



Long-Acting Injectable Medication Products

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Disclosures

Dr. Waters is a consultant with Janssen Pharmaceuticals. She will discuss all drugs without bias. All financial interests with ineligible companies (as noted) have been mitigated.

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Learning Objectives

- Compare and contrast among different long-acting injectable (LAI) medications currently available for the treatment of schizophrenia, bipolar disorder and substance use disorders including:
 - Dosing
 - Generic and brand names
 - Adverse effects
 - Administration schedule
 - Overlap with oral medications
 - FDA-approved indications

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Long-acting Injectable Antipsychotics



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Currently Available LAI Antipsychotics	
Generic Name	Brand Name
First-generation antipsychotics	
Fluphenazine decanoate	Prolixin Decanoate
Haloperidol decanoate	Haldol Decanoate
Second-generation antipsychotics	
Aripiprazole lauroxil	Aristada Aristada Initio
Aripiprazole monohydrate	Abilify Maintena Abilify Asimtufi
Olanzapine pamoate	Zyprexa Relprevv
Paliperidone palmitate	Invega Sustenna Invega Trinza Invega Hafyera
Risperidone	Risperdal Consta Perseris Rykindo Uzedy

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Establishing Tolerability

- Tolerability to oral formulation should be established prior to administration of LAI antipsychotic (**safety**)
- Best practice to also establish **efficacy** prior to LAI initiation

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Oral Overlap with LAI Antipsychotics

- Some LAI antipsychotics require that patient continue treatment with oral antipsychotic for a specified time
 - LAI may not immediately be at therapeutic level



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Oral Antipsychotic Overlap Requirements			
LAI Antipsychotic		Oral Overlap Required?	Duration of Required Overlap
Generic	Brand		
Fluphenazine decanoate	Prolixin decanoate	Yes	Not definitively established
Haloperidol decanoate	Haldol decanoate	Yes	Not definitively established
Aripiprazole lauroxil	Aristada®	Yes*	21 days*
	Aristada Initio®	Yes	14 days
Aripiprazole monohydrate	Abilify Maintena®	Yes	14 days
	Abilify Asimtufii®	Yes	14 days
Olanzapine pamoate	Zyprexa Relprevv®	No	
Paliperidone palmitate	Invega Sustenna®, Invega Trinza®, Invega Hafyera®	No	
	Risperdal Consta®	Yes	21 days
Risperidone	Perseris®	No	
	Rykindo®	Yes	7 days
	Uzedly™	No	

*Requires oral overlap only if Aristada Initio® is not administered along with Aristada®

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Storage Requirements

- All risperidone-based products require refrigeration:
 - Risperdal Consta
 - Perseris
 - Rykindo
 - Uzedly
- Must be allowed to come to room temperature prior to administration



Risperdal Consta [package insert], Janssen Pharmaceuticals, 2007; Perseris [package insert], Indivior, Inc., 2022; Rykindo [package insert], Shandong Luye Pharmaceutical Co., Ltd., 2023; Uzedly [package insert], Teva Neuroscience, Inc., 2023.

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First-Generation LAI Antipsychotics: Dosing and Clinical Pearls

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FGA LAI Dosing

FGA LAI Dosing (IM)				
Medication	Loading Dose?	Initial Dose	Target Dose	Frequency
Fluphenazine decanoate	No	1.25 x daily oral dose	6.25-50 mg (Max 100 mg)	2-4 weeks
Haloperidol decanoate	Yes	10-20 x daily oral dose *1st injection max 100 mg* For initiation doses > 100 mg must split the dose: 100 mg on day 1 then the remainder any day from day 4-8	10-15 x daily oral dose (May administer >100 mg per injection, max 450 mg)	4 weeks

Fluphenazine decanoate [package insert], APP Pharmaceuticals, LLC, 2012; Haldol decanoate [package insert], Janssen Pharmaceuticals, 2005.

