



# DOSING & ADMINISTRATION GUIDE

 **INVEGA SUSTENNA<sup>®</sup>**  
paliperidone palmitate extended-release  
injectable suspension  
39mg, 78mg, 117mg, 156mg, 234mg

 **INVEGA TRINZA<sup>®</sup>**  
paliperidone palmitate extended-release  
injectable suspension  
273mg, 410mg, 546mg, 819mg

 **INVEGA HAFYERA<sup>®</sup>**  
paliperidone palmitate extended-release  
injectable suspension  
1092mg, 1560mg

## Overview

INVEGA SUSTENNA<sup>®</sup>, INVEGA TRINZA<sup>®</sup>, and INVEGA HAFYERA<sup>®</sup> are dosed monthly, every 3 months, or every 6 months, respectively, per their individual Prescribing Information.

Each product requires different preparation and administration. It is critical to prepare the medication following the Instructions for Use to ensure a complete injection of the full dose. Administering less than the full dose could negatively impact the patient's outcome.

Utilize this guide to familiarize yourself with the distinctions between dosing and administering INVEGA SUSTENNA<sup>®</sup>, INVEGA TRINZA<sup>®</sup>, and INVEGA HAFYERA<sup>®</sup>.

## Overview

INVEGA SUSTENNA® (paliperidone palmitate) is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.<sup>1</sup>

INVEGA TRINZA® (paliperidone palmitate), a 3-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in patients after they have been adequately treated with INVEGA SUSTENNA® for at least four months.<sup>2</sup>

INVEGA HAFYERA® (paliperidone palmitate), a 6-month injection, is indicated for the treatment of schizophrenia in patients after they have been adequately treated with either INVEGA SUSTENNA® for at least four months or INVEGA TRINZA® following at least one 3-month injection cycle.<sup>3</sup>

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.**

*See full prescribing information for complete Boxed Warning.*

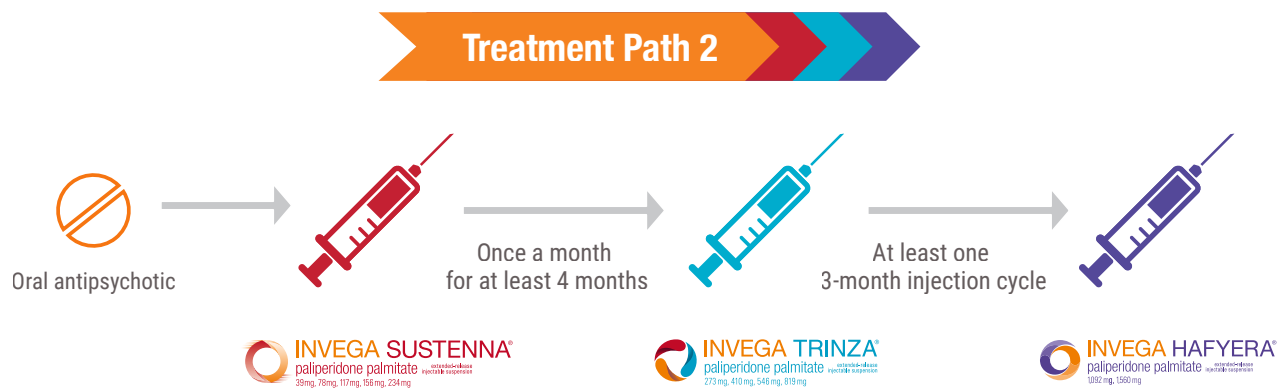
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA SUSTENNA®, INVEGA TRINZA®, and INVEGA HAFYERA™ are not approved for use in patients with dementia-related psychosis.

# Treatment Pathways

If patient has never taken oral paliperidone or oral/injectable risperidone, establish tolerability first. All patients transitioning from oral antipsychotics must follow the recommended INVEGA SUSTENNA® initiation dosing of 234 mg (Day 1) and 156 mg (Day 8) with both doses administered in the deltoid muscle.<sup>1</sup>



- Must be adequately treated for at least 4 months with INVEGA SUSTENNA® to transition to INVEGA HAFYERA®<sup>3</sup>
- It is recommended that the last 2 doses of INVEGA SUSTENNA® be the same strength (**156 mg or 234 mg**) before starting INVEGA HAFYERA®<sup>3</sup>

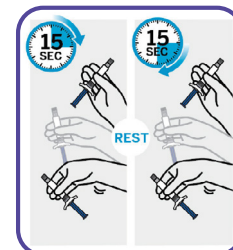
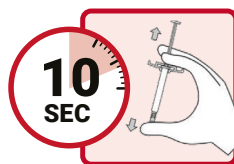


- Must be adequately treated for at least 4 months with INVEGA SUSTENNA® to transition to INVEGA TRINZA®.<sup>2</sup> It is recommended that the last 2 doses of INVEGA SUSTENNA® be the same dosage strength before starting INVEGA TRINZA®. Refer to page 13 for additional transition information for INVEGA TRINZA®
- Must be adequately treated with at least one 3-month injection cycle of INVEGA TRINZA® at doses of **546 mg or 819 mg** to transition to INVEGA HAFYERA®<sup>3</sup>

# Product Snapshot



DOSING INTERVAL		Once monthly <sup>1</sup>	Every 3 months <sup>2</sup>	Every 6 months <sup>3</sup>
INJECTION SITE		Deltoid or gluteal muscle (2 initiation doses in deltoid)	Deltoid or gluteal muscle	Gluteal muscle only
NEEDLE SIZE  Must be administered using only the needles that are provided in the kit.	For patients weighing <90 kg	<b>Deltoid:</b> 1-inch, 23-gauge needle <b>Gluteal:</b> 1½-inch, 22-gauge needle	<b>Deltoid:</b> 1-inch, 22-gauge needle <b>Gluteal:</b> 1½-inch, 22-gauge needle	1½-inch, 20-gauge needle
	For patients weighing ≥90 kg	<b>Deltoid:</b> 1½-inch, 22-gauge needle <b>Gluteal:</b> 1½-inch, 22-gauge needle	<b>Deltoid:</b> 1½-inch, 22-gauge needle <b>Gluteal:</b> 1½-inch, 22-gauge needle	
PREPARATION INSTRUCTIONS		Shake vigorously	Shake vigorously with loose wrist and tip up	Shake very fast with loose wrist and tip up
SHAKE TIME		10 seconds	15 seconds If more than <b>5 minutes</b> pass before injection, shake vigorously, with the syringe tip pointing up, again for <b>15 seconds</b> .	15 seconds, rest briefly, shake again for 15 seconds If more than <b>5 minutes</b> pass before the injection is administered, shake the syringe again, as above, to resuspend the medication.



