Six-Monthly Paliperidone (Invega Hafyera™)
FDA approved September 2021
Manufacturer: Johnson & Johnson's Janssen subsidiary

Invega Hafyera, the extended release IM formulation of paliperidone offers the first half yearly injection option for the treatment of schizophrenia in adults. It can only be used

1. after monthly paliperidone LAI (Invega Sustenna) has been established *as* *adequate treatment for at least 4 months* OR
2. after quarterly paliperidone LAI (Invega Trinza) has been established *as* *adequate treatment for at least* one three-month cycle

Conversion from monthly Sustenna or quarterly Trinza to 6-monthly Hafyera

- Dosing based on the client's last dose of Invega Sustenna or Invega Trinza
- Initiate Invega Hafyera when the next monthly or quarterly paliperidone LAI dose is scheduled

INVEGA HAFYERA Doses for Adults Adequately Treated with Once-a-month paliperidone palmitate extended-release injectable suspension (PP1M)*

If the Last Dose of PP1M is:	Initiate INVEGA HAFYERA at the Following Dose:
156 mg	1,092 mg
234 mg	1,560 mg

*Switching from the PP1M 39 mg, 78 mg and 117 mg doses was not studied.

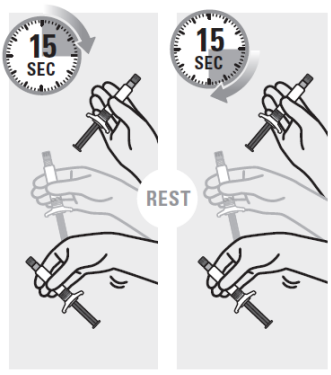
INVEGA HAFYERA Doses for Adults Adequately Treated with Every-three-month paliperidone palmitate injectable suspension (PP3M)*

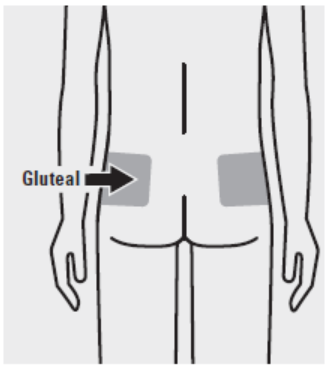
If the Last Dose of PP3M is:	Initiate INVEGA HAFYERA at the Following Dose:
546 mg	1,092 mg
819 mg	1,560 mg

*Switching from the PP3M 273 mg and 410 mg doses was not studied.

Administration

- Prior to injection - shake syringe VERY FAST for at least 15 seconds, rest briefly, and then shake again for 15 seconds
- After shaking, the suspension should appear uniform, thick & milky white
- If the injection is not administered within 5 minutes, shake the syringe again VERY FAST for at least 30 seconds (to resuspend)
- Inject slowly (~30 seconds) as a single injection deep into the upper-outer quadrant of the gluteal muscle using only the thin wall needle provided in the kit (to reduce the risk of blockage)
- While the needle is in the muscle, confirm that the entire content of the syringe has been injected
- Avoid inadvertent injection into a blood vessel





Dosage form & strengths
1,092 mg/3.5 mL or 1,560 mg/5 mL single-dose prefilled ER injectable suspension syringes

Pharmacodynamics/Kinetics

	Invega Sustenna®	Invega Trinza™	Invega Hafyera™
Absorption	From day 1 up to 126 days	From day 1 up to 18 months	From day 1, predicted to last longer than 18 months
Time to peak	13 days	30 to 33 days	29 to 32 days
$T_{1/2}$	25 to 49 days	Deltoid inj: 84 to 95 days Gluteal inj: 118 to 139 days	148 days (1,092 mg) 159 days (1,560 mg)
Metabolism	• Paliperidone palmitate is hydrolyzed to paliperidone, the major active metabolite of risperidone • not extensively metabolized in the liver • no evidence *in vivo* that CYP2D6 & 3A4 play a significant role in paliperidone metabolism		
Excretion	• Urine (80%), feces (11%)		

- NanoCrystal® technology enables solubility of poorly water-soluble compounds gradually releasing a controlled amount of medication consistently over time
- Mean trough concentrations were about 25% lower, whereas mean peak concentration was about 1.5-fold higher compared to Invega Trinza
- Inter-subject variability ranged from 42 to 48% for $AUC_{6months}$ and from 56 to 103% for Cmax

Drug Interactions

- No specific drug interaction studies have been performed with Invega Hafyera (information obtained from PO paliperidone)
- Avoid using strong CYP3A4 and/or P-glycoprotein inducers
    - If administering a strong inducer is necessary, consider managing the client using paliperidone ER tablets

Adverse Reactions

The safety profile of Invega Hafyera is similar to Sustenna and Trinza. The most common (≥5%) adverse reactions in the Invega Hafyera clinical trial were