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FGA LAI Clinical Pearls

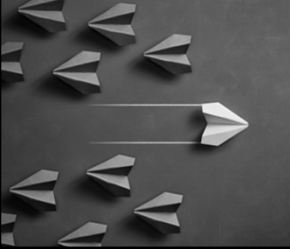
- Both fluphenazine and haloperidol are **high-potency** antipsychotics
 - More likely to experience extrapyramidal symptoms (EPS) including acute dystonic reactions
 - Most patients will continue treatment with an oral anticholinergic (i.e. benztropine) to prevent EPS
- Both medications are intramuscular injections
- Both are in a **sesame seed oil base**
 - May consider Z-track injection technique
 - Oil-based injections may be more painful than water-based

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Second-Generation LAI Antipsychotics: Dosing and Clinical Pearls

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Different Aripiprazole LAI Formulations



- Aripiprazole monohydrate vs. aripiprazole lauroxil
- Activity of aripiprazole monohydrate mostly from parent drug
- Aripiprazole lauroxil = prodrug (N-lauroyloxymethyl aripiprazole)
- **Not interchangeable**

Hard ML, et al. / Clin Psychopharmacol. 2017;37:289-95

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Aripiprazole Monohydrate LAI Dosing

- Dose of LAI not based on oral aripiprazole dose
- Continue oral aripiprazole for 14 days after initiation for both medications

Medication	Dose	Frequency	Dose Adjustments	Administration Method
Abilify Maintena	400 mg	Monthly	300 mg if experiencing ADEs	IM (deltoid or gluteal)
Abilify Asimtufii	960 mg	Q 2 months (56 days)	720 mg if experiencing ADEs	IM (gluteal)

Abilify Maintena [package insert]. Otsuka America Pharmaceutical, Inc.; 2002. Abilify Asimtufii [package insert]. Otsuka Pharmaceutical Co., Ltd; 2023

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Aripiprazole Lauroxil LAI Dosing

Aristada Initio + Aristada		Aristada only	
Day	Dose	Day	Dose
Day 1	30 mg oral aripiprazole + Aristada Initio® 675 mg	Day 1	First dose of Aristada based on oral aripiprazole dose*
Any day from day 1 to day 10	First dose of Aristada based on oral aripiprazole dose*	Day 1 to 21	Continue oral aripiprazole
No overlap with oral aripiprazole			

Aristada [package insert]. Alkermes, Inc.; 2015. Aristada Initio [package insert]. Alkermes, Inc.; 2020

*Dose conversion on next slide

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Aripiprazole Lauroxil LAI Dosing

Oral Aripiprazole Dosing		
10 mg po daily	15 mg po daily	≥ 20 mg po daily
440 mg Aristada IM monthly	662 mg Aristada IM monthly or 882 mg IM q 6 weeks or 1064 mg IM q 2 months	882 mg Aristada IM monthly

Aristada [package insert]. Alkermes, Inc.; 2015. Aristada Initio [package insert]. Alkermes, Inc.; 2020

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Olanzapine Pamoate LAI Dosing & Considerations

- Zyprexa Relprevv can only be administered in a registered healthcare facility with ready access to emergency response services
- **Risk of post-injection delirium/sedation syndrome: risk for severe sedation (including coma) or delirium after each injection**
- Requires direct monitoring for ≥ 3 hours after each dose
- Only available through restricted distribution program
 - REMS: Olanzapine Pamoate Patient Care Program
- Dosed every 2 weeks or every 4 weeks

Zyprexa Relprevv [package insert]. Eli Lilly and Company; 2009

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Audience Question 1

A patient with bipolar disorder has been treated with aripiprazole 25mg po daily for several months. The provider would like to initiate LAI aripiprazole and prefers the medication with the longest dosing frequency so that the patient can receive injections less often. The patient also prefers if they did not have to take oral aripiprazole at all after receiving their injection. Which of the following is true?

- A. Aristada could be administered every 2 months for this patient.
- B. The dosing frequency for Aristada and Abilify Maintena would be the same for this patient.
- C. The patient could receive Aristada every 2 months as long as they also receive Aristada Initio on day 1.
- D. The patient could be treated with Abilify Asimtufii every 2 months without any oral overlap.

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Paliperidone Palmitate LAI Dosing

- Available in 3 formulations:
 - Every 1 month (Invega Sustenna)
 - Every 3 months (Invega Trinza)
 - Every 6 months (Invega Hafyera)
- **All patients must start with Invega Sustenna**
 - If patients receives ≥ 4 monthly injections (with last 2 doses being the same strength) can transition to Invega Trinza or Invega Hafyera

Invega Sustenna [package insert], Janssen Pharmaceuticals, Inc.; 2009; Invega Trinza [package insert], Janssen Pharmaceuticals, 2015, Inc.; Invega Hafyera [package insert], Janssen Pharmaceuticals, Inc.; 2021

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Paliperidone Palmitate LAI Initiation Dosing



Invega Sustenna [package insert], Janssen Pharmaceuticals, Inc.; 2009; Invega Trinza [package insert], Janssen Pharmaceuticals, 2015, Inc.; Invega Hafyera [package insert], Janssen Pharmaceuticals, Inc.; 2021 *Dose conversion on next slide