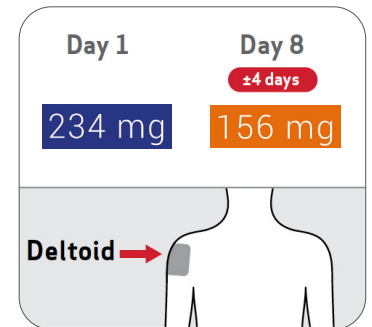
 **INVEGA SUSTENNA<sup>®</sup>**  
paliperidone palmitate extended-release  
injectable suspension  
39mg, 78mg, 117mg, 156mg, 234mg

# Initiation & Maintenance

## Initiating INVEGA SUSTENNA®<sup>1</sup>

- No oral supplementation required
- For patients who have not taken oral paliperidone, oral risperidone, or injectable risperidone, establish tolerability first
- Previous oral antipsychotics can be discontinued at the time of initiation of treatment with INVEGA SUSTENNA®
- All patients transitioning from oral antipsychotics must follow the recommended initiation dosing of 234 mg (Day 1) and 156 mg (Day 8)
- Both initiation doses administered in the deltoid muscle
- To avoid a missed dose, patients may be given the second initiation dose within a  $\pm 4$ -day flexible window

### FOR INITIATION DOSE

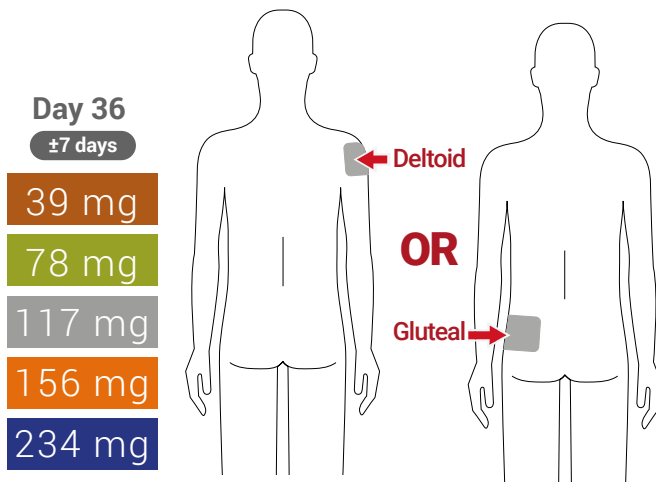


## Monthly Maintenance Doses for INVEGA SUSTENNA®

First monthly maintenance dose\* should be administered 5 weeks after the first injection (regardless of the timing of the second injection).<sup>1</sup>

\*The recommended maintenance dose for the treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).

### FOR MAINTENANCE DOSE



To avoid a missed dose, monthly maintenance doses may be given within a  $\pm 7$ -day flexible window.

Utilizing the maintenance dosing window to help avoid missed doses should be considered the exception rather than the rule.

Please see page 20 for Additional Dosing Information for patients with renal impairment.

## Transitioning From INVEGA® (paliperidone) Extended-Release Tablets<sup>1</sup>

INITIATION DOSING (DELTOID)		RECOMMENDED MONTHLY MAINTENANCE DOSE (DELTOID OR GLUTEAL)	
DAY 1	DAY 8	INVEGA® Extended-Release Tablet (daily)	INVEGA SUSTENNA® Injection (once monthly)
234 mg	156 mg	3 mg	39-78 mg
		6 mg	117 mg
		9 mg	156 mg
		12 mg	234 mg

## Transitioning From Risperidone Tablets<sup>4,5</sup>

INITIATION DOSING (DELTOID)		MONTHLY MAINTENANCE DOSE (DELTOID OR GLUTEAL)	
DAY 1	DAY 8	Risperidone Tablet (daily)	INVEGA SUSTENNA® Injection (once monthly)
234 mg	156 mg	Patients stabilized on risperidone tablets can attain similar steady-state exposure on INVEGA SUSTENNA® as follows <sup>5</sup> :	
<p>There are no systematically collected data to specifically address transitioning patients with schizophrenia from other antipsychotics to INVEGA SUSTENNA®.</p> <p>This information is based on pharmacokinetic (PK) modeling performed to compare steady-state exposure during maintenance treatment between risperidone tablets and INVEGA SUSTENNA® (after both the 234 mg/156 mg deltoid starting doses). This information is not included in the INVEGA SUSTENNA® Prescribing Information.</p>		1 mg	39 mg
		2 mg	78 mg
		3 mg	117 mg
		4 mg	156 mg
		6 mg	234 mg

## Additional Maintenance Dosing Information

The first monthly maintenance dose should be administered 5 weeks after the first injection (regardless of the timing of the second injection).

The recommended maintenance dose for the treatment of schizophrenia is 117 mg.

Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).



## Transitioning From RISPERDAL CONSTA® (risperidone)<sup>1</sup>

INITIATION DOSING (DELTOID)		DAY 8 Not required	RECOMMENDED MONTHLY MAINTENANCE DOSE (DELTOID OR GLUTEAL)	
<b>DAY 1</b> Administer in place of the next scheduled injection <sup>4</sup> :			Some patients may benefit from lower or higher maintenance doses within the additional available strengths:	
RISPERDAL CONSTA® injection (dose at study entry)	INVEGA SUSTENNA® injection	<div style="display: flex; justify-content: space-around;"> <div style="background-color: #76923c; color: white; padding: 5px;">78 mg</div> <div style="background-color: #666666; color: white; padding: 5px;">117 mg</div> </div> <div style="display: flex; justify-content: space-around;"> <div style="background-color: #e69d00; color: white; padding: 5px;">156 mg</div> <div style="background-color: #003366; color: white; padding: 5px;">234 mg</div> </div>		
25 mg	78 mg			
37.5 mg	117 mg			
50 mg	156 mg			

Transition dosing was based on pharmacokinetic modeling. The Prescribing Information for INVEGA SUSTENNA® and RISPERDAL CONSTA® does not include conversion charts between the 2 agents.<sup>4</sup>

During the open-label stabilization phase of a long-term maintenance trial for INVEGA TRINZA® for the treatment of schizophrenia, enrolled patients treated with RISPERDAL CONSTA® long-acting injection were switched to INVEGA SUSTENNA® in place of the next scheduled injection at a dose determined by the conversion guide.<sup>2</sup> It is important to note that the INVEGA SUSTENNA® conversion dose may not reflect the eventual stabilization dose that was achieved during the remainder of the open-label transition phase.

