Invega Trinza: The First Four-Times-a-Year, Long-Acting Injectable Antipsychotic Agent
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INTRODUCTION
Schizophrenia is a chronic mental illness known as one of the most complex and challenging psychiatric disorders to treat. It is a heterogeneous clinical syndrome involving a compilation of cognitive, behavioral, and emotional dysfunctions. The mainstay of treatment for schizophrenia is pharmacotherapy, and in many cases it is impossible to implement effective psychosocial rehabilitation without antipsychotic treatment. However, one of the difficulties in the treatment of schizophrenia is patient nonadherence to medication regimens, with the percentage of nonadherence reported as 40% to 60% to antipsychotics and 11% to 80% in patients with schizophrenia. Many consequences of poor compliance are known, including relapse, hospitalization, exacerbations, behavior harmful to one’s self or others, suicide, and overall negative impacts on patients, their families, and society as a whole. The most common cause of relapse is poor adherence, with relapse in first-episode patients increasing almost fivefold when antipsychotic drug treatment is discontinued.

Not only does nonadherence to antipsychotics present an important clinical problem, it also presents a significant economic burden. Schizophrenia accounts for 1.5% to 3% of national health care expenditures among different countries worldwide, with relapses leading to hospitalization rates and costs. In addition, several studies have found a link between nonadherence, relapse, and cost. For example, one study revealed that approximately 30% of total costs were due to relapses, while another study found hospitalizations comprising 52.5% to 80.7% of total costs of care.

The clinical and economic problems that arise due to nonadherence illustrate the importance of ensuring continuous delivery of antipsychotic treatment. Long-acting injectables (LAIs) were formulated to improve adherence within this patient population. Several studies suggest that better medication adherence because of LAI use leads to improved outcomes, such as lower rates of relapse, reductions in hospitalization, and decreases in hospital length of stay. These improvements in outcomes may lead to a decrease in the economic burden. One study demonstrated better cost-effectiveness per month per patient when patients were switched from oral medications to LAIs due to a decrease in relapse and hospitalization. Several LAI antipsychotics exist that are given on either a biweekly or monthly regimen. However, a recent study using a model to estimate the benefits of longer intervals between injections demonstrated that administration every three months was less costly than daily oral therapy and monthly injections. This extended dosing interval is now possible due to the novel formulation paliperidone palmitate three-month injection (PP3M), recently approved by the Food and Drug Administration under the trade name Invega Trinza (Janssen Pharmaceuticals, Inc.).

CHEMICAL AND PHYSICAL PROPERTIES
Paliperidone palmitate three-month injection is an atypical antipsychotic containing a racemic mixture of the active ingredient paliperidone. This active ingredient belongs to the chemical class of benzisoxazole derivatives. The PP3M formulation utilizes NanoCrystal technology similar to the paliperidone one-month injection (PP1M) but with increased particle size, allowing for an extended sustained release. Paliperidone palmitate is very slightly soluble in ethanol and methanol and slightly soluble in ethyl acetate. Invega Trinza is available in dose strengths of 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate. Paliperidone palmitate undergoes hydroxylation into the active moiety paliperidone via esterases in muscle tissue. Hydroxylation results in dose strengths of 175 mg, 263 mg, 350 mg, and 525 mg of paliperidone, respectively.

PHARMACOLOGY AND MECHANISM OF ACTION
The exact mechanism of action of paliperidone is unknown. It has been proposed that paliperidone’s therapeutic actions in treating the symptoms of schizophrenia are mediated through antagonism of serotonin 5HT2A and central dopamine D2 receptors. Paliperidone is also known to act as an antagonist on alpha-1 and alpha-2 adrenergic receptors and histamine H1 receptors.
**INDICATION**

PP3M is indicated for the treatment of schizophrenia in patients who have been adequately treated for at least four months with PP1M (Invega Sustenna, Janssen Pharmaceuticals, Inc.).

