New Drug Overview
Invega Trinza® (paliperidone palmitate)

- **Overview/Summary:** Invega Trinza® (paliperidone palmitate) is an atypical antipsychotic intramuscular injection given every three months which is indicated for the treatment of schizophrenia in adult patients after they have been adequately treated with Invega Sustenna® (paliperidone palmitate) monthly injection for at least four months.[1] Paliperidone is an active metabolite of risperidone.[1-3] It is hypothesized that its therapeutic activity in schizophrenia is mediated by the antagonism of the central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor sites. Paliperidone has $5HT_{2A}$ activity and is also an antagonist of the adrenergic (α_1 and α_2) and histamine (H_1) receptors.[1-3]

  Prior to the availability of Invega Trinza® (paliperidone palmitate), paliperidone was only available in an oral formulation as Invega® (paliperidone) extended-release tablet and a monthly intramuscular injection as Invega Sustenna® (paliperidone palmitate). The extended-release tablets and monthly intramuscular injection are indicated for schizophrenia and schizoaffective disorder as monotherapy and an adjunct to mood stabilizers and/or antidepressant therapy.[2,3] Of note, Invega® (paliperidone) extended-release tablets have been studied and FDA-approved for the treatment of schizophrenia in adolescents (12 to 17 years of age).[2] The safety and efficacy of Invega Sustenna® (paliperidone palmitate) and Invega Trinza® (paliperidone palmitate) in pediatrics has not been established.[1,3]

  Invega Trinza® (paliperidone palmitate) is a novel formulation allowing for medication administration to occur four times a year, which is the longest atypical antipsychotic dosing interval currently available for the treatment of schizophrenia.

  The National Institute for Health and Clinical Excellence 2014 practice guideline for psychosis and schizophrenia in adults identifies candidates for injectable antipsychotic formulations as patients who prefer an injectable formulation after an acute episode or if the clinical treatment priority is to avoid non-adherence.[4] Similarly, the American Psychiatry Association 2004 practice guidelines for schizophrenia state candidates for long-acting injectable antipsychotics may include patients that may need options to improve treatment adherence.[5] Clinical guidelines do not note a preference among the antipsychotic agents available as long-acting injectables.

Table 1. Dosing and Administration[1]

<table>
<tr><th>Generic Name</th><th>Adult Dose</th><th>Pediatric Dose</th><th>Availability</th></tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Schizophrenia:
ER injection: initial, inject 273 to 819 mg IM (deltoid or gluteal muscle) every three months based on the dose of once-monthly paliperidone palmitate in which the patient was stabilized.
<table>
<tr><th>Invega Sustenna® Stabilized Dose</th><th>Invega Trinza® Starting Dose</th></tr>
<tr><td>78 mg</td><td>273 mg</td></tr>
<tr><td>117 mg</td><td>410 mg</td></tr>
<tr><td>156 mg</td><td>546 mg</td></tr>
<tr><td>234 mg</td><td>819 mg</td></tr>
</table>
</td>
<td>Safety and efficacy in children have not been established.</td>
<td>ER injection:
273 mg
410 mg
546 mg
819 mg

This agent must be administered by a health-care professional.</td>
</tr>
</table>

Evidence-based Medicine

- The efficacy of Invega Trinza® (paliperidone palmitate) was evaluated in a double-blind, placebo-controlled, randomized-withdrawal trial designed to evaluate time to relapse involving adult subjects with schizophrenia.[6]
    - The study included four phases: screening and oral tolerability testing phase, open-label transition phase, open-label maintenance phase, and a double-blind phase. Patients stable on other long-acting injectable antipsychotics were eligible.
    - After randomization, a pre-planned interim analysis showed a statistically significantly longer time to first relapse with Invega Trinza® (paliperidone palmitate) compared to placebo (hazard ratio [HR],3.45; 95% confidence interval [CI], 1.73 to 6.88; P<0.001).
    - Twenty-three percent of patients in the placebo group and 7.4% of patients in the Invega Trinza® (paliperidone palmitate) group experienced a relapse event.