## Transitioning From Other LAI Antipsychotics<sup>1</sup>

INITIATION DOSING (DELTOID)		DAY 8 Not required	RECOMMENDED MONTHLY MAINTENANCE DOSE (DELTOID OR GLUTEAL)			
<b>DAY 1</b> Administer in place of the next scheduled injection:			Some patients may benefit from lower or higher maintenance doses within the additional available strengths:			
<div style="background-color: #003366; color: white; padding: 5px; text-align: center; width: 100px; margin: 0 auto;">234 mg*</div> Some patients may benefit from lower initiation doses:		<div style="display: flex; justify-content: space-around;"> <div style="background-color: #76923c; color: white; padding: 5px;">39 mg</div> <div style="background-color: #666666; color: white; padding: 5px;">78 mg</div> <div style="background-color: #333333; color: white; padding: 5px;">117 mg</div> </div> <div style="display: flex; justify-content: space-around;"> <div style="background-color: #e69d00; color: white; padding: 5px;">156 mg</div> <div style="background-color: #003366; color: white; padding: 5px;">234 mg</div> </div>				
39 mg	78 mg					
117 mg	156 mg					

\*The 234 mg INVEGA SUSTENNA® strength was used in the pivotal clinical trial for INVEGA TRINZA® (paliperidone palmitate) as an initiation dose for patients who were being transitioned from another LAI antipsychotic.

## Additional Maintenance Dosing Information

Administered 1 month after the initial dose.

The recommended maintenance dose for the treatment of schizophrenia is 117 mg.

Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).

# Addressing Missed Doses

Missing doses should be avoided.<sup>1</sup> It is understood that adherence can be a concern. If any doses are missed, refer to the charts below to resume treating your patient with INVEGA SUSTENNA®.

INVEGA SUSTENNA®: what to do if the <b>second</b> initiation does is missed <sup>1</sup>			
Time since last injection	Less than 4 weeks since first injection	4-7 weeks since first injection	More than 7 weeks since first injection
<b>Action steps:</b>	Administer the second initiation dose of 156 mg in the deltoid muscle as soon as possible  1. Administer a third injection of 117 mg in either the deltoid or gluteal muscle 5 weeks after the first injection (regardless of timing of the second injection) 2. Resume regular monthly dosing in either the deltoid or gluteal muscle	Resume dosing with 2 injections of 156 mg:  1. Deltoid injection as soon as possible 2. Second deltoid injection 1 week later 3. Resume regular monthly dosing in either the deltoid or gluteal muscle	Restart dosing with normal initiation plan:  1. 234 mg deltoid injection at Day 1 2. 156 mg deltoid injection 1 week later 3. Resume regular monthly injections in either the deltoid or gluteal muscle

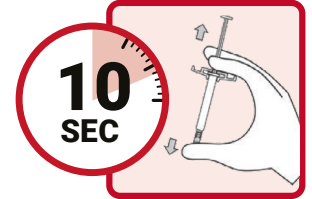
INVEGA SUSTENNA®: what to do if a <b>monthly dose</b> is missed <sup>1</sup>			
Time since last injection	4 to 6 weeks since last injection	More than 6 weeks to 6 months since last injection	More than 6 months since last injection
<b>Action steps:</b>	Resume regular dosing as soon as possible at patient's previously stabilized dose, followed by injections at monthly intervals	Continue dosing at patient's previously stabilized dose* by giving:  1. Deltoid injection as soon as possible 2. Second deltoid injection 1 week later at same dose 3. Resume monthly deltoid or gluteal injections at patient's previously stabilized dose 1 month after second injection  *If the patient was stabilized on 234 mg, the first 2 doses should be 156 mg.	Restart dosing with normal initiation plan:  1. 234 mg deltoid injection at Day 1 2. 156 mg deltoid injection 1 week later 3. Resume regular monthly injections either in the deltoid or gluteal muscle 1 month after second injection

To help avoid a missed monthly maintenance dose, patients may be given their monthly maintenance dose within a  $\pm 7$ -day flexible dosing window. The utilization of this practice should be considered the exception rather than the rule.

# Preparation & Administration

## Administration Instructions<sup>1</sup>

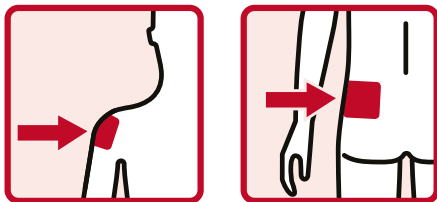
INVEGA SUSTENNA® is injected once monthly into the deltoid or gluteal muscle. Refer to the Administration Notes below to select the appropriate needle for each patient.



1. Shake vigorously for at least 10 seconds to ensure a homogenous suspension
2. Proceed immediately to inject INVEGA SUSTENNA®

## Administration Notes<sup>1</sup>

- For patients weighing <90 kg:
  - If injecting in the deltoid muscle, use the 1-inch, 23-gauge needle
  - If injecting in the gluteal muscle, use the 1½-inch, 22-gauge needle
- For patients weighing ≥90 kg:
  - If injecting in the deltoid muscle, use the 1½-inch, 22-gauge needle
  - If injecting in the gluteal muscle, use the 1½-inch, 22-gauge needle





**INVEGA TRINZA<sup>®</sup>**

paliperidone palmitate extended-release  
injectable suspension

273 mg, 410 mg, 546 mg, 819 mg

# Initiation & Maintenance

## Transitioning from INVEGA SUSTENNA® (paliperidone palmitate) to INVEGA TRINZA®<sup>2</sup>

- Patients must be adequately treated with INVEGA SUSTENNA® for at least 4 months before transitioning to INVEGA TRINZA®<sup>2</sup>
- It is recommended that the last 2 doses of INVEGA SUSTENNA® be the same dosage strength before starting INVEGA TRINZA®<sup>2</sup>

### INVEGA TRINZA® Initiation Doses<sup>2</sup>

If the last INVEGA SUSTENNA® dose was:	Initiate INVEGA TRINZA® at the following dose:
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Conversion from the INVEGA SUSTENNA® 39 mg dose was not studied.

