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Drug Class Literature Scan: Antipsychotics, Parenteral

Date of Review: October 2023

Date of Last Review: February 2022
Literature Search: 01/01/2022 – 07/21/2023

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- The purpose of this review is to scan recently published evidence for injectable antipsychotic medicines.
- Oral antipsychotics are used to relieve symptoms such as delusions or hallucinations that can occur in people with schizophrenia or bipolar disorder. If a person has a hard time remembering to take the oral forms of these medicines, they can be started on a long-acting injection that can be given anywhere from every 2 weeks to every 6 months (depending on the prescribed medication) by a health care provider.
- Six different antipsychotics (fluphenazine, haloperidol, aripiprazole, olanzapine, paliperidone, and risperidone) are available to be administered as an injection. These medicines can help prevent a relapse or admission to the hospital.
- Side effects reported with antipsychotics include tremors, restlessness, muscle stiffness, dizziness, weight gain, diabetes, or sleepiness. Using the lowest dose that helps symptoms in order to limit the side effects.
- The Oregon Health Plan provides open access to injectable antipsychotic medicines for members with a valid prescription.

Conclusions:

- Since the last Pharmacy and Therapeutics (P & T) Committee review two systematic reviews[1],[2] and one guideline[3] were published. New formulations of long-acting risperidone and aripiprazole injections received Food and Drug Administration (FDA) approval.
- A 2021 systematic review and meta-analysis evaluated comparative evidence for LAI antipsychotics and oral antipsychotics.[2] Long acting injectable antispychotics (LAIs) were associated with a lower risk of hospitalization or relapse than oral antipsychotics in each of 3 study designs (randomized controlled studies [RCTs]: 29 studies, 7,833 patients, relative risk [RR] 0.88, 95% confidence interval [CI] 0.79 to 0.99, p=0.033; cohort studies: 44 studies, 106,136 patients, RR 0.92, 95% CI 0.88 to 0.98, p=0.0044; pre–post studies: 28 studies, 17,876 patients, RR 0.44, 95% CI 0.39 to 0.51, p<0.0001).[2]
- A 2022 CADTH systematic review evaluated evidence for safety and efficacy of second-generation LAI antipsychotic medications versus first-generation LAI antipsychotics or second-generation oral antipsychotics in patients with schizophrenia and/or bipolar disorders.[1] The evidence in this report is low quality because limited statistical information was adequately reported in the included studies.[1] No difference in treatment success or adverse events were identified between paliperidone palmitate and haloperidol decanoate LAI formulations (low quality of evidence).[1] No differences in discontinuation of treatment or hospitalization rates were noted between: risperidone LAI versus haloperidol LAI administered concurrently with fluphenazine LAI; risperidone LAI and any oral second-generation antipsychotics; olanzapine LAI and oral olanzapine; and aripiprazole LAI and oral aripiprazole (low quality of evidence).[1] No differences in adverse events were observed between aripiprazole LAI and oral aripiprazole (low quality of evidence).[1] Hospitalization rates appear

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higher for patients who received haloperidol LAI compared with those who received risperidone LAI or aripiprazole LAI (low quality of evidence; no statistical comparison was reported).[1] Patients on olanzapine LAI had a shorter number of hospital days than those on oral olanzapine (low quality of evidence; no statistical comparison was reported).[1]

- In 2023, the Department of Veterans Affairs and the Department of Defense (VA/DoD) updated their guidance for management of schizophrenia.[3] The VA/DoD now recommends LAI antipsychotics to improve medication adherence in individuals with schizophrenia (weak recommendation; very low quality of evidence).[3] Limitations to the adherence evidence for LAIs include small study sample sizes, imprecision across studies, and risk of bias from lack of blinding.[3] The benefits of LAIs, including greater adherence and lower rates of hospitalization observed over oral medications, may outweigh potential risk of adverse events and the resource training needed with LAIs.[3]
- In January 2023, the FDA approved a new extended release intramuscular (IM) formulation of risperidone (RYKINDO) injection.[4] RYKINDO is indicated for treatment of schizophrenia and as monotherapy or as an adjunctive therapy to lithium or valproate for the maintenance of bipolar I disorder in adults.[4] The recommended dose is 25 mg IM every 2 weeks administered in the gluteal muscle by a healthcare provider.[4]
- The FDA approved a new extended-release IM formulation of aripiprazole (ABILIFY ASIMTUFII) injection in April 2023.[5] This product is indicated for treatment of schizophrenia and as maintenance monotherapy treatment of bipolar I disorder in adults.[5] The recommended dose is 960 mg IM once every 2 months in the gluteal muscle by a healthcare professional.[5]
- In April 2023 the FDA approved a new extended-release subcutaneous (SC) formulation of risperidone (UZEDY) injection.[6] This medication is indicated for treatment of schizophrenia in adults.[6] Dosing ranges from 50 mg to 125 mg SC once a month or 100 mg to 250 mg SC every 2 months administered in the abdomen or upper arm by a healthcare professional.[6]

Recommendations:

- No changes to the PDL are recommended based on the clinical evidence.
- After evaluation of costs in executive session, UZEDY (risperidone) was made PDL preferred.

Summary of Prior Reviews and Current Policy

- The Oregon P&T committee last reviewed evidence for the comparative effectiveness of parenteral antipsychotic products in February 2022.
- In the Oregon Health Plan, antipsychotic medications are exempt from traditional PDL and prior authorization (PA) requirements. However, clinical PA criteria, which address safety concerns or medically inappropriate use, may be implemented. The parenteral antipsychotics included on the Oregon PDL are presented in **Appendix 1.** Injectable formulations of aripiprazole, chlorpromazine, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and trifluoperazine are preferred on the PDL. A summary of LAI antipsychotic medications is presented in **Table 1**.
- During the second quarter of 2023, paliperidone, aripiprazole, risperidone, fluphenazine decanoate, and haloperidol decanoate were the most frequently prescribed injectable agents in this class.
- Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms for schizophrenia, bipolar mania or major depressive disorder (MDD). There is insufficient evidence to determine if new formulations of LAI aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents.

Table 1. Long-Acting Injectable Antipsychotic Medications

Generic Name	Brand Name	Route	Frequency	Need for Initial Oral Supplementation
First-generation Agents				
Fluphenazine decanoate	PROLIXIN	IM	2-4 weeks	Decrease oral dose by half after first injection, then discontinue with second injection
Haloperidol decanoate	HALDOL	IM	4 weeks	Taper and discontinue after 2 to 3 injections
Second-generation