### Table 1 Initial Invega Trinza Doses

<table>
<thead>
<tr>
<th>Last Dose of Invega Sustenna</th>
<th>Initial Invega Trinza Dose</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

**ADVERSE EFFECTS**

The safety findings for PP3M were consistent with the data seen in other clinical trials with the PP1M formulation of paliperidone palmitate. The most common adverse reactions with an incidence of 3% or more were injection-site reaction, weight increase, headache, upper respiratory tract infection, akathisia, and parkinsonism. Discontinuation of treatment with PP3M due to adverse effects in one of the clinical trials was 5.1% during the open-label phase; however, no subjects discontinued PP3M due to adverse effects during the double-blind phase. Additional adverse effects noted are tachycardia, nausea and vomiting, hyperinsulinemia, and anxiety. Adverse effects with PP3M injection observed in clinical trials will be discussed in greater detail later.

### Table 2 Re-initiation Regimen After Missing Four to Nine Months of Invega Trinza

<table>
<thead>
<tr>
<th>Last Dose of Invega Trinza</th>
<th>Administer Invega Sustenna two doses one week apart (deltoid)</th>
<th>Invega Trinza Dose (deltoid or gluteal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 8</td>
</tr>
<tr>
<td>273 mg</td>
<td>78 mg</td>
<td>78 mg</td>
</tr>
<tr>
<td>410 mg</td>
<td>117 mg</td>
<td>117 mg</td>
</tr>
<tr>
<td>546 mg</td>
<td>156 mg</td>
<td>156 mg</td>
</tr>
<tr>
<td>819 mg</td>
<td>156 mg</td>
<td>156 mg</td>
</tr>
</tbody>
</table>

**General Recommendations**

PP3M should only be used after PP1M has been established as an effective treatment for at least four months. It is advised that the last two doses of PP1M be the same dosage strengths before initiating PP3M. The PP3M dose should be administered at the time that the next PP1M dose is scheduled, using an equivalent 3.5-fold higher dosing.

**Special Populations**

There are no available data on the use of PP3M in pregnant, breastfeeding, and pediatric patients. Studies have detected paliperidone in plasma 18 months after a single-dose administration of PP3M; however, the clinical significance of the administration of PP3M before and during pregnancy is unknown. Studies in rats did not show teratogenicity with the one-month formulation of paliperidone palmitate, and no increases in fetal abnormalities were observed in animal studies with oral paliperidone. It is important to note, however, that neonatal complications such as prematurity, respiratory difficulties, extrapyramidal symptoms (EPS), and withdrawals have been reported in neonates exposed to antipsychotics during pregnancy.

In addition, too few geriatric subjects were enrolled in clinical studies to establish safety data in this population. However, the drug is known to...
be substantially excreted via the kidneys, and geriatric patients most often have reduced kidney function.14,16 Therefore, monitoring of renal function is highly advised in geriatric patients. In addition, the use of PP3M is not recommended in patients with moderate-to-severe renal impairment, while its use in mild impairment can be based on the patients’ previously established dose of PP1M.13 Paliperidone palmitate three-month formulation was not studied in patients with hepatic impairments; however, based on oral paliperidone studies, no dosage adjustments are required in patients with mild-to-moderate hepatic impairment.14

**DRUG INTERACTIONS, CONTRAINDICATIONS, AND PRECAUTIONS**

Drug interactions observed in studies of oral paliperidone should be taken into consideration when using PP3M because paliperidone palmitate is hydrolyzed to paliperidone.14 Clinically important drug interactions with PP3M include drugs that potentially induce orthostatic hypotension, strong CYP3A4 and P-glycoprotein (P-gp) inducers, and dopamine agonists. Paliperidone palmitate has the potential for inducing orthostatic hypotension; therefore, additive effects may be seen when it is coadministered with other drugs that can also cause orthostatic hypotension.14 Orthostatic vital signs should be monitored in patients at risk for hypotension. In addition, the coadministration of strong inducers of CYP3A4 and P-gp may reduce paliperidone plasma levels; therefore, use of these agents should be avoided if possible.13–14 Finally, paliperidone may antagonize the effects of levodopa and other dopamine agonists, requiring close monitoring and management of individuals receiving these medications concomitantly.14