### Three-Month Maintenance Doses for INVEGA TRINZA®<sup>2</sup>

- Following the initial INVEGA TRINZA® dose, INVEGA TRINZA® should be administered once every 3 months
- If needed, dose adjustments can be made every 3 months in increments within the range of 273 mg to 819 mg, based on tolerability or efficacy
  - Due to the long-acting nature of INVEGA TRINZA®, the patient's response to an adjusted dose may not be apparent for several months
- Between doses, patients can maintain scheduled treatment plans and routine interactions with their treatment team

Please see page 20 for Additional Dosing Information for patients with renal impairment.

# Addressing Missed Doses

Missed doses should be avoided.<sup>2</sup> If necessary, patients may be given the injection up to 2 weeks before or after the 3-month time point. Utilizing the flexible dosing window should be considered the exception rather than the rule.

It is understood that adherence can be a concern. If any doses are missed, refer to the information on this page to resume treating your patient with INVEGA TRINZA®.

## Time since last injection<sup>2</sup>:

- Longer than 3½ months, but less than 4 months: Previous dose should be administered as soon as possible, and then continue with 3-month injections
- 4 months up to and including 9 months: Do not administer the next dose; instead, use the reinitiation table below
- Longer than 9 months: Reinitiate treatment with INVEGA SUSTENNA® (paliperidone palmitate) per its Prescribing Information. INVEGA TRINZA® can be resumed after ≥4 monthly INVEGA SUSTENNA® treatments

## Reinitiation regimen after missing 4 to 9 months of INVEGA TRINZA®

If the last dose of	Administer	Then administer
INVEGA TRINZA® was:	INVEGA SUSTENNA® 2 doses, 1 week apart (into deltoid muscle)	INVEGA TRINZA® (into deltoid or gluteal muscle)
	Day 1 → Day 8 →	1 month after day 8
<b>273 mg</b>	78 mg → 78 mg →	273 mg
<b>410 mg</b>	117 mg → 117 mg →	410 mg
<b>546 mg</b>	156 mg → 156 mg →	546 mg
<b>819 mg</b>	156 mg → 156 mg →	819 mg

# Preparation & Administration

## Administration Instructions<sup>2</sup>

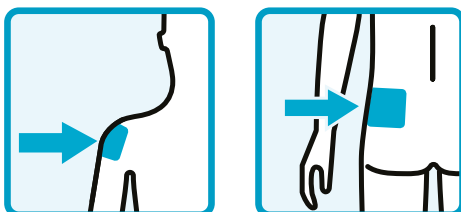
INVEGA TRINZA® is injected every 3 months into the deltoid or gluteal muscle. Refer to the Administration Notes below to select the appropriate needle for each patient.

1. With the syringe tip pointing up, shake vigorously with a loose wrist for at least 15 seconds
  - a. Note: This medication requires longer and more vigorous shaking than INVEGA SUSTENNA®
2. Check the viewing window to ensure that the suspension appears uniform and milky white—it is normal to see small air bubbles
3. Proceed immediately to inject INVEGA TRINZA®
4. If more than 5 minutes pass before injection, shake again as in step 1 to resuspend the medication



## Administration Notes<sup>2</sup>

- For patients weighing <90 kg:
  - If injecting in the deltoid muscle, use the 1-inch, 22-gauge needle
  - If injecting in the gluteal muscle, use the 1½-inch, 22-gauge needle
- For patients weighing ≥90 kg, use the 1½-inch, 22-gauge needle (deltoid or gluteal)
- Alternate injections between left and right gluteal and/or deltoid muscles
- Inadequate preparation could result in a clogged needle and incomplete administration of the dose



[View INVEGA TRINZA®  
Injection Training Video](#)



**INVEGA HAFYERA<sup>®</sup>**

paliperidone palmitate extended-release  
injectable suspension

1,092 mg, 1,560 mg



# Initiation Dosing

## Transitioning to INVEGA HAFYERA<sup>®3</sup>

If the last dose of INVEGA SUSTENNA <sup>®</sup> (paliperidone palmitate) was:	Initiate INVEGA HAFYERA <sup>®</sup> in the gluteal muscle at the following dose:	If the last dose of INVEGA TRINZA <sup>®</sup> (paliperidone palmitate) was:	Initiate INVEGA HAFYERA <sup>®</sup> in the gluteal muscle at the following dose:
156 mg	1,092 mg	546 mg	1,092 mg
234 mg	1,560 mg	819 mg	1,560 mg

Initiate INVEGA HAFYERA<sup>®</sup> when the next INVEGA SUSTENNA<sup>®</sup> dose is scheduled with an INVEGA HAFYERA<sup>®</sup> dose based on the previous 1-month injection dose, as shown above. INVEGA HAFYERA<sup>®</sup> may be administered up to 1 week before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.

Initiate INVEGA HAFYERA<sup>®</sup> when the next INVEGA TRINZA<sup>®</sup> dose is scheduled with an INVEGA HAFYERA<sup>®</sup> dose based on the previous 3-month injection dose, as shown above. INVEGA HAFYERA<sup>®</sup> may be administered up to 2 weeks before or after the time point of the next scheduled paliperidone palmitate 3-month dose.

\*Conversion from the INVEGA SUSTENNA<sup>®</sup> 39 mg, 78 mg, and 117 mg doses was not studied.

†Conversion from the INVEGA TRINZA<sup>®</sup> 273 mg and 410 mg doses was not studied.

- INVEGA HAFYERA<sup>®</sup> is to be used only after adequate treatment has been established with INVEGA SUSTENNA<sup>®</sup> for at least 4 months (with the last 2 doses being 156 mg or 234 mg), or INVEGA TRINZA<sup>®</sup> for at least one 3-month injection cycle (at doses of 546 mg or 819 mg)<sup>3</sup>
- To establish a consistent maintenance dose, it is recommended that the last 2 doses of INVEGA SUSTENNA<sup>®</sup> be the same dosage strength before starting INVEGA HAFYERA<sup>®3</sup>
- Following the initial dose, INVEGA HAFYERA<sup>®</sup> should be administered every 6 months

