PALIPERIDONE

THERAPEUTICS

Brands • INVEGA • INVEGA SUSTENNA • INVEGA TRINZA
see index for additional brand names

Generic? No

Class • Neuroscience-based Nomenclature: dopamine, serotonin receptor antagonist (DS-RAn)
• Atypical antipsychotic (serotonin-dopamine antagonist; second generation antipsychotics; also a mood stabilizer)

Commonly Prescribed for (bold for FDA approved)
• Schizophrenia (ages 12 and older)
• Maintaining response in schizophrenia
• Schizoaffective disorder
• Other psychotic disorders
• Bipolar disorder
• Behavioral disturbances in dementia
• Behavioral disturbances in children and adolescents
• Disorders associated with problems with impulse control

How the Drug Works
• Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
• Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms
• Serotonin 7 antagonist properties may contribute to antidepressant actions

How Long Until It Works
• Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition
• Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients may require up to 16–20 weeks to show a good response, especially on cognitive symptoms

If It Works
• Most often reduces positive symptoms but does not eliminate them
• Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
• Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
• Perhaps 5–15% of schizophrenia patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
• Such patients are considered superresponders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
• Continue treatment until reaching a plateau of improvement
• After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
• For second and subsequent episodes of psychosis, treatment may need to be indefinite
• Even for first episodes of psychosis, it may be preferable to continue treatment

If It Doesn’t Work
• Try one of the other atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, amisulpride, asenapine, iloperidone, lurasidone)
• If 2 or more antipsychotic monotherapies do not work, consider clozapine
• Some patients may require treatment with a conventional antipsychotic
• If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
• Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection (a depot formulation of paliperidone is in development)
• Consider initiating rehabilitation and psychotherapy such as cognitive remediation
• Consider presence of concomitant drug abuse

Best Augmenting Combos for Partial Response or Treatment Resistance
• Valproic acid (valproate, divalproex, divalproex ER)
• Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
• Lithium
• Benzodiazepines

Tests
Before starting an atypical antipsychotic:

✽ Weigh all patients and track BMI during treatment
• Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
✽ Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
• Determine if the patient is
  • overweight (BMI 25.0–29.9)
  • obese (BMI >30)
  • has pre-diabetes (fasting plasma glucose 100–126 mg/dL)
  • has diabetes (fasting plasma glucose >126 mg/dL)
  • has hypertension (BP >140/90 mm Hg)
  • has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
• Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic:

✽ BMI monthly for 3 months, then quarterly
✽ Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
✽ Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% of initial weight
• Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic

Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma
• Should check blood pressure in the elderly before starting and for the first few weeks of treatment
• Monitoring elevated prolactin levels of dubious clinical benefit
• Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and paliperidone should be discontinued at the first sign of decline of WBC in the absence of other causative factors

SIDE EFFECTS

How Drug Causes Side Effects
• By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
• By blocking dopamine 2 receptors in the striatum, it can cause motor side effects, especially at high doses
• By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
• Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

Notable Side Effects

✽ Dose-dependent extrapyramidal symptoms
✽ Hyperprolactinemia
✽ May increase risk for diabetes and dyslipidemia
• Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)
• Sedation, hypersalivation
• Dose-dependent orthostatic hypotension
• Tachycardia
• Injection site reactions
DOSING AND USE

Usual Dosage Range
- 6 mg/day (oral)
- 39–234 mg/month (Sustenna; see Paliperidone Palmitate section after Pearls for dosing and use)
- 273–819 mg/3 months (Trinza; see Paliperidone Palmitate section after Pearls for dosing and use)

Dosage Forms
- Tablet (extended-release) 1.5 mg, 3 mg, 6 mg, 9 mg
- 1-month injection 39 mg, 78 mg, 117 mg, 156 mg, 234 mg
- 3-month injection 273 mg, 410 mg, 546 mg, 819 mg

How to Dose
- Initial dose 6 mg/day taken in the morning
- Can increase by 3 mg/day every 5 days; maximum dose generally 12 mg/day
- LAI paliperidone is not recommended for patients who have not first demonstrated tolerability to oral paliperidone or risperidone
- See also the Switching section, after Pearls