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Paliperidone Palmitate LAI Initiation Dosing

- Paliperidone = active metabolite of risperidone
- Most patients convert from oral risperidone (instead of oral paliperidone)

Daily Oral Paliperidone Dose (mg)	Daily Oral Risperidone Dose (mg)	Monthly IM Paliperidone Palmitate Dose (mg)
3	1	39
3	2	78
6	3	117
9	4	156
12	6	234

Invega Sustenna [package insert], Janssen Pharmaceuticals, Inc.; 2009; Invega Trinza [package insert], Janssen Pharmaceuticals, 2015, Inc.; Invega Hafyera [package insert], Janssen Pharmaceuticals, Inc.; 2021

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Transitioning to Every 3- or 6-Month LAI Dosing

- Can convert directly from every 1-month formulation to EITHER every 3-month or every 6-month formulations

Every 1-Month (Invega Sustenna) Dose	Every 3-Month (Invega Trinza) Dose	Every 6-Month (Invega Hafyera) Dose
39 mg	N/A	N/A
78 mg	273 mg IM every 3 months	N/A
117 mg	410 mg IM every 3 months	N/A
156 mg	546 mg IM every 3 months	1,092 mg IM every 6 months
234 mg	819 mg IM every 3 months	1,560 mg IM every 6 months

Invega Sustenna [package insert], Janssen Pharmaceuticals, Inc.; 2009; Invega Trinza [package insert], Janssen Pharmaceuticals, 2015, Inc.; Invega Hafyera [package insert], Janssen Pharmaceuticals, Inc.; 2021

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Paliperidone Palmitate LAI Clinical Pearls

- Requires renal dose adjustments for CrCl 50-80 mL/min including for initiation doses
 - Not recommended for patients with CrCl <50 mL/min
- Initiation doses should be administered IM in deltoid muscle
 - Maintenance doses of 1-month formulation: Deltoid or gluteal
 - 3-month formulation: Deltoid or gluteal
 - 6-month formulation: Gluteal

Invega Sustenna [package insert], Janssen Pharmaceuticals, Inc.; 2009; Invega Trinza [package insert], Janssen Pharmaceuticals, 2015; Inc.; Invega Halvera [package insert], Janssen Pharmaceuticals, Inc.; 2021

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Risperidone LAI Dosing

	Risperdal Consta	Rykindo	Perseris	Uzedy
Initial Dose	25 mg	25 mg	90 or 120 mg	50-250 mg*
Maintenance Dose	12.5-50 mg	25-50 mg	90 or 120 mg	50-250 mg*
Frequency	Every 2 weeks	Every 2 weeks	Monthly	Monthly or every 2 months*
Administration Method	IM	IM	SQ	SQ
Administration Site	Deltoid or gluteal	Gluteal	Abdomen	Abdomen, back and outer area of upper arms

Risperdal Consta [package insert], Janssen Pharmaceuticals; 2007; Perseris [package insert], Indivior, Inc.; 2022
Rykindo [package insert], Shandong Luye Pharmaceutical Co., Ltd.; 2023; Uzedy [package insert], Teva Neuroscience, Inc.; 2023

*Dose conversion on next slide

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Uzedy Dose Conversion

Daily Oral Risperidone Dose	Corresponding SQ LAI Risperidone (Uzedy) Dose	Frequency
2 mg	50 mg	Monthly
	100 mg	Every 2 months
3 mg	75 mg	Monthly
	150 mg	Every 2 months
4 mg	100 mg	Monthly
	200 mg	Every 2 months
5 mg	125 mg	Monthly
	250 mg	Every 2 months

Risperdal Consta [package insert], Janssen Pharmaceuticals; 2007; Perseris [package insert], Indivior, Inc.; 2022
Rykindo [package insert], Shandong Luye Pharmaceutical Co., Ltd.; 2023; Uzedy [package insert], Teva Neuroscience, Inc.; 2023

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LAI Risperidone Clinical Pearls

- Some LAI risperidone products do not have equivalent dosing to common oral risperidone daily doses:
 - Perseris may not be good option if patient treated with <3 mg or >4 mg oral risperidone
 - Uzedy does not have equivalent dosing for 6 mg daily of risperidone
- FDA-approved max daily dose of oral risperidone is 6 mg
 - In practice up to 8 mg/day may be used