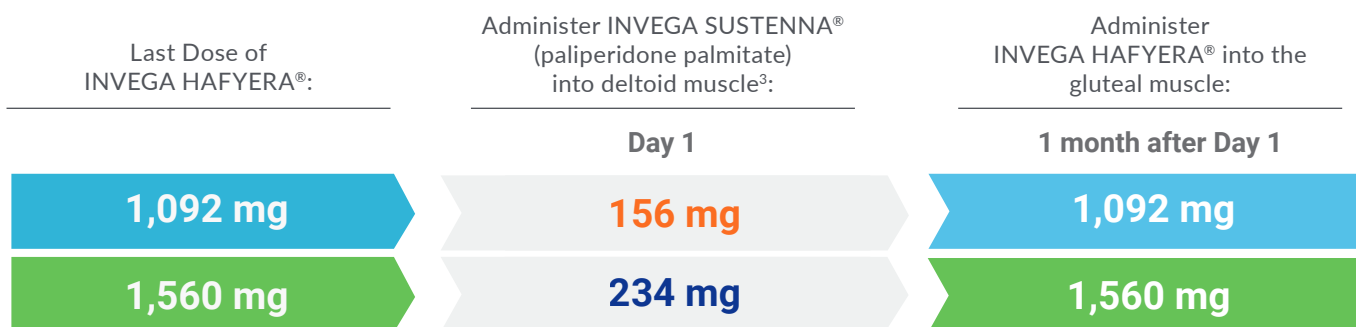
Please see page 20 for Additional Dosing Information for patients with renal impairment.

# Addressing Missed Doses

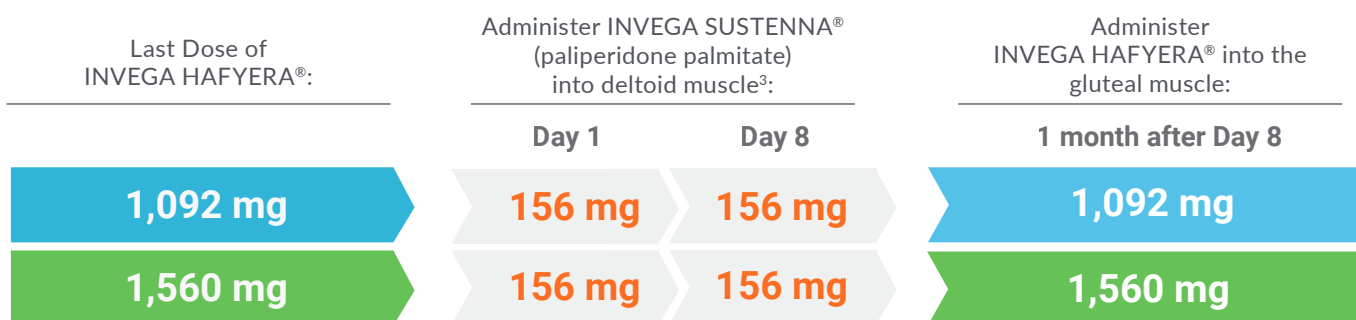
- To avoid a missed dose, patients may be given the injection up to 2 weeks before or 3 weeks after the scheduled 6-month time point

## Time Since Last Injection:

- If more than **6 months and 3 weeks but less than 8 months** have elapsed since the last injection of INVEGA HAFYERA<sup>®</sup>, do NOT administer the next dose. Instead, use this reinitiation regimen<sup>3</sup>:



- If **8 months but up to and including 11 months** have elapsed since the last injection of INVEGA HAFYERA<sup>®</sup>, do NOT administer the next dose. Instead, use this reinitiation regimen<sup>3</sup>:



- If **more than 11 months** have elapsed since the last injection of INVEGA HAFYERA<sup>®</sup>, reinitiate treatment with INVEGA SUSTENNA<sup>®</sup> as described in the Prescribing Information for that product. INVEGA HAFYERA<sup>®</sup> can then be resumed after the patient has been adequately treated with INVEGA SUSTENNA<sup>®</sup> for at least 4 months.<sup>3</sup>

# Preparation & Administration

## Administration Instructions<sup>3</sup>

- INVEGA HAFYERA<sup>®</sup> is injected every 6 months into the gluteal muscle. Use the 1½-inch, 20-gauge needle, regardless of patient weight.
- INVEGA HAFYERA<sup>®</sup> should be administered by a healthcare professional as a single injection. **DO NOT** divide dose into multiple injections.
- INVEGA HAFYERA<sup>®</sup> requires longer and faster shaking than INVEGA SUSTENNA<sup>®</sup> (paliperidone palmitate).



### Step 1

Holding the syringe with the tip cap pointing up, **shake the syringe with a loose wrist, using a very fast up-and-down motion**, for at least 15 seconds.



### Step 2

Rest briefly, just for a few seconds, then shake again in the same way, **using a very fast up-and-down motion with a loose wrist** for an additional 15 seconds.



### Step 3

Proceed immediately to inject INVEGA HAFYERA<sup>®</sup>.

- INVEGA HAFYERA<sup>®</sup> **must** be injected into the gluteal muscle only, using the 1½-inch, 20-gauge needle provided (regardless of patient's weight)
- Do not administer by any other route
- INVEGA HAFYERA<sup>®</sup> is injected into the **upper-outer quadrant of the gluteal muscle**, so there is no need for your patient to fully disrobe
- Use slow, firm, consistent pressure to press the plunger completely. This should take approximately 30 seconds. Continue to press the plunger if you feel resistance. This is normal. While the needle is in the muscle, confirm that the entire content of the syringe has been injected
- If more than 5 minutes pass before the injection is administered, shake the syringe again very fast with the tip pointing up for at least 30 seconds to resuspend the medication
- Alternate injections between the left and right gluteal muscles

[View INVEGA HAFYERA<sup>®</sup> Injection Training Video](#)

# Contraindications & Guidance for Patients With Renal Impairment

## Contraindications

INVEGA HAFYERA<sup>®</sup>, INVEGA TRINZA<sup>®</sup> and INVEGA SUSTENNA<sup>®</sup> are contraindicated in patients with a known hypersensitivity to either paliperidone, risperidone, or to any excipients of their formulation.<sup>1-3</sup>

### For Patients With Renal Impairment

**INVEGA SUSTENNA<sup>®</sup>** can be administered to patients with mild renal impairment (creatinine clearance  $\geq$  50 mL/min to  $<$  80 mL/min). Administer 156 mg on treatment Day 1 and 117 mg on Day 8, both in the deltoid muscle. To avoid a missed dose, patients may be given the second initiation dose within a  $\pm$ 4-day flexible window.

Follow with the recommended monthly maintenance dose of 78 mg, administered in the deltoid or gluteal muscle. Adjust monthly maintenance dosage based on tolerability and/or efficacy within the strengths of 39 mg, 78 mg, 117 mg, or 156 mg. The maximum monthly dose is 156 mg for patients with mild renal impairment.