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The National Institute for Health and Clinical Excellence 2014 practice guideline for psychosis and schizophrenia in adults identifies candidates for injectable antipsychotic formulations as patients who prefer an injectable formulation after an acute episode or if the clinical treatment priority is to avoid non-adherence.[4]
    - the American Psychiatry Association 2004 practice guidelines for schizophrenia state candidates for long-acting injectable antipsychotics may include patients that may need options to improve treatment adherence.[5]
    - Clinical guidelines do not note a preference among the antipsychotic agents available as long-acting injectables.[4,5]

- Other Key Facts:
    - Invega Trinza® (paliperidone palmitate) is the first antipsychotic that offers an extended duration of action, requiring injection only every three months.
    - Injectable antipsychotics are a treatment option for patients with non-adherence concerns.
    - Administration by a health care professional may help ensure adherence to the antipsychotic regimen. Administration every three months may also be advantageous for those patients who have limited access to medical care and/or transportation.

References

1. Invega Trinza® [package insert]. Titusville (NJ): Janssen Pharmaceuticals; 2015 May.
2. Invega® [package insert]. Titusville (NJ): Janssen Pharmaceuticals; 2015 May.
3. Invega Sustenna® [package insert]. Titusville (NJ): Janssen Pharmaceuticals; 2015 May.
4. National Institute for Clinical Excellence. Psychosis and Schizophrenia: treatment and management [monograph on the internet]. London (UK): National Institute for Clinical Excellence; 2014 [cited 2015 Aug 4]. Available from: http://www.nice.org.uk/guidance/cg178.
5. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia [monograph on the internet]. 2nd ed. Arlington (VA): American Psychiatric Association; 2004 [cited 2015 Aug 4]. Available from: http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.
6. Berwaerts J, Liu Y, Gopal S, Nuamah I, Xu H, Savitz A, Coppola D et al. Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. JAMA Psychiatry. 2015 Mar 29. doi: 10.1001/jamapsychiatry.2015.0241.

New Drug Review
Invega Trinza® (paliperidone palmitate)

Overview/Summary

Invega Trinza® (paliperidone palmitate) is an atypical antipsychotic intramuscular injection given every three months which is indicated for the treatment of schizophrenia in adult patients after they have been adequately treated with Invega Sustenna® (paliperidone palmitate) monthly injection for at least four months.[1] Paliperidone is an active metabolite of risperidone.[1-3] It is hypothesized that its therapeutic activity in schizophrenia is mediated by the antagonism of the central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor sites. Paliperidone has $5HT_{2A}$ activity and is also an antagonist of the adrenergic (α_1 and α_2) and histamine (H_1) receptors.[1-3]

Prior to the availability of Invega Trinza® (paliperidone palmitate), paliperidone was only available in an oral formulation as Invega® (paliperidone) extended-release tablet and a monthly intramuscular injection as Invega Sustenna® (paliperidone palmitate). The extended-release tablets and monthly intramuscular injection are indicated for schizophrenia and schizoaffective disorder as monotherapy and an adjunct to mood stabilizers and/or antidepressant therapy.[2,3] Of note, Invega® (paliperidone) extended-release tablets have been studied and FDA-approved for the treatment of schizophrenia in adolescents (12 to 17 years of age).[2] The safety and efficacy of Invega Sustenna® (paliperidone palmitate) and Invega Trinza® (paliperidone palmitate) in pediatrics has not been established.[1,3]

Invega Trinza® (paliperidone palmitate) is a novel formulation allowing for medication administration to occur four times a year, which is the longest atypical antipsychotic dosing interval currently available for the treatment of schizophrenia.

The National Institute for Health and Clinical Excellence 2014 practice guideline for psychosis and schizophrenia in adults identifies candidates for injectable antipsychotic formulations as patients who prefer an injectable formulation after an acute episode or if the clinical treatment priority is to avoid non-adherence.[4] Similarly, the American Psychiatry Association 2004 practice guidelines for schizophrenia state candidates for long-acting injectable antipsychotics may include patients that may need options to improve treatment adherence.[5] Clinical guidelines do not note a preference among the antipsychotic agents available as long-acting injectables.