Because PP3M is an antipsychotic, it carries the same boxed warning of tardive dyskinesia, metabolic changes, orthostatic hypotension and syncope, leukopenia, hyperprolactinemia, potential for cognitive and motor impairment, and seizures.13

Additional precautions should be taken when PP3M is to be used in patients with Parkinson’s disease or dementia with Lewy bodies. These patients have an increased sensitivity to PP3M and can experience adverse effects such as confusion, obtundation, postural instability, EPS, and neuroleptic malignant syndrome.15

**CLINICAL TRIALS**

The two currently published trials evaluating the safety and efficacy of Invega Trinza are reviewed in this section.

**Ravenstijn et al.15**

A multicenter, randomized, open-label, parallel-group, phase 1 study was conducted to assess the pharmacokinetics, safety, and tolerability of PP3M in patients with schizophrenia or schizoaffective disorder. Men and women 18 to 65 years of age diagnosed with schizophrenia or schizoaffective disorder consistent with the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* for at least one year before screening and with a total score of 70 or lower on the Positive and Negative Syndrome Scale (PANSS) at both screening and day 1 of the study were included. Patients were excluded if:

- They had a DSM-IV diagnosis of alcohol or substance dependence within 12 months before screening.
- They had a DSM-IV diagnosis of substance abuse within three months before screening.
- They had a history of suicide attempt within 12 months.
- They had a history of neuroleptic malignant syndrome or tardive dyskinesia at screening.
- They were taking oral or LAI risperidone or paliperidone or they had plasma levels of these medications exceeding the predefined threshold (0.1 ng/mL).

The study consisted of four panels (A, B, C, and D), with each panel comprising a screening phase up to 21 days and an open-label treatment phase composed of two sequential single-dose treatment periods (period 1 and period 2) with a washout period of seven to 21 days between the two periods. During period 1, patients received a 1-mg intramuscular injection of paliperidone immediate-release solution and were followed for 96 hours. During period 2, patients received a single dose of PP3M, with the panels receiving differing doses in different administration sites, and were followed for 364 days. Modifications in the patients’ antipsychotic medications were not necessary for enrollment and all allowed medications were continued throughout the study.

Bioavailability results from panels A and C indicated that some patients had received incomplete injections of study material due to improper shaking of the syringe before injection. Therefore, a formal training procedure was implemented at all sites prior to the start of panels B and D. Pharmacokinetic (PK) assessments were established by collecting blood samples in both periods at prespecified time intervals. Safety data were gathered by monitoring treatment-emergent adverse events (TEAEs), physical examination, clinical laboratory examination, electrocardiograms, vital signs, and local tolerability evaluations. The visual analogue scale (VAS) was utilized to assess injection-site pain, and the Abnormal Involuntary Movement Scale, Simpson and Angus Rating Scale, and Barnes Akathisia Rating Scale were all used to monitor EPS. PK and safety data were summarized using descriptive statistics.

A total of 328 patients were enrolled in the four panels, with 245 (74.7%) completing the study. Most patients were white men and the mean age range for all four panels was 41.4 to 42.6 years.

PK results could only be established from panels B and D because of compromised data due to improper administration techniques in panels A and C. The median $C_{\text{max}}$ ranged from 21.2 to 57.9 ng/mL with deltoid administration and from 8.3 to 56.3 ng/mL with gluteal administration, and median $T_{\text{max}}$ was obtained for all dose groups. There was a dose-proportional increase in median AUC$_{\text{inf}}$ that was not influenced by body mass index (BMI), race, or gender. The $C_{\text{max}}$ however, was observed to be lower in women and overweight or obese patients when compared to men and
patients with normal BMI. Paliperidone plasma concentrations ranged from 0.27 to 19.20 ng/mL with deltoid administration and 0.23 to 4.13 ng/mL with gluteal administration. These plasma levels had no impact on safety.