Risperdal Consta [package insert], Janssen Pharmaceuticals; 2007; Perseris [package insert], Indivior, Inc.; 2022
Rykindo [package insert], Shandong Luye Pharmaceutical Co., Ltd.; 2023; Uzedy [package insert], Teva Neuroscience, Inc.; 2023

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Missed Doses



- All LAI antipsychotics have specific recommendations for how to re-initiate dosing if patient misses dose(s)
- Within the medication-specific timeframe, may be able to simply resume dosing
 - Sometimes have to re-initiate or change dose

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LAI Antipsychotics per FDA-Approved Indication

	Schizophrenia	Schizoaffective Disorder	Bipolar I Disorder
Haldol decanoate	x		
Prolixin decanoate	x		
Aristada	x		
Aristada Initio	x		
Abilify Maintena	x		x
Abilify Asimtufii	x		
Zyprexa Relprevv	x		
Invega Sustenna	x	x	
Invega Trinza	x		
Invega Halvera	x		
Risperdal Consta	x		x
Rykindo	x		
Perseris	x		
Uzedy	x		

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Audience Question 2

- Which of the following patients would be eligible to receive Invega Hafyera?
- A. A patient transitioning from oral risperidone 4 mg daily to an LAI for the first time
 - B. A patient who has been treated with Risperdal Consta 50 mg monthly for several years and prefers an extended dosing frequency
 - C. A patient treated with oral paliperidone who is only accepting of injections into the deltoid muscle
 - D. A patient who has been treated with Invega Sustenna for 6 months and has received 156 mg monthly for the last 3 months

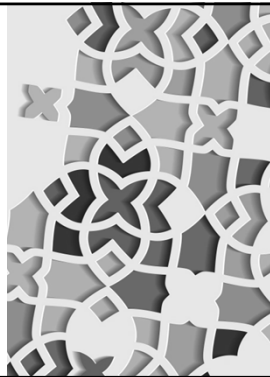
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 - C. A patient treated with oral paliperidone who is only accepting of injections into the deltoid muscle
 - D. **A patient who has been treated with Invega Sustenna for 6 months and has received 156 mg monthly for the last 3 months**

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Long-acting Injectable SUD Medications



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Naltrexone LAI (Vivitrol)

- Approved for alcohol use disorder (AUD) and opioid use disorder (OUD)
- 380 mg IM monthly in gluteal muscle
- **Patients must be opioid-free for 7-10 days prior to administration**
 - Pretreatment with oral naltrexone not required


Vivitrol (package insert). Alkermes, 2022

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Naltrexone LAI (Vivitrol)



Consider recommending naloxone



Requires refrigeration



REMS program due to risk of severe injection site reactions

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Buprenorphine ER LAI Products & Dosing

- Buprenorphine LAI products require induction with SL buprenorphine prior to initiation (if not already established on treatment):
 - Sublocade: ≥ 7 days
 - Brixadi: ≥ 1 dose
- All products are administered SQ
 - Sublocade: Abdomen
 - Brixadi: Buttock, thigh, abdomen, or upper arm

Medication	Dose	
Sublocade	300 mg SQ monthly x 2 months THEN: 100 mg SQ monthly* (may be increased to 300 mg monthly)	
Brixadi: Available in weekly and monthly formulations (not interchangeable, cannot combine)		
Daily dose of SL buprenorphine	Brixadi (weekly)	Brixadi (monthly)
≤ 6 mg	8 mg	x
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

*May be increased to 300 mg monthly if clinically indicated

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Buprenorphine LAI Clinical Pearls

- Consider recommending naloxone
- Caution in patients taking other CNS/respiratory depressants (i.e. benzodiazepines)
- Sublocade: Available through restricted program (SUBLOCADE REMS Program)
 - **Risk of serious harm or death from IV self-administration**
 - Healthcare settings and pharmacies that order and dispense Sublocade must be certified
 - Can only be dispensed directly to healthcare provider for administration (**not to patient**)
 - Pharmacies cannot distribute, transfer, loan, or sell Sublocade
- Brixadi: Anticipated to become available in September 2023
 - Similar REMS program as Sublocade

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LAI Medications for SUDs per FDA-Approved Indication		
	Alcohol Use Disorder	Opioid Use Disorder
Vivitrol	x	x
Sublocade		x
Brixadi		x

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Audience Question 3

A patient with polysubstance use disorder (alcohol, cocaine, opioids) presents to receive LAI naltrexone (Vivitrol). Which of the following is the best course of action?