INVEGA SUSTENNA<sup>®</sup> is not recommended for use in patients with moderate to severe renal impairment (creatinine clearance  $<$  50 mL/min).<sup>1</sup>

**INVEGA TRINZA<sup>®</sup>** can be used in patients with mild renal impairment (creatinine clearance  $\geq$  50 mL/min to  $<$  80 mL/min). Adjust dosage and stabilize the patient using INVEGA SUSTENNA<sup>®</sup>, then transition to INVEGA TRINZA<sup>®</sup>. INVEGA TRINZA<sup>®</sup> is not recommended for use in patients with moderate or severe renal impairment (creatinine clearance  $<$  50 mL/min).<sup>2</sup>

**INVEGA HAFYERA<sup>®</sup>** is not recommended for use in patients with mild, moderate, or severe renal impairment (creatinine clearance  $<$  90 mL/min) because necessary dosage adjustment is not possible with available strengths of INVEGA HAFYERA<sup>®</sup>.<sup>3</sup>

**REFERENCES:** 1. INVEGA SUSTENNA<sup>®</sup> [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; July 2022. 2. INVEGA TRINZA<sup>®</sup> [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2021. 3. INVEGA HAFYERA<sup>®</sup> [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2021. 4. Samtani MN, Gopal S, Gassmann-Mayer C, et al. Dosing and switching strategies for paliperidone palmitate: based on population pharmacokinetic modelling and clinical trial data. *CNS Drugs*. 2011;25(10):829-845. 5. Russu A, Sliwa JK, Ravenstijn P, et al. Maintenance dose conversion between oral risperidone and paliperidone palmitate 1 month: practical guidance based on pharmacokinetic simulations. *Int J Clin Pract*. 2018;72(6):e13089.

## INDICATION

INVEGA HAFYERA™, an every-six-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in adults after they have been adequately treated with:

- A once-a-month paliperidone palmitate extended release injectable suspension (e.g., INVEGA SUSTENNA®) for at least four months or
- An every-three-month paliperidone palmitate extended release injectable suspension (e.g., INVEGA TRINZA®) for at least one three-month cycle.

INVEGA TRINZA® is an atypical antipsychotic indicated for the treatment of schizophrenia in patients after they have been adequately treated with INVEGA SUSTENNA® for at least four months.

INVEGA SUSTENNA® is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.

## IMPORTANT SAFETY INFORMATION

### **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.**

*See full prescribing information for complete Boxed Warning.*

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® are not approved for use in patients with dementia-related psychosis.**

**Contraindications:** INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® are contraindicated in patients with a known hypersensitivity to either paliperidone, risperidone, or to any excipients of their formulation.

**Cerebrovascular Adverse Reactions:** Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attacks), including fatalities, were reported at a higher incidence in elderly patients with dementia-related psychosis taking risperidone, aripiprazole, and olanzapine compared to placebo. No studies have been conducted with oral paliperidone, INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA® in elderly patients with dementia. These medications are not approved for the treatment of patients with dementia-related psychosis.

**Neuroleptic Malignant Syndrome (NMS):** NMS, a potentially fatal symptom complex, has been reported in association with antipsychotic drugs, including paliperidone.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse of blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA® and provide symptomatic treatment and monitoring.

**QT Prolongation:** Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QTc interval and in patients with risk factors for prolonged QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

**Tardive Dyskinesia (TD):** TD, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing TD and the likelihood that it will become irreversible appear to increase with the duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation. TD may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

If signs and symptoms of TD appear in a patient on INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA® despite the presence of the syndrome. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

**Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

**Hyperglycemia and Diabetes Mellitus:** Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes mellitus should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia during treatment should also undergo fasting blood glucose testing. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia. Some patients require continuation of antidiabetic treatment despite discontinuation of the suspect drug.

**Dyslipidemia:** Undesirable alterations have been observed in patients treated with atypical antipsychotics.

**Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

**Orthostatic Hypotension and Syncope:** INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® may induce orthostatic hypotension in some patients due to its alpha-adrenergic blocking activity. INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, treatment with antihypertensive medications). Monitoring should be considered in patients for whom this may be of concern.

**Falls:** Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

**Leukopenia, Neutropenia and Agranulocytosis** have been reported with antipsychotics, including INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA®. In patients with a history of clinically significant low white blood cell count (WBC)/ absolute neutrophil count (ANC) or drug-induced leukopenia/neutropenia, perform a complete blood count frequently during the first few months of therapy. Consider discontinuing INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count <1000/mm<sup>3</sup>) and follow their WBC until recovery.

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D<sub>2</sub> receptors, INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® elevate prolactin levels, and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.

**Potential for Cognitive and Motor Impairment:** Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA®. INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities that require mental alertness such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® do not adversely affect them.

**Seizures:** INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold. Conditions that lower seizure threshold may be more prevalent in patients 65 years or older.

**Administration:** For intramuscular injection only by a healthcare professional using only the needles provided in the INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA® kits. Care should be taken to avoid inadvertent injection into a blood vessel.

**Drug Interactions:** Strong CYP3A4/P-glycoprotein (P-gp) inducers: Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John's Wort) during a dosing interval for INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA®. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets.

**Pregnancy/Nursing:** INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare professional if they become pregnant or intend to become pregnant during treatment with INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA®. Patients should be advised that there is a pregnancy registry that monitors outcomes in women exposed to INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA® during pregnancy. INVEGA HAFYERA™, INVEGA TRINZA® and INVEGA SUSTENNA® can pass into human breast milk. The benefits of breastfeeding should be considered along with the mother's clinical need for INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA® and any potential adverse effect on the breastfed infant from INVEGA HAFYERA™, INVEGA TRINZA® or INVEGA SUSTENNA® or the mother's underlying condition.

**Commonly Observed Adverse Reactions for INVEGA HAFYERA™:** The most common adverse reactions (incidence at least 5% in the double-blind phase) in the INVEGA HAFYERA™ clinical trial were upper respiratory tract infection, injection site reaction, weight increased, headache and parkinsonism.

**Commonly Observed Adverse Reactions for INVEGA TRINZA®:** The most common adverse reactions (incidence  $\geq$  5% and occurring at least twice as often as placebo) were injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia and parkinsonism.