Indications

Paliperidone palmitate (Invega Trinza®), a three-month injection, is indicated for the treatment of schizophrenia in patients after they have been adequately treated with one-month paliperidone palmitate injection (Invega Sustenna®) for at least four months.

Pharmacokinetics

Due to its extremely low water solubility, the three-month formulation of paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. The release of the drug starts as early as day 1 and lasts for as long as 18 months.[1]

Table 1. Pharmacokinetics[1]

Generic Name	Time to Peak Concentration (days)	Renal Excretion (%)	Hepatic Metabolism (active metabolites)	Serum Half-Life (days)
Paliperidone palmitate	30 to 33	80 (59 unchanged)	limited	84 to 95* 118 to 139†

*Administered via the deltoid muscle
†Administered via the gluteal muscle

Clinical Trials

The efficacy of Invega Trinza® (paliperidone palmitate) was evaluated in a double-blind, placebo-controlled, randomized-withdrawal trial designed to evaluate time to relapse involving adult subjects who met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) criteria for schizophrenia and a Positive and Negative Syndrome Scale (PANSS) total score lower than 120 at screening and at baseline.[6] The study included four phases: screening and oral tolerability testing phase, open-label transition phase, open-label maintenance phase, and a double-blind phase. Patients stable on other long-acting injectable antipsychotics were eligible.

The three treatment periods included the following:

- A 17 week flexible-dose open-label period (transition phase) with the one month paliperidone palmitate injection (N=506). During this phase, at week five and nine, dosing of the one month paliperidone palmitate was individualized based on symptom response, tolerability, and previous medication history. Patients had to be maintained on the same dose from week nine and be clinically stable (positive and negative symptoms score [PANSS] <70) at the end of the study phase to be transitioned to Invega Trinza® (paliperidone palmitate).
- A 12 week open-label treatment period (maintenance phase) with Invega Trinza® (paliperidone palmitate) in which patients received the first dose of the agent (at a 3.5 multiple) (N=379). Patients had to be clinically stable (PANSS <70 and ≤4 for seven specific PANSS items) at the end of the study phase to continue into the final phase.
- A variable length double-blind treatment period (N=305), in which patients were randomized to Invega Trinza® (paliperidone palmitate) at the dose the patient received during the previous open-label phase (i.e., 273 mg, 410 mg, 546 mg, or 819 mg) (N=160) or placebo every 12 weeks (N=145).

A pre-planned interim analysis showed a statistically significantly longer time to first relapse with Invega Trinza® (paliperidone palmitate) compared to placebo (hazard ratio [HR],3.45; 95% confidence interval [CI], 1.73 to 6.88; P<0.001). Median time to relapse was 274 days with placebo and could not be estimated for Invega Trinza® (paliperidone palmitate) as the study was terminated early. Relapse was defined as at least one of the following: psychiatric hospitalization, ≥25% increase (baseline score>40) or a ten-point increase (baseline score ≤ 40) in total PANSS score on two consecutive assessments, increase in PANSS item scores for two consecutive assessments between three and seven days apart, deliberate self-injury or violent behavior resulting in damage or harm, and suicidal/homicidal ideation or aggression. Twenty-three percent of patients in the placebo group and 7.4% of patients in the Invega Trinza® (paliperidone palmitate) group experienced a relapse event.

In the double-blind study phase, 183 of 305 patients, 62% receiving Invega Trinza® (paliperidone palmitate) and 58% receiving placebo, had at least one treatment-emergent adverse event. The events noted to occur more frequently in the group receiving Invega Trinza® (paliperidone palmitate) compared to those receiving placebo group included headache (9% vs 4%), weight gain (9% vs 3%), nasopharyngitis (6% vs 1%), and akathisia (4% vs 1%).