- Upper respiratory tract infection (12%)
- Injection site reaction (11%)
- Increased weight (9%)
- Headache (7%), and
- Parkinsonism (5%)

Dosage adjustments

- Dose adjustments can be made every 6 months between 1,092 mg to 1,560 mg based on response & tolerability
- Due to the long-acting formulation, client's response to an adjusted dose may not be apparent for several months

Dosing window

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

Product	Dosing WIndow
Invega Sustenna	up to 7 days before or after the monthly dose date
Invega Trinza	up to 2 weeks before or after the next scheduled time point
Invega Hafyera	up to 2 weeks before or 3 weeks after the scheduled 6-month time point

Missed dose

1. Missed dose more than 6 months and 3 weeks, but < 8 months since last injection: Do not administer the next dose, use the re-initiation regimen below

Last Dose of INVEGA HAFYERA	Administer PP1M Product* into deltoid muscle	Administer INVEGA HAFYERA into gluteal muscle
	Day 1	1 month after Day 1
1,092 mg	156 mg	1,092 mg
1,560 mg	234 mg	1,560 mg

*PP1M: Once-a-month paliperidone palmitate extended-release injectable suspension

2. Missed dose 8 months up to and including 11 months since last injection: Do not administer the next dose, follow the re-initiation regimen below

Last dose of INVEGA HAFYERA	Administer PP1M Product* into deltoid muscle		Administer INVEGA HAFYERA into gluteal muscle
	Day 1	Day 8	1 month after Day 8
1,092 mg	156 mg	156 mg	1,092 mg
1,560 mg	156 mg	156 mg	1,560 mg

*PP1M: Once-a-month paliperidone palmitate extended-release injectable suspension

3. Missed dose longer than 11 months since last injection
    a. Re-initiate treatment with monthly IM paliperidone (Invega Sustenna) as described in the prescribing information for that product
    b. 6-mpnthly paliperidone LAI can then be resumed after the client has been adequately treated with monthly IM paliperidone for at least 4 months

Role in Therapy

- Invega Hafyera's less frequent dosing may improve adherence and offer more convenience for patients, providers, and reduced burden on caregivers. However, it may be less advantageous compared to other LAIs
    - clts stable on Invega Sustenna doses of 39 mg, 78 mg or 117 mg and clts stable on Invega Trinza doses of 273 mg or 410 mg may not be candidates for the six monthly Hafyera
    - gluteal administration only
    - less opportunities for dose adjustment
        - long dosing interval
        - available in 2 strengths only (1,092 mg & 1,560 mg)
- The efficacy of Hafyera was evaluated in a 12-month randomized, double-blind phase 3 non-inferiority trial designed to evaluate if the time to relapse for half-yearly Hafyera provided similar effectiveness as quarterly Trinza
    - Study subjects: 702 adults with schizophrenia who had previously been stably treated with either Invega Sustenna for at least 4 months, or one-time injection of Invega Trinza
    - Study results showed non-inferiority of Invega Hafyera compared to Trinza on the primary endpoint of time to first relapse at the end of 12-months
        - 7.5% of the Hafyera administered pts experienced relapse compared to 4.9% of patients in the Trinza group [estimated difference of 2.9% (95% CI, -1.1, 6.8)]
        - 92.5% of pts in the Invega Hafyera group & 95% in the Invega Trinza group were relapse-free at 12 months
        - Relapse was defined as psychiatric hospitalization, increase in Positive and Negative Syndrome Scale [PANSS] total score, increase in individual PANSS item scores, self-injury, violent behavior, or suicidal/homicidal ideation
- Like other LAI antipsychotics, its effects cannot be reversed if toxicity occur. Use of Invega Hafyera may lead to side-effects like upper respiratory tract infection, increased weight, headache, and Parkinsonism
- Use in pregnancy may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. The clinical significance of Invega Hafyera administered before pregnancy or anytime during pregnancy is not known
- Not recommended for use in renal impairment (dosage adjustments not possible with available strengths)
- Seven other LAI atypical antipsychotics are currently available for the treatment of schizophrenia (comparison table below)

- Invega Hafyera® and Zyprexa Relprevv® are approved for gluteal administration only, whereas Perseris® is administered subcutaneously. All other LAIs may be administered IM into the deltoid or gluteal muscle
- Abilify Maintena® & Risperdal Consta® are also indicated for bipolar 1 disorder whereas Invega Sustenna® has an additional indication for schizoaffective disorder
- All paliperidone LAIs have QT prolongation warning, other atypical LAIs do not