**Commonly Observed Adverse Reactions for INVEGA SUSTENNA®:** The most common adverse reactions in clinical trials in patients with schizophrenia (incidence  $\geq$  5% and occurring at least twice as often as placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

Please [click here](#) to read the full Prescribing Information, including Boxed WARNING, for INVEGA HAFYERA™, [click here](#) to read the full Prescribing Information, including Boxed WARNING, for INVEGA TRINZA® and [click here](#) to read the full Prescribing Information, including Boxed WARNING, for INVEGA SUSTENNA®.

cp-256260v1

## INDICATION

INVEGA® (paliperidone) extended-release tablets are indicated for the treatment of schizophrenia.

### IMPORTANT SAFETY INFORMATION FOR INVEGA® (paliperidone)

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.**

*See full prescribing information for complete Boxed Warning.*

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA® is not approved for use in patients with dementia-related psychosis.**

**Contraindications:** Paliperidone is contraindicated in patients with a known hypersensitivity to paliperidone, risperidone, or to any excipients in INVEGA®.

**Cerebrovascular Adverse Events (CAEs):** CAEs (eg, stroke, transient ischemia attacks), including fatalities, were reported in placebo-controlled trials in elderly patients with dementia-related psychosis taking oral risperidone, aripiprazole, and olanzapine. The incidence of CAEs was significantly higher than with placebo. INVEGA® is not approved for the treatment of patients with dementia-related psychosis.

**Neuroleptic Malignant Syndrome (NMS):** NMS, a potentially fatal symptom complex, has been reported in association with antipsychotic drugs, including paliperidone.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue INVEGA® and provide symptomatic treatment and monitoring.

**QT Prolongation:** Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QTc interval and in patients with risk factors for prolonged QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

**Tardive Dyskinesia (TD):** TD, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing TD and the likelihood that it will become irreversible appear to increase with the duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation. TD may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

If signs and symptoms of TD appear in a patient on INVEGA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA® despite the presence of the syndrome. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

**Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. The metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes – Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death has been reported in patients treated with atypical antipsychotics (APS), including INVEGA®. Patients starting treatment with APS who have or are at risk for diabetes mellitus should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia. Some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia – Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain – Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D<sub>2</sub> receptors, INVEGA® elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.

**Gastrointestinal:** INVEGA® should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing. Rare instances of obstructive symptoms have been reported in patients with known strictures taking non-deformable formulations. INVEGA® should only be used in patients who are able to swallow the tablet whole

**Orthostatic Hypotension and Syncope:** INVEGA® may induce orthostatic hypotension in some patients due to its alpha-blocking activity. INVEGA® should be used with caution in patients with known cardiovascular disease (eg, heart failure, history of MI or ischemia, conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (eg, dehydration, hypovolemia, treatment with anti-hypertensive medications). Monitoring should be considered in patients who are vulnerable to hypotension.



**Falls:** Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including INVEGA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

**Leukopenia, Neutropenia, and Agranulocytosis** have been reported temporally related to antipsychotic agents, including INVEGA®. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) or drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. Discontinuation should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly. Patients with severe neutropenia should discontinue INVEGA® and follow their WBC until recovery.

**Potential for Cognitive and Motor Impairment:** Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA®. Antipsychotics including INVEGA® have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities that require mental alertness such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA® does not adversely affect them.

**Seizures:** INVEGA® should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold. Conditions that lower seizure threshold may be more prevalent in patients 65 years or older.

**Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Use cautiously in patients at risk for aspiration pneumonia.

**Priapism** has been reported. Severe priapism may require surgical intervention.

**Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with INVEGA® use.

**Thrombotic Thrombocytopenic Purpura (TTP)** has been reported.

**Increased sensitivity in patients with Parkinson's disease** or those with dementia with Lewy bodies has been reported. Manifestations and features are consistent with NMS.

**Use INVEGA® with caution** in patients with medical conditions that could affect metabolism or hemodynamic responses (e.g., recent myocardial infarction or unstable cardiac disease).

**Drug Interactions:** Strong CYP3A4/P-glycoprotein (P-gp) inducers: It may be necessary to increase the dose of INVEGA® when a strong inducer of both CYP3A4 and P-gp (eg, carbamazepine, rifampin, St. John's wort) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of INVEGA®.

**Pregnancy/Nursing:** INVEGA® may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare professional if they become pregnant or intend to become pregnant during treatment with INVEGA®. Patients should be advised that there is a pregnancy registry that monitors outcomes in women exposed to INVEGA® during pregnancy. INVEGA® can pass into human breast milk. The benefits of breastfeeding should be considered along with the mother's clinical need for INVEGA® and any potential adverse effects on the breastfed infant from INVEGA® or the mother's underlying condition.

**Fertility:** INVEGA® may cause a reversible reduction in fertility in females.

**Commonly Observed Adverse Reactions:** The most commonly observed adverse reactions in clinical trials occurring at an incidence of ≥5% and at least 2 times placebo in the treatment of adults with schizophrenia were extrapyramidal symptoms, tachycardia, and akathisia.

Please [click here](#) to read the full Prescribing Information, including Boxed WARNING, for INVEGA®.

cp-64196v3

## INDICATION

RISPERDAL<sup>®</sup> (risperidone) is indicated for the treatment of schizophrenia.

## IMPORTANT SAFETY INFORMATION FOR RISPERDAL<sup>®</sup> (risperidone)

### WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

*See full prescribing information for complete Boxed Warning.*

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL<sup>®</sup> is not approved for use in patients with dementia-related psychosis.**

**CONTRAINDICATIONS:** RISPERDAL<sup>®</sup> is contraindicated in patients with a known hypersensitivity to either risperidone or paliperidone, or to any of the excipients in the RISPERDAL<sup>®</sup> formulation.

**Cerebrovascular Adverse Reactions:** Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL<sup>®</sup> is not approved for the treatment of patients with dementia-related psychosis.

**Neuroleptic Malignant Syndrome (NMS):** NMS, a potentially fatal symptom complex, has been reported in association with antipsychotic drugs, including risperidone.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue RISPERDAL<sup>®</sup> and provide symptomatic treatment and monitoring.