Most TEAEs were mild to moderate in severity, with 26.8% of patients in period 1 and 73.7% of patients in period 2 experiencing at least one TEAE. The most common TEAE during period 1 was headache. During period 2 the most common TEAEs were headache and nasopharyngitis. Other common TEAEs experienced in period 2 included weight increases, back pain, and anxiety. Seven subjects dropped out of the study due to TEAEs. Twenty-five patients in period 2 reported injection-site–related TEAEs with low mean VAS scores across all panels that decreased within two to four days. One patient from panel B was reported to have a QT interval (corrected for heart rate [QTc] using Fridericia’s formula [QTcF]) over 500 milliseconds on day 140 and another from panel D had a reported QTcF over 480 milliseconds on day 224. A total of 35 patients reported serious TEAEs and one death occurred during the study from metastatic melanoma, which was determined to be unrelated to the study medication. Psychiatrically related events were the most commonly observed serious TEAEs. No clinically meaningful variations in EPS scales were observed throughout the study and no clinically significant changes in vital parameters, chemistry, hematology, and urinalysis were observed in any of the panels.

This study provides evidence that the new formulation PP3M results in a longer t1/2 and Tmax when compared to the PP1M formulation. The PP3M formulation was generally well tolerated with both deltoid and gluteal administration at all doses evaluated.

Berwaerts et al.17

This randomized, multicenter, double-blind, placebo-controlled study was designed to assess the efficacy and safety of the PP3M formulation compared to placebo in delaying time to relapse in patients with schizophrenia who had been adequately treated with the once-monthly paliperidone formulation for at least four months. Men and women 18 to 70 years of age diagnosed with schizophrenia consistent with DSM-IV criteria for at least one year before screening and a total score lower than 120 on the PANSS at screening and at baseline were included. Patients were also required to have a stable place of residence for the preceding three months before screening in order to be included. Patients effectively treated with other antipsychotic LAIs were eligible. Patients were excluded if:

- They had any other primary active DSM-IV diagnosis.
- They had a significant risk of suicidal behavior.
- They had a history of substance dependence within six months before screening.
- They had an involuntary status at a psychiatric hospital during screening.
- They had a history of tardive dyskinesia, neuroleptic malignant syndrome, or any malignant neoplasm, except for basal cell carcinoma, within the last five years.

The study had four phases: a screening and oral tolerability testing phase, an open-label transition phase, an open-label maintenance phase, and a double-blind phase. Patients in the transition phase were given the PP1M formulation for 120 days. At the start of the 12-week maintenance phase, patients received a single injection of PP3M at a 3.5-fold dose of the last PP1M formulation received. Patients who were stabilized were then randomized to receive either PP3M or placebo in the double-blind phase. Patients randomized to PP3M were given the same dose they had previously received in the open-label phase throughout the double-blind phase. The study’s primary efficacy endpoint was time to first relapse episode in the double-blind phase, and the secondary endpoints included changes from double-blind baseline in Clinical Global Impression–Severity score, Personal and Social Performance scores, and PANSS total, subscale, and five-factor scores. Relapse criteria included: worsening of specific symptoms within the PANSS, increases in PANSS total score of 25% or more, hospitalization for schizophrenia symptoms, significant self-injury or harm to others, and suicidal/homicidal ideation or aggressive behavior.

An independent data monitoring committee performed safety monitoring. One efficacy interim analysis provided recommendations on modifying, stopping, or continuing the study. The committee advised terminating the study based on interim results revealing that 23% of patients in the placebo group versus 7% of patients in the PP3M group had experienced a relapse. The results through the end of the double-blind phase are reported in the article as final analysis.