Price Comparison

Medication	Dose/Freq	Cost per dose ($)	Monthly Cost ($)
Invega Sustenna	234mg Q mo	2940.01	2940.01
Invega Trinza	819mg Q 3 mo	8820.03	2940.01
Invega Hafyera	1560mg Q 6 mo	17640.05	2940.01
Abilify Maintena	400mg Q mo	2388.47	2388.47
Aristada	1064mg Q 2 mo	3410.55	1705.28
Perseris	120mg Q mo	2513.70	2513.70
Risperdal Consta	50mg Q2 wks	1065.89	2131.78

*RxNova Drug pricing 10/7/2021

Formulary Recommendation

BHRS: PA required

CA/CMC: PA required

HPSM MC/HF/HW: NF

Approval Criteria
Covered Uses: All medically accepted indications

Required Medical Information:

History of noncompliance with oral antipsychotics or difficulty in swallowing oral medications AND

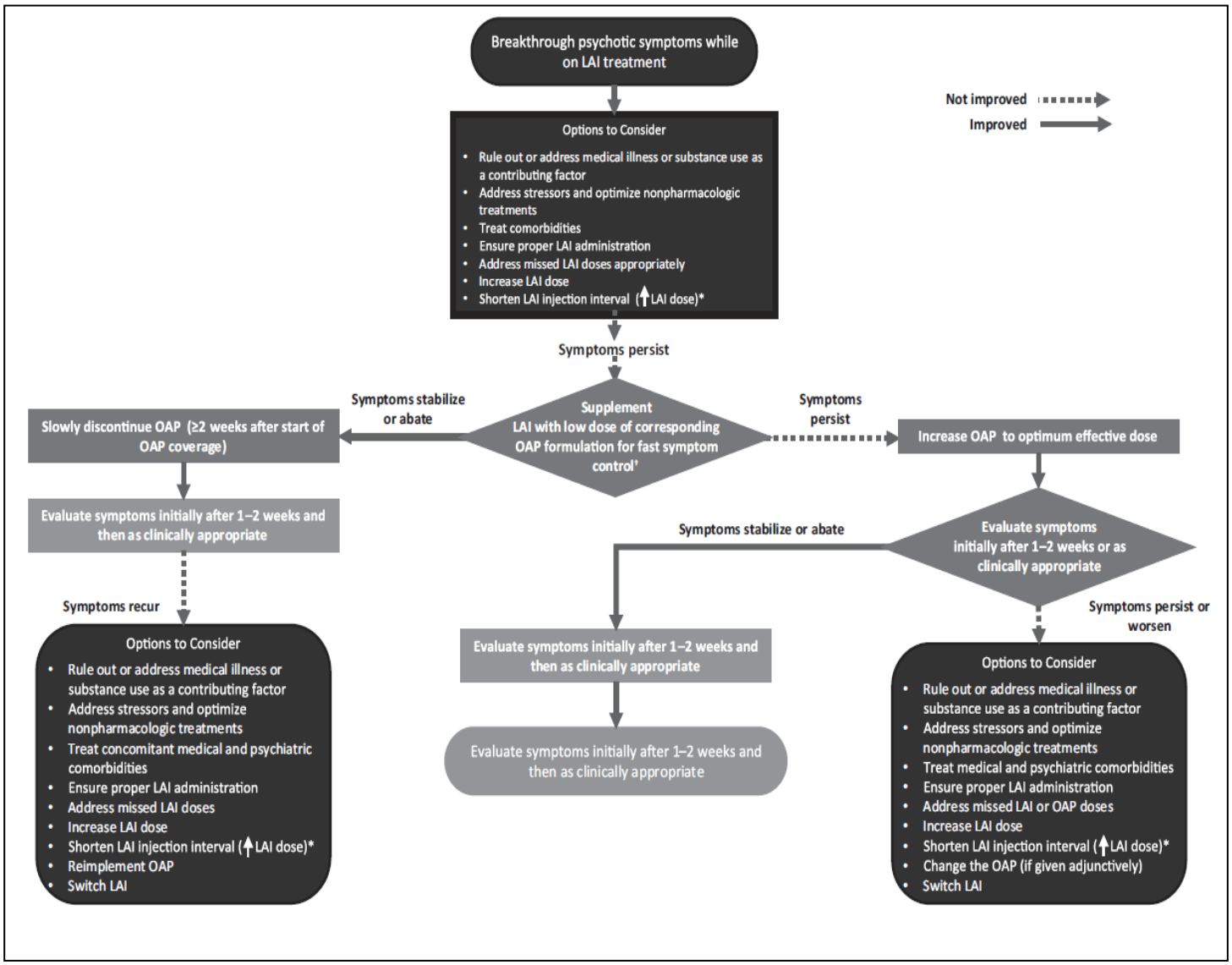
monthly paliperidone LAI (Invega Sustenna) has been established at least 4 months OR

quarterly paliperidone LAI (Invega Trinza) has been established for one three-month cycle