Dosing Tips – Oral
- Tablet should not be divided or chewed, but rather should only be swallowed whole
- Tablet does not change shape in the gastrointestinal tract and generally should not be used in patients with gastrointestinal narrowing because of the risk of intestinal obstruction
- Some patients may benefit from doses above 6 mg/day; alternatively, for some patients 3 mg/day may be sufficient
- A common dosage error is to assume the paliperidone ER oral dose is the same as the risperidone oral dose in mg, and that paliperidone should be titrated. However, many patients do well initiating a dose of 6 mg orally of paliperidone ER without titration
- There is a dose-dependent increase in some side effects, including extrapyramidal symptoms and weight gain, above 6 mg/day

Life-Threatening or Dangerous Side Effects
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures

Weight Gain
- Many patients experience and/or can be significant in amount
- May be dose-dependent
- May be less than for some antipsychotics, more than for others

Sedation
- Many experience and/or can be significant in amount
- May be dose-dependent
- May be less than for some antipsychotics, more than for others

What to Do About Side Effects
- Wait
- Wait
- Wait
- Anticholinergics may reduce motor side effects when present
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects
- Benztropine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent

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Best Augmenting Agents for Side Effects
- Benztropine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent
• Rather than raise the dose above these levels in acutely agitated patients requiring acute antipsychotic actions, consider augmentation with a benzodiazepine or conventional antipsychotic, either orally or intramuscularly
• Rather than raise the dose above these levels in partial responders, consider augmentation with a mood-stabilizing anticonvulsant, such as valproate or lamotrigine
• Children and elderly should generally be dosed at the lower end of the dosage spectrum
• Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³
• Oral doses correspond to injection doses as follows: 3 mg oral to 39–78 mg injection, 6 mg oral to 117 mg injection, 12 mg oral to 234 mg injection

Extrapyramidal symptoms, gait unsteadiness, sedation, tachycardia, hypotension, QT prolongation

Approved for maintenance in schizophrenia

• No

• See Switching section of individual agents for how to stop paliperidone ER and LAI
• Rapid oral discontinuation may lead to rebound psychosis and worsening of symptoms

• Active metabolite of risperidone
• Half-life approximately 23 hours
• Absorption is reduced if taken on an empty stomach

• May increase effects of antihypertensive agents
• May antagonize levodopa, dopamine agonists
• May enhance QTc prolongation of other drugs capable of prolonging QTc interval

• Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
• Dysphagia has been associated with antipsychotic use, and paliperidone should be used cautiously in patients at risk for aspiration pneumonia
• Paliperidone prolongs QTc interval more than some other antipsychotics
• Priapism has been reported with other antipsychotics, including risperidone

If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
If patient has a preexisting severe gastrointestinal narrowing
If there is a proven allergy to paliperidone or risperidone

Rather than raise the dose above these levels in partial responders, consider augmentation with a mood-stabilizing anticonvulsant, such as valproate or lamotrigine

Some patients may tolerate lower doses better
PALIPERIDONE

• Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
• Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

Children and Adolescents
• Safety and efficacy have not been established under age 12
• Adolescents <51 kg: initial 3 mg/day; recommended 3–6 mg/day; maximum 6 mg/day
• Adolescents >51 kg: initial 3 mg/day; recommended 3–12 mg/day; maximum 12 mg/day
• Children and adolescents using paliperidone may need to be monitored more often than adults

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
• Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
• Paliperidone may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy

• Effects of hyperprolactinemia on the fetus are unknown
• National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/

Breast Feeding
• Some drug is found in mother’s breast milk
• Recommended either to discontinue drug or bottle feed
• Infants of women who choose to breast feed while on paliperidone should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• Some cases of psychosis and bipolar disorder refractory to treatment with other antipsychotics
• Patients requiring rapid onset of antipsychotic action without dosage titration

Potential Disadvantages
• Patients for whom elevated prolactin may not be desired (e.g., possibly pregnant patients; pubescent girls with amenorrhea; postmenopausal women with low estrogen who do not take estrogen replacement therapy)

Primary Target Symptoms
• Positive symptoms of psychosis
• Negative symptoms of psychosis
• Cognitive symptoms
• Unstable mood (both depression and mania)
• Aggressive symptoms