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Berwaerts et al[6] Paliperidone palmitate (Invega Trinza®) IM every three months, fixed dose (based on individualized maintenance phase dose) vs placebo All patients were stabilized on once-monthly paliperidone palmitate (Invega Sustenna®) prior to randomization. Patients randomized to the placebo group discontinued once-monthly paliperidone palmitate.	DB, MC, PC, RCT Patients 18 to 70 years of age with a diagnosis of schizophrenia for at least one year before screening, PASS total score <120 at screening and baseline, stabilized on a long-acting injectable antipsychotic, a stable place of residence for the previous three months before screening	N=305 Variable Length (16 to 540 days)	Primary: Time from randomization to the first relapse event Secondary: Change from randomization baseline to end point in PANSS total, subscale, and 5-factor scores, CGIS score and PSP scores; safety assessments	Primary: Time to relapse of schizophrenia in the per-protocol analysis (considered the primary analysis) was significantly different in favor of the paliperidone palmitate group when compared to placebo (HR,3.45; 95% CI, 1.73 to 6.88; P<0.001). The median time to relapse was not estimable for the group receiving paliperidone palmitate and was 274 days for the placebo group. Overall, 31 patients (23%) in the placebo group and 11 patients (7%) in the group receiving paliperidone palmitate experienced a relapse event. The independent data monitoring committee recommended early study termination for efficacy. The intention-to-treat analysis was consistent with the per-protocol analysis. Time to relapse of schizophrenia was significantly different in favor of the paliperidone palmitate group when compared to placebo (HR,3.81; 95% CI, 2.08 to 6.99; P<0.001). As with the per-protocol analysis, median time to relapse was not estimable for the paliperidone palmitate group. For the placebo group, median time to relapse was 395 days. A total of 42 patients (29%) in the placebo group and 14 patients (9%) in the group receiving paliperidone palmitate experienced a relapse event. Secondary: The mean (standard deviation) PANSS total score at randomization baseline was 54.9 (9.95) in the paliperidone palmitate group and 54.2 (9.34) for the placebo group. The mean PANSS total score remained stable in the paliperidone palmitate group and increased in the placebo group. Mean (standard deviation) change in PANSS total score was −0.5 (8.36) in the paliperidone palmitate group compared with 6.7 (14.40) for the placebo group. Difference in mean change in PANSS total score was statistically significant in favor of paliperidone palmitate (P<0.001; least-squares means difference of −7.2; 95% CI, −9.87 to −4.60). There were also significant differences in mean change from randomization baseline to end point in favor of paliperidone palmitate in PANSS subscale and Marder factor scores (except negative subscale

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and negative symptoms factor; P≤0.005), CGIS score (P<0.001), and PSP scores (P<0.001). A total of 330 of 506 patients (65%) in the open-label phase and 183 of 305 patients (60%) in the randomized phase (62% of those receiving paliperidone palmitate three-month injection compared with 58% of those receiving placebo) had at least one treatment emergent adverse event. The most frequently reported treatment emergent adverse events (≥2%) in the group receiving paliperidone palmitate during the maintenance phase (part of the open-label phase) were anxiety (6%), insomnia (5%), weight increased (4%), and headache (3%). During the maintenance phase, the treatment emergent adverse events that led to study discontinuation in more than one patient included psychiatric disorders (1%) and schizophrenia (0.5%). The most commonly occurring EPS-related treatment-emergent adverse events (≥1%) were those grouped under hyperkinesia (2%) and parkinsonism (1%). One patient (0.3%) experienced a hyperglycemia-related treatment emergent adverse event of type 2 diabetes mellitus during the maintenance phase. During the randomization phase, the most common treatment emergent adverse events occurring in the paliperidone group were EPS-related adverse events, headache, nasopharyngitis and increased weight.

