
- Nausea (12%)
- Somnolence (20%)

Drug Interactions ^{3,4}

All interaction studies have been conducted with oral ziprasidone

Pharmacodynamic interactions (combined pharmacological effects):

- (1) Ziprasidone should not be used with any drug that prolongs the QT interval
- (2) Given the primary CNS effects, caution should be used when it is taken in combination with other centrally acting drugs.
- (3) Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents.
- (4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

Pharmacokinetic interactions (alteration of plasma levels):

Drug/Drug Class	Outcome
The Effect of Other Drugs on Ziprasidone	
Carbamazepine	Carbamazepine is an inducer of CYP3A4; administration of 200mg BID for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.
Ketoconazole	Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400mg for 5 days, increased the AUC and Cmax of ziprasidone by about 25-40%. Other inhibitors of CYP3A4 would be expected to have similar effects
Cimetidine	Cimetidine at a dose of 800mg QD for 2 days did not affect ziprasidone pharmacokinetics.
Antacid	The co administration of 30mL of Maalox [®] with ziprasidone did not affect the pharmacokinetics of ziprasidone.
Benzotropine Propranolol Lorazepam	Population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of a clinically significant pharmacokinetic interactions with the either of these agents.
The Effect of Ziprasidone on Other Drugs	
Lithium	Ziprasidone at a dose of 40mg BID administered concomitantly with lithium at a dose of 450mg BID for 7 days did not affect the steady-state level or renal clearance of lithium.



Oral Contraceptives	Ziprasidone at a dose of 20mg BID did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03mg) and levonorgestrel (0.15mg)
Dextromethorphan	Consistent with <i>in vitro</i> results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrophan. There was no statistically significant change in the urinary dextromethorphan/dextrophan ratio.

In vitro studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement.

Interactions with Laboratory Tests

- Patients being considered for ziprasidone treatment that are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low potassium and magnesium should be repleted before proceeding with treatment.
- Patients who are started on diuretics during ziprasidone therapy need periodic monitoring of serum potassium and magnesium.
- Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500msec.

Dosage and Administration ^{3,4}

Intramuscular Administration

The recommended dose is 10 to 20mg administered as required up to a maximum dose of 40mg per day. Doses of 10mg may be administered every two hours; doses of 20mg may be administered every four hours up to a maximum of 40mg/day.

Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible.

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

Preparation for Administration

Geodon[®] for injection (ziprasidone mesylate) should only be administered by intramuscular injection. Single-dose vials require reconstitution prior to administration; any unused portion should be discarded.

Add 1.2mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20mg ziprasidone. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be



used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Dosing in Special Populations

Intramuscular: Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race.

Cost Comparison ⁵ (at commonly used dosages)

Drug	Dose	Dosing Frequency	Maximum dose/day [#]	Cost / Dose*
Geodon [®] for injection (ziprasidone mesylate)				
	10mg	Every 2 hours	40mg/day	\$ 21.88
	20mg	Every 4 hours	40mg/day	\$ 43.75

*AWP: Facts and Comparisons (Medi-Span) St. Louis, MO: November 2002.

Dosing Geodon for Injection for more than 3 days has not been clinically evaluated.

Conclusion

Ziprasidone (Geodon[®]) for injection is the first atypical antipsychotic approved by the FDA. It does have a few characteristics that seem to differentiate it from the other agents in its class, such as a low risk of weight gain and a high incidence of QT prolongation on electrocardiogram. However, since one of the limitations of the atypical antipsychotic class was no available parenteral formulation, acutely agitated patients with schizophrenia were given older, typical antipsychotics, such as haloperidol (Haldol). The older antipsychotic agents were effective in these situations, but would frequently cause unpleasant side effects such as dystonias, sedation, and extrapyramidal side effects (EPS). Since June of 2002, Geodon[®] for injection has been indicated for use in patients with acute exacerbations of schizophrenia - assisting in rapidly controlling the agitated behavior and psychotic symptoms, such as hallucinations and delusions, in these patients. The maximum daily dose of Geodon[®] for injection is 40mg per day. The safety of the intramuscular dosing has not been shown beyond three days. Therefore, in order to maintain control, the patient should be switched to oral Geodon[®].

Recommendation(s)

It is recommended that Geodon[®] for Injection (20mg/mL) remain on the prior authorization approval status list – classified as ‘Clinical Edit’ status.



Approval Criteria

- Diagnosis of Schizophrenia
- Prescribing physician is a Psychiatrist
- Emergency Room use will not be impacted by this program

References

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2. Kehoe WA. New product: ziprasidone mesylate for injection (Geodon). Therapeutics Research Center. Pharmacist's Letter/Prescriber's Letter. August 2002; 18(8): 180807.
3. Geodon for Injection package insert. Pfizer, Inc. New York, New York. 2002 July.
4. Short RM, Burnham TH, et al., editors. Facts and Comparisons. Missouri: Facts and Comparisons.
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Date: November 18, 2002