Pearls
• Some patients respond to paliperidone or tolerate paliperidone better than the parent drug risperidone
• Hyperprolactinemia in women with low estrogen may accelerate osteoporosis
• Less weight gain than some antipsychotics, more than others
• May cause more motor side effects than some other atypical antipsychotics,
especially when administered to patients with Parkinson’s disease or Lewy body dementia
• Trilayer tablet consists of 3 compartments (2 containing drug, 1 a “push” compartment) and an orifice at the head of the first drug compartment; water fills the push compartment and gradually pushes drug up and out of the tablet through the orifice
• LAI does not require simultaneous oral medication
• LAI may work better and better after a few weeks of treatment in some patients
• LAI may be very well tolerated
• LAI may be combined with a second antipsychotic administered orally for difficult cases
• Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and, if low, a dosage increase even beyond the usual prescribing limits
• For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy

with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring
• In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic
• Patients with inadequate responses to atypical antipsychotics may also benefit from a trial of augmentation with a conventional antipsychotic or switching to a conventional antipsychotic
• However, long-term polypharmacy with a combination of a conventional antipsychotic with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either
• Although a frequent practice by some prescribers, adding 2 conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy

**PALMITATE**

<table>
<thead>
<tr>
<th>1-month (Sustenna)</th>
<th>3-month (Trinza)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>Water</td>
</tr>
<tr>
<td>Tmax</td>
<td>13 days</td>
</tr>
<tr>
<td>T1/2 with multiple dosing</td>
<td>25–49 days</td>
</tr>
<tr>
<td>Time to reach steady state</td>
<td>1 week</td>
</tr>
<tr>
<td>Able to be loaded</td>
<td>Yes</td>
</tr>
<tr>
<td>Dosing schedule (maintenance)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Injection site</td>
<td>Intramuscular (deltoid at initiation, then either deltoid or gluteal)</td>
</tr>
<tr>
<td>Needle gauge</td>
<td>22 or 23</td>
</tr>
<tr>
<td>Dosage forms</td>
<td>39 mg, 78 mg, 117 mg, 156 mg, 234 mg</td>
</tr>
<tr>
<td>Injection volume</td>
<td>156 mg/mL; range 0.25–1.5 mL</td>
</tr>
</tbody>
</table>
**Usual Dosage Range**
- 1-month injectable maintenance dose: 117 mg/month (range 39–234 mg/month)
- 3-month injectable maintenance dose: 273–819 mg/3 months

**How to Dose – 1-month Injectable**
- Not recommended for patients who have not first demonstrated tolerability to oral paliperidone or risperidone (in clinical trials, 2 oral or short-acting IM doses are generally used to establish tolerability)
- Conversion from oral: 234 mg delivered intramuscularly in the deltoid on Day 1; 156 mg delivered intramuscularly in the deltoid on Day 8; maintenance dose should start 4 weeks after the 2nd loading injection

<table>
<thead>
<tr>
<th>Oral paliperidone</th>
<th>1-month Sustenna</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg</td>
<td>39–78 mg</td>
</tr>
<tr>
<td>6 mg</td>
<td>117 mg</td>
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<tr>
<td>9 mg</td>
<td>156 mg</td>
</tr>
<tr>
<td>12 mg</td>
<td>234 mg</td>
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**How to Dose – 3-month Injectable**
- Only for patients who have received adequate treatment with paliperidone Sustenna for at least 4 months

**Oral Equivalence (Approximate)**

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**How to Dose – 1-month Injectable**
- The last 2 doses of paliperidone Sustenna should ideally be the same dosage strength, so that a consistent maintenance dose is established prior to starting paliperidone Trinza
- Conversion from 1-month injectable: initiate 3-month LAI when the next 1-month LAI injection is scheduled; dosing is based on the previous 1-month injection dose