Medications:

Acamprosate 666 mg po TID
 Gabapentin 300 mg po TID
 Methadone 80 mg po daily
 Sertraline 100 mg po daily

- Administer Vivitrol 380 mg IM today.
- Do not administer Vivitrol today because patient is being treated with methadone.
- Do not administer Vivitrol today because of patient's active cocaine use disorder.
- Do not administer Vivitrol today because patient is on multiple sedating medications.

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Audience Question 3

A patient with polysubstance use disorder (alcohol, cocaine, opioids) presents to receive LAI naltrexone (Vivitrol). Which of the following is the best course of action?

Medications:

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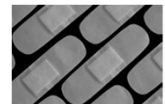
Injection-Related Adverse Effects



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Types of Injection-Site Reactions

- Pain
- Tenderness
- Swelling
- Bleeding
- Infection
- Erythema
- Hematoma (bruising)
- Leakage
- Induration



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Incidence of Injection-Site Reactions: Antipsychotics		
Generic Name	Brand Name	Incidence of Injection-Site Reactions
Fluphenazine decanoate	Prolixin Decanoate	Unknown
Haloperidol decanoate	Haldol Decanoate	<1%
Aripiprazole lauroxil	Aristada Aristada Initio	4-5%
Aripiprazole monohydrate	Abilify Maintena	5-19%
Olanzapine pamoate	Zyprexa Relprevv	2-4%
Paliperidone palmitate	Invega Sustenna	Up to 12%
	Invega Trinza	5-9%
	Invega Hafyera	11-13%
Risperidone	Risperdal Consta	1%
	Perseris	>5%
	Rykindo	1%
	Uzedy	5-21%

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Incidence of Injection-Site Reactions: SUD Medications		
Generic Name	Brand Name	Incidence of Injection-Site Reactions
Naltrexone	Vivitrol	Overall: 65%
		Injection site pain: 13%
Buprenorphine	Sublocade Brixadi	Induration: 30%
		Pruritis: 8%
		Rash: 6%
		16%
		20%

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Management of Injection-Site Reactions

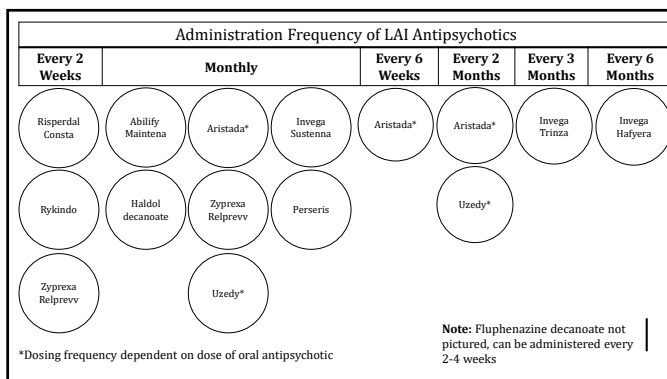
- Recommendations for **pharmacist**:
 - Change injection site with each administration
 - Consider topical anesthetic
- Recommendations for **patient**:
 - Report any reaction that does not resolve in 2 weeks
 - Cold compress
 - OTC analgesic for pain
 - OTC antihistamine for itching

Cole B. Pharmacy Times 2019:1

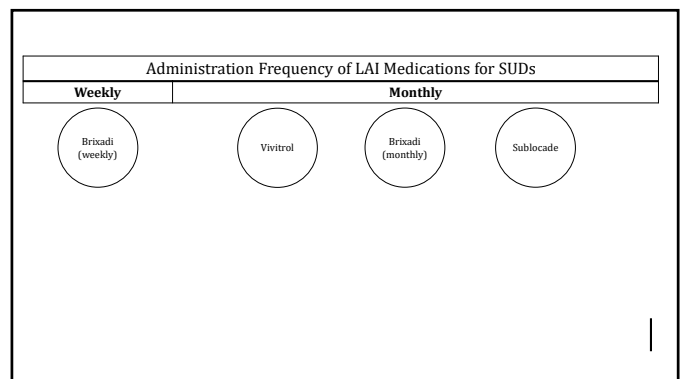
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Summary

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Summary

- Multiple LAI medications are available for the treatment of schizophrenia, bipolar disorder, and substance use disorders
- Administration frequency can range from weekly to every 6 months
- Some LAI medication dosing is dependent on the dose of the oral medication patient was receiving prior to initiation
- Patients may need to continue oral medication for a specified period depending on the medication administered

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Long-Acting Injectable Medication Products

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