**Tardive Dyskinesia (TD):** TD, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing TD and the likelihood that it will become irreversible appear to increase with the duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation. TD may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

If signs and symptoms of TD appear in a patient on RISPERDAL<sup>®</sup>, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL<sup>®</sup> despite the presence of the syndrome. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

**Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus: Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes mellitus should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia during treatment should also undergo fasting blood glucose testing. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia. Some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D<sub>2</sub> receptors, RISPERDAL® elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

**Orthostatic Hypotension and Syncope:** RISPERDAL® may induce orthostatic hypotension in some patients due to its alpha-blocking activity. RISPERDAL® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, treatment with antihypertensive medications). Monitoring should be considered in patients for whom this may be of concern.

**Falls:** Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including RISPERDAL®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

**Leukopenia, Neutropenia, and Agranulocytosis** have been reported temporally related to antipsychotic agents, including RISPERDAL®. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) or drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. Discontinuation should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly. Patients with severe neutropenia should discontinue RISPERDAL® and follow their WBC until recovery.

**Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse reaction associated with RISPERDAL® treatment. Since RISPERDAL® has the potential to impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

**Seizures:** RISPERDAL® should be used cautiously in patients with a history of seizures.

**Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Use cautiously in patients at risk for aspiration pneumonia.

**Priapism** has been reported. Severe priapism may require surgical intervention.

**Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL®.

**Maintenance Treatment:** Physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

**Pregnancy/Nursing:** RISPERDAL® may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare professional if they become pregnant or intend to become pregnant during treatment with RISPERDAL®. Patients should be advised that there is a pregnancy registry that monitors outcomes in women exposed to RISPERDAL® during pregnancy. RISPERDAL® can pass into human breast milk. The benefits of breastfeeding should be considered along with the mother's clinical need for RISPERDAL® and any potential adverse effect on the breastfed infant from RISPERDAL® or the mother's underlying condition.

**Fertility:** RISPERDAL® may cause a reversible reduction in fertility in females.

**Commonly Observed Adverse Reactions for RISPERDAL®:** The most common adverse reactions in all clinical trials (≥5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting,

upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain.

Please [click here](#) to read the full Prescribing Information, including Boxed WARNING, for RISPERDAL®.

cp-64210v4

## INDICATION

RISPERDAL CONSTA® (risperidone) long-acting injection is indicated for the treatment of schizophrenia.

## IMPORTANT SAFETY INFORMATION FOR RISPERDAL CONSTA® (risperidone)

### WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.

*See full prescribing information for complete Boxed Warning.*

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL CONSTA® is not approved for use in patients with dementia-related psychosis.**

**Contraindications:** RISPERDAL CONSTA® is contraindicated in patients with a known hypersensitivity to risperidone, paliperidone, or to any excipients in RISPERDAL CONSTA®.

**Cerebrovascular Adverse Events (CAEs):** CAEs (e.g., stroke, transient ischemia attacks), including fatalities, were reported in placebo-controlled trials in elderly patients with dementia-related psychosis taking oral risperidone. The incidence of CAEs was significantly higher than with placebo. RISPERDAL CONSTA® is not approved for the treatment of patients with dementia-related psychosis.

**Neuroleptic Malignant Syndrome (NMS):** NMS, a potentially fatal symptom complex, has been reported in association with antipsychotic drugs.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue RISPERDAL CONSTA® and provide symptomatic treatment and monitoring.

**Tardive Dyskinesia (TD):** TD, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing TD and the likelihood that it will become irreversible appear to increase with the duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation. TD may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

If signs and symptoms of TD appear in a patient on RISPERDAL CONSTA®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL CONSTA® despite the presence of the syndrome. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

**Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus: Hyperglycemia and diabetes mellitus, some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics (APS), including RISPERDAL CONSTA®. Patients starting treatment with APS who have or are at risk for diabetes mellitus should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia. Monitor glucose regularly in patients with diabetes or at risk for diabetes. Some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D<sup>2</sup> receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

**Orthostatic Hypotension and Syncope:** RISPERDAL CONSTA® may induce orthostatic hypotension in some patients due to its alpha-adrenergic blocking activity. RISPERDAL CONSTA® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, treatment with antihypertensive medications). Monitoring should be considered in patients for whom this may be of concern.

**Falls:** Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including RISPERDAL CONSTA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

**Leukopenia, Neutropenia and Agranulocytosis** have been reported with antipsychotics, including RISPERDAL CONSTA®. Patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia should have frequent complete blood cell counts during the first few months of therapy. At the first sign of a clinically significant decline in WBC, and in the absence of other causative factors, discontinuation of RISPERDAL CONSTA® should be considered. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm<sup>3</sup>) should discontinue RISPERDAL CONSTA® and have their WBC followed until recovery.

**Potential for Cognitive and Motor Impairment:** Somnolence was reported in multiple trials in subjects treated with RISPERDAL CONSTA®. Since RISPERDAL CONSTA® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that RISPERDAL CONSTA® does not adversely affect them.

**Seizures:** RISPERDAL CONSTA® should be used cautiously in patients with a history of seizures.

**Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Use cautiously in patients at risk for aspiration pneumonia.

**Priapism** has been reported. Severe priapism may require surgical intervention.

**Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with RISPERDAL CONSTA® use.

**Thrombotic Thrombocytopenic Purpura (TTP)** has been reported.

**Administration:** For intramuscular injection only. Care should be taken to avoid inadvertent injection into a blood vessel.

**Increased sensitivity in patients with Parkinson's disease** or those with dementia with Lewy bodies has been reported. Manifestations and features are consistent with NMS.

**Use RISPERDAL CONSTA® with caution** in patients with conditions and medical conditions that could affect metabolism or hemodynamic responses (e.g., recent myocardial infarction or unstable cardiac disease).

**Pregnancy/Nursing:** RISPERDAL CONSTA® may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare professional if they become pregnant or intend to become pregnant during treatment with RISPERDAL CONSTA®. Patients should be advised that there is a pregnancy registry that monitors outcomes in women exposed to RISPERDAL CONSTA® during pregnancy. RISPERDAL CONSTA® can pass into human breast milk. The benefits of breastfeeding should be considered along with the mother's clinical need for RISPERDAL CONSTA® and any potential adverse effect on the breastfed infant from RISPERDAL CONSTA® or the mother's underlying condition.

**Fertility:** RISPERDAL CONSTA® may cause a reversible reduction in fertility in females.

**Commonly Observed Adverse Reactions for RISPERDAL CONSTA®:** The most common adverse reactions in clinical trials in patients with schizophrenia (≥5%) were headache, Parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increase, pain in extremities, and dry mouth.

Please [click here](#) to read the full Prescribing Information, including Boxed WARNING, for RISPERDAL CONSTA®.

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