<table>
<thead>
<tr>
<th>1-month Sustenna</th>
<th>3-month Trinza</th>
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<tbody>
<tr>
<td>78 mg</td>
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**Dosing Tips**
- With LAIs, the absorption rate constant is slower than the elimination rate
- If dose has been missed for more than 9 months, re-initiate treatment with paliperidone Sustenna according to its prescribing information; paliperidone Trinza can be used after the patient has been adequately treated with paliperidone Sustenna for at least 4 months
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<tr>
<th>Last Trinza Dose</th>
<th>Day 1</th>
<th>Day 8</th>
<th>1 Month After Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>273 mg</td>
<td>78 mg Sustenna (deltoid)</td>
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• In general, 5 half-lives of any medication are needed to achieve 97% of steady-state levels
• The long half-lives of depot antipsychotics mean that one must either adequately load the dose (if possible) or provide oral supplementation
• The failure to adequately load the dose leads either to prolonged cross-titration from oral antipsychotic or to sub-therapeutic antipsychotic plasma levels for weeks or months in patients who are not receiving (or adhering to) oral supplementation
• Because plasma antipsychotic levels increase gradually over time, dose requirements may ultimately decrease from initial; obtaining periodic plasma levels can be beneficial to prevent unnecessary plasma level creep
• The time to get a blood level for patients receiving LAI is the morning of the day they will receive their next injection
• Kinetics for paliperidone palmitate are determined by particle size: smaller particles (1-month) vs. larger particles (3-month)
• Advantages: no need for oral coverage; 3-month injection schedule with Trinza
• Disadvantages: plasma levels have limited value in guiding treatment
### THE ART OF SWITCHING

#### Switching from Oral Antipsychotics to Paliperidone palmitate (1-Month)

<table>
<thead>
<tr>
<th>Target dose</th>
<th>Initiation dose</th>
<th>Paliperidone palmitate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 week</strong></td>
<td><em>amisulpride</em></td>
<td>1 week</td>
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<tr>
<td></td>
<td><em>aripiprazole</em></td>
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<td></td>
<td><em>Brexpiprazole</em></td>
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<td></td>
<td><em>Cariprazine</em></td>
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<tr>
<td></td>
<td><em>Paliperidone ER</em></td>
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<td><strong>1 week</strong></td>
<td><em>Iloperidone</em></td>
<td>1 week</td>
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<tr>
<td></td>
<td><em>Lurasidone</em></td>
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<td></td>
<td><em>Risperidone</em></td>
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<td><em>Ziprasidone</em></td>
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<tr>
<td><strong>1 week</strong></td>
<td><em>Asenapine</em></td>
<td>1 week</td>
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<tr>
<td></td>
<td><em>Olanzapine</em></td>
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<td></td>
<td><em>Quetiapine</em></td>
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<tr>
<td><strong>1 week</strong></td>
<td><em>Clozapine</em></td>
<td>1 week</td>
</tr>
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</table>

- Discontinuation of oral antipsychotic can begin immediately if adequate loading is pursued
- How to discontinue oral formulations
  - Down-titration is not required for: amisulpride, aripiprazole, brexpiprazole, cariprazine, paliperidone ER
  - 1-week down-titration is required for: iloperidone, lurasidone, risperidone, ziprasidone
  - 3–4-week down-titration is required for: asenapine, olanzapine, quetiapine
  - 4+ week down-titration is required for: clozapine
- For patients taking benzodiazepine or anticholinergic medication, this can be continued during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis. Once the patient is stable on LAI, these can be tapered one at a time as appropriate.
**THE ART OF SWITCHING**

**Switching from Oral Antipsychotics to Paliperidone ER**

- Due to OROS technology, paliperidone ER can be initiated at full desired dose; however, titration over 1–2 weeks may be appropriate for some patients.
- With aripiprazole and amisulpride, immediate stop is possible; begin paliperidone ER at an intermediate, or if needed, effective dose.
- Risperidone, ziprasidone, iloperidone, and lurasidone can be tapered off over a period of 1 week due to the risk of withdrawal symptoms such as insomnia.
- Clinical experience has shown that quetiapine, olanzapine, and asenapine should be tapered off slowly over a period of 3–4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha 1 receptors.
- Clozapine should always be tapered off slowly, over a period of 4 weeks or more.

* Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis.

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<th>Target dose</th>
<th>1 week</th>
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<tr>
<td><strong>dose</strong></td>
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<tr>
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Suggested Reading