Drug regimen abbreviations: IM=intramuscular
Study abbreviations: CI=confidence interval, DB=double blind, HR=hazard ratio, MC=multicenter, PC=placebo-controlled, RCT=randomized controlled trial
Miscellaneous abbreviations: CGIS=Clinical Global Impression–Severity, PSP=Personal and Social Performance, PANSS=Positive and Negative Syndrome Scale

Special Populations

Table 3. Special Populations[1]

Population	Precaution
Elderly	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.
Renal Dysfunction	Use of Invega Trinza® (paliperidone palmitate) is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Use of the agent in patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min) is based on the previous dose of the one month paliperidone palmitate extended-release injectable suspension that the patient was stabilized on prior to initiation.
Hepatic Dysfunction	Not studied in hepatic dysfunction.*
Pregnancy / Nursing	Invega Trinza® (paliperidone palmitate) may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise pregnant women of the potential risk to a fetus. Paliperidone is present in human breast milk; however, there are insufficient data to assess the amount in human milk, the effects on the breastfed infant, or the effects on milk production.
Children	Safety and efficacy in children have not been established. This formulation is not recommended in the pediatric population due to the longer duration of action.
Age Restrictions	FDA approved for use in patients ages ≥18 years.
Patients with Parkinson's Disease or Lewy Body Dementia	Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to Invega Trinza® (paliperidone palmitate). Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

*No adequate or well-controlled trials.

Adverse Drug Events

The safety data for Invega Trinza® (paliperidone palmitate) is based on the results of two clinical trials.[1]

Table 4. Adverse Events Occurring in ≥2% of Patients (and Greater than Placebo) for the Double-Blind Phase of a Long-Term Maintenance Trial in Patients with Schizophrenia[1]

Adverse Event	Reported Frequency	
	Invega Trinza® (paliperidone palmitate) dosed every three months %, N=160	Placebo %, N=145
General disorders and administration site conditions		
Injection site reaction	3	0
Infections and infestations		
Upper respiratory tract infection	10	4
Urinary tract infection	3	1
Metabolism and nutrition disorders		
Weight increased	9	3
Nervous system disorders		
Akathisia	5	2
Headache	9	4
Parkinsonism	4	0

Contraindications and Warnings/Precautions

Table 5. Contraindications[1]

Contraindication	Paliperidone palmitate
Known hypersensitivity to either paliperidone or risperidone or to any excipients	a

Black Box Warning for Invega Trinza® (paliperidone palmitate)[1]

WARNING
INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS · Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. · Invega Trinza® (paliperidone palmitate) is not approved for use in patients with dementia-related psychosis.

Table 6. Warnings and Precautions[1]

Warning/Precaution	Paliperidone palmitate
Cerebrovascular adverse reactions, including stroke, occurred at a higher incidence in placebo-controlled trials when treated with certain antipsychotics.	a
Cognitive and Motor Impairment have been reported. Use caution when performing activities requiring mental alertness.	a
Dementia-related Psychosis; patients treated with antipsychotic drugs are at an increased risk of death.	a
Disruption of body temperature regulation has been attributed to antipsychotic agents.	a
Dysphagia; esophageal dysmotility and aspiration have been associated with antipsychotic drug use.	a
Hyperprolactinemia, due to dopamine-2 antagonism, occurs during chronic administration.	a
Leukopenia, neutropenia and agranulocytosis have been reported when antipsychotic agents have been used.	a
Metabolic changes associated with antipsychotics may increase cardiovascular/cerebrovascular risk. Changes include hyperglycemia, dyslipidemia, and body weight gain.	a
Neuroleptic Malignant Syndrome has been reported in association with antipsychotic drugs, including paliperidone. Immediately discontinue use of the antipsychotic drug and begin intensive symptom management.	a
Orthostatic hypotension and syncope have been reported.	a
Priapism may occur in drugs with alpha-adrenergic blocking effects.	a
QT prolongation and Torsades de pointes and/or sudden death; a modest increase in the correct QT (QTc) internal has been reported. Torsades de pointes and/or sudden death have been reported in association with drugs that prolong the QTc interval. Avoid use with other drugs that may prolong QTC.	a
Tardive Dyskinesia may develop in patients treated with antipsychotic drugs and is irreversible.	a