A total of 506 patients were initially enrolled; however, 308 were randomized in the double-blind phase. Of the 308 randomized patients, 270 (89%) completed the study. Consent withdrawal was cited as the most common reason for study discontinuation. The percentage of patients who entered the double-blind phase for each PP3M dose of 175 mg eq, 263 mg eq, 350 mg eq, and 525 mg eq were 4%, 9%, 49%, and 38%, respectively. A greater proportion of patients who received the 525 mg eq dose continued to week 36 of the double-blind phase when compared to other doses.

The final analysis included 305 patients and confirmed that PP3M was superior to placebo in delaying time to relapse. Final analysis revealed that 29% of patients in the placebo group versus 9% of patients in the PP3M group experienced relapse during the double-blind phase. The mean PANSS scores remained stable for the PP3M group in the double-blind phase, while scores increased for patients in the placebo group. Significant differences were seen between the two groups in mean changes from double-blind baseline in PANSS, Clinical Global Impression–Severity score, and Personal and Social Performance scores.

At least one TEAE was experienced by 65% of patients who received PP3M in the open-label maintenance phase, 60% of patients who received PP3M in the double-blind phase, and 58% of patients who received placebo.

In the maintenance phase, the most frequently reported TEAEs in the group receiving the PP3M formulation were anxiety (6%), insomnia (5%), weight increase (4%), and headache (3%). Psychiatric disorders and schizophrenia were cited as the most common TEAEs leading to study discontinuation in this phase. Additionally, the most common EPS-related TEAEs during this phase
were those grouped under hyperkinesia and parkinsonism.

During the double-blind phase, the TEAEs experienced more frequently by the PP3M group were headache (9%), weight increase (9%), EPS (8%), and nasopharyngitis (6%). Four percent of patients receiving PP3M during this phase reported injection-site–related TEAEs, with injection-site pain being the most common. However, the placebo group experienced serious TEAEs four times more often, and these TEAEs were usually due to increased psychiatric symptoms. Only one TEAE led to study discontinuation in a patient randomized to placebo during this phase.

This study demonstrates the efficacy of PP3M in delaying time to relapse of schizophrenia symptoms compared with placebo. In addition, safety findings were consistent with those observed in other paliperidone palmitate trials and no new safety issues were found.

**COST**¹⁹

Average costs of PP3M depend on the dosage strength. The average cost of one PP3M injection is equal in cost to three of the equivalent PP1M doses. For example, if a patient was previously on 78 mg of PP1M, which costs around $843, the appropriate PP3M dose for this patient would be 273 mg, which costs around $2,530. Therefore, the monthly cost of PP3M is equal to the costs of PP1M. The approximate costs for 410 mg, 546 mg, and 819 mg of PP3M are $3,794, $5,059, and $7,589, respectively. Although PP3M costs appear to be high, they are no different than the cost of using PP1M injection monthly.

**P&T COMMITTEE CONSIDERATIONS**

Invega Trinza is a revolutionary LAI antipsychotic. It is the first and only LAI that requires administration just four times a year. Research has shown that LAIs help improve adherence, resulting in better clinical and economic outcomes. This novel formulation may help improve clinical outcomes by delaying time to relapse and further alleviating issues with poor compliance as a result of the lower frequency of administration, especially for those with limited access to health care. With improved adherence and delays in relapse, PP3M may also help alleviate costs to the health care system as a whole. Some studies have shown that PP1M results in lowering overall costs of care more effectively when compared to other LAIs.⁹ The monthly drug cost of PP3M does not differ much from the cost of PP1M. However, PP3M will have fewer costs surrounding drug administration compared to PP1M due to decreased dosing frequency. This is not to suggest that persons with schizophrenia should be seen less frequently due to this quarterly treatment, but that the use of PP3M will allow patients, caregivers, and their providers more time to focus on other aspects of treatment, such as psychological and social interventions. Therefore, in theory, PP3M has an even greater potential to improve clinical and economic outcomes for patients, their families, and society at large. It will be exciting to see what future results are observed in clinical trials with this innovative formulation.

**REFERENCES**