Prescriber Restrictions: psychiatrist
Duration of Approval: 12 months
QL: 1,092 mg or 1,560 mg per 182DS

Invega Sustenna - Invega Trinza - Invega Hafyera – Management of Breakthrough Psychotic Symptoms

- Patients may experience an acute exacerbation while receiving an LAI antipsychotic
- No systematically collected data for the management of breakthrough symptoms for pts treated with Invega Sustenna, Trinza, or Hafyera
- Clinicians should exercise clinical judgment and weigh the potential benefits and risks of dose escalation or oral supplementation
    - 1st line approach: optimize LAI treatment by increasing dose and monitoring for tolerance
    - 2nd line approach: consider a combination of an oral antipsychotic with the current LAI or changing the current LAI for another LAI antipsychotic per clinical judgment
- Exercise caution when considering coadministration of paliperidone palmitate with risperidone or oral paliperidone, since paliperidone is the major active metabolite of risperidone (similar pharmacological profile as risperidone)
- Below is a decision tree to guide treatment considerations for the management of breakthrough psychotic symptoms based on clinical, pharmacokinetic and dosing considerations (Correll et al, 2018)



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Comparison of 2nd generation long-acting injectable antipsychotics

Generic (Brand)	Indication	Dosing	Oral dosing at initiation	Administration/Storage
Aripiprazole lauroxil (Aristada Initio®)	▪ Schizophrenia	675 mg IM once + 30 mg aripiprazole PO once + one Aristada IM inj within 10 days	Yes, aripiprazole 30 mg PO once	▪Tap & shake syringe vigorously for at least 30 seconds prior to use ▪Store at room temperature
Aripiprazole lauroxil (Aristada®)	▪ Schizophrenia	441, 662, 882 mg IM once monthly, or 882 mg Q6-weeks or 1064 mg Q2-months	Yes, aripiprazole PO for 21 days	▪Tap 10 times, shake syringe vigorously for at least 30 seconds prior to use ▪ Inject over *<10 seconds* into deltoid or gluteal muscle (441 mg), gluteal only (662 or 882 mg) ▪Store at room temperature
Aripiprazole (Abilify Maintena®)	▪ Schizophrenia ▪ Bipolar I	300 or 400 mg IM once monthly	Yes, aripiprazole PO for 14 days	• Shake syringe vigorously for 20 seconds, shake vials for 30 sec • Inject *slowly* into deltoid or gluteal muscle (300 or 400 mg) •Protect from light. Store in the original package
Paliperidone palmitate (Invega Halfyera®)	▪ Schizophrenia	1,092 mg or 1,560 mg once 6-monthly	Not needed	▪ Shake syringe VERY FAST for at least 15 seconds, rest briefly & shake again for 15 seconds ▪ Administer within 5 minutes using the needles provided in the kit ▪ Inject slowly (~30 seconds) as a single injection deep into the gluteal muscle ▪ Store at room temperature
Paliperidone palmitate (Invega Trinza®)	▪ Schizophrenia	273 mg, 410 mg, 546 mg, or 819 mg IM Q3-months. Previous treatment with once monthly Invega Sustenna is required	Not needed	▪Shake syringe vigorously for at least 15 seconds within 5 minutes prior to use ▪Administer using only the needles provided in the kit
Paliperidone palmitate (Invega Sustenna®)	▪ Schizophrenia ▪ Schizoaffective Disorder	▪Initiation: 234 mg IM followed by 156 mg IM one week later ▪39 mg, 78 mg, 117 mg, 156 mg, or 234 mg IM once monthly	Not needed	▪ Shake the syringe vigorously for at least 10 seconds ▪ Select the appropriate needle -- For deltoid inj, use 1-inch 23G needle for pts < 90 kg or 1½-inch 22G needle for pts ≥ 90 kg -- For gluteal inj, use 1½-inch 22G needle regardless of pt's weight
Olanzapine (Zyprexa Relprevv®)	▪ Schizophrenia	▪150 or 210 mg IM Q-2 weeks ▪300 or 405 mg IM Q-4 weeks	Not needed	▪ Reconstituted suspension may be stored at room temperature and used within 24 hours. Shake vigorously to resuspend prior to use
Risperidone (Risperdal Consta®) **Perseris®**	▪ Schizophrenia ▪ Bipolar I Schizophrenia	12.5 mg, 25 mg, 37.5 mg, and 50 mg IM Q-2 weeks 90 mg or 120 mg once monthly SC injection in the abdomen	Yes, 21 days Loading or supplemental PO dose not recommended	▪ Store dose pack in the refrigerator, protect from light ▪Constitute by coupling the liquid & powder syringes & passing the contents back & forth between the syringes. Incorrectly mixed medication could result in incorrect dosage ▪Administer using the prepackaged syringe & enclosed safety needle