Drug Interactions

Based on pharmacokinetic studies with oral paliperidone, no dosage adjustment of paliperidone palmitate (Invega Trinza®) is required when administered concomitantly with valproate or vise-versa.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes.[1]

Dosage and Administration

Paliperidone palmitate (Invega Trinza®) should only be administered after at least four months of stability on the one-month formulation of paliperidone extended-release injectable suspension (Invega Sustenna®) for at least four months. The first dose of Invega Trinza® should be scheduled when the next dose of the once-monthly injection is due. Doses may be adjusted within the 273 mg to 819 mg dosing range every three months. Information regarding missed doses can be found in the FDA-approved drug label.[1]

Table 7. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
Paliperidone palmitate	**Schizophrenia**: ER injection: initial, inject 273 to 819 mg IM (deltoid or gluteal muscle) every three months based on the dose of once-monthly paliperidone palmitate in which the patient was stabilized. **Invega Sustenna® Stabilized Dose** / **Invega Trinza® Starting Dose** 78 mg / 273 mg 117 mg / 410 mg 156 mg / 546 mg 234 mg / 819 mg	Safety and efficacy in children have not been established.	ER injection: 273 mg 410 mg 546 mg 819 mg This agent must be administered by a health-care professional.

ER=extended-release, IM=intramuscular

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
National Institute for Health and Clinical Excellence: **Psychosis and Schizophrenia in Adults: Treatment and Management (2014)**[4]	· If a person is considered to be at increased risk of developing psychosis: o Offer individual cognitive behavioral therapy (CBT) with or without family intervention and o Offer interventions recommended in National Institute for Health and Clinical Excellence guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse. · Do not offer antipsychotic medication: o To people considered to be at increased risk of developing psychosis or o With the aim of decreasing the risk of or preventing psychosis. First episode psychosis · Oral antipsychotic medication in conjunction with psychological interventions · Psychological interventions are more effective when delivered in conjunction with antipsychotic medication. · The choice of antipsychotic medication should take into account: o Metabolic (weight gain and diabetes) o extrapyramidal (akathisia, dyskinesia and dystonia) o cardiovascular (QT prolongation) o hormonal (increased prolactin)

Clinical Guideline	Recommendations
	o other (unpleasant subjective experience) · Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication) <u>Acute episode</u> · For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication in conjunction with psychological interventions · For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication. The choice of drug should be influenced by the same criteria recommended for starting treatment o A single antipsychotic agent is first line. Regular use of combination therapy should not be initiated except when changing agents. · If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse. · Clinical response and side effects should be routinely monitored. · Large loading doses should not be used with antipsychotics. · Combination antipsychotic therapy should not be prescribed except for a short duration while transitioning to a different antipsychotic agent. · Due to the high risk of relapse following an acute episode, it is recommended to continue antipsychotic medications for up to one to two years. <u>Recovery/relapse prevention</u> · The goal of pharmacologic treatment is to prevent relapse and maintain the patient's quality of life. · The same considerations for drug treatment should be given as in acute episodes: potential side effects, patient characteristics and preferences. · Depot preparations should be considered when adherence to oral medication is in question. <u>Inadequate response to treatment</u> · Factors for inadequate response should be evaluated including diagnosis, adherence to treatment, and comorbid conditions. · Consider clozapine for patients who have tried two antipsychotic agents (including one second generation antipsychotic) without significant improvement. · Adding a second antipsychotic to clozapine may be considered for patients who are unresponsive to clozapine alone at standard doses; however, the use of more than one antipsychotic is not recommended in other situations except during the conversion from one agent to another. <u>Treatment with long-acting injectable antipsychotic medication</u> · The main practical clinical advantage of using long-acting injectable antipsychotic medications to emerge has been the avoidance of covert nonadherence (both intentional and unintentional) to antipsychotic drug treatment, where there is close supervision and documentation of clinic attendance · For those who continue with long-acting injections, there may be some adherence advantage over oral antipsychotics, indicated by a longer time to medication discontinuation and reduced risk of hospitalization.

Clinical Guideline	Recommendations
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Schizophrenia (2004)**[5]	Acute phase · Pharmacological treatment with aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone should begin at once with the first episode. · Patients with persistent suicidal behavior or persistent hostility and aggressive behavior should be treated with clozapine. · Patients with tardive dyskinesia should be treated with clozapine or second generation antipsychotics. · Patients sensitive to extrapyramidal symptoms side effects should be treated with a second generation antipsychotics (except clozapine); if risperidone is used, high doses are not recommended. · Patients sensitive to prolactin elevations should be treated with a second generation antipsychotics (except clozapine and risperidone). · Patients sensitive to weight gain, hyperglycemia, or hyperlipidemia should be treated with either aripiprazole or ziprasidone. · Patients nonadherent to pharmacological treatment should be treated with long-acting injectable antipsychotic agents. · Agent should be chosen based on clinical circumstances and side effects. · For intolerable side effects, one of the following should be chosen: aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. · For an inadequate response, a different agent should be chosen: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. · For an inadequate response to a second agent, a different agent should be chosen: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. · Clozapine should be used to treat persistent psychotic symptoms. Consider electroconvulsive therapy for persistent severe psychosis, catatonia, and/or suicidal behavior in patients who failed prior treatments (including clozapine). · Clozapine has the greatest efficacy on suicidal behavior and it should be considered in patients with suicidal ideation. · Electroconvulsive therapy is used when a patient has not responded to antipsychotic treatment. When electroconvulsive therapy is administered in conjunction with an antipsychotic agent (either a first or second generation antipsychotic) it provides the largest benefit; however electroconvulsive therapy should not be used prior to a trial of clozapine. Stabilization or maintenance phase · The goal of medication in the stable phase is to minimize the risk of relapse, severity of side effects and possible residual symptoms. · Continue with acute phase treatment. Electroconvulsive therapy should be considered for maintenance therapy for patients who have used electroconvulsive therapy in acute treatment with good response and who were not controlled with medication alone. · Maintenance electroconvulsive therapy may help patients who have responded to acute electroconvulsive therapy and pharmacological prophylaxis is ineffective or intolerable. Evidence shows that antipsychotics should be used with electroconvulsive therapy maintenance. · For intolerable side effects, another agent should be chosen: aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone.

Conclusions

Invega Trinza® (paliperidone palmitate) is a novel atypical antipsychotic formulation that allows for a longer interval between injections and is the first long-acting injectable antipsychotic dosed only four times a year.[1] The safety and efficacy of Invega Sustenna® (paliperidone palmitate) and Invega Trinza® (paliperidone palmitate) in pediatrics has not been established; however, Invega® (paliperidone) extended-release tablets have been studied and FDA-approved for the treatment of schizophrenia in adolescents (12 to 17 years of age). Both injections are not recommended in moderate or severe renal impairment.[1-3] Current clinical guidelines recommend extended-release injectable antipsychotics for patients with adherence issues or for patients who prefer the injectable once stabilized.[4,5] Invega Trinza® (paliperidone palmitate) may serve as an additional medication formulation option for patients with adherence concerns or who prefer four injections a year as opposed to 12 injections per year.

References

1. Invega Trinza® [package insert]. Titusville (NJ): Janssen Pharmaceuticals; 2015 May.
2. Invega® [package insert]. Titusville (NJ): Janssen Pharmaceuticals; 2015 May.
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DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Invega Trinza (paliperidone palmitate) is subject to prior authorization.

1. Coverage and limitations:

   Authorization will be given if the following criteria are met and documented:
   a. Diagnosis of schizophrenia
      AND
   b. The recipient has been stabilized on once-monthly paliperidone palmitate injection (Invega Sustenna) for at least four months with the two most recent doses of the once-monthly injection being the same strength.
      AND
   c. Member is ≥ 18 years of age
      AND
   d. The requested dose is one injection every three months.

2. Prior Authorization Guidelines:
   a. Prior Authorization approval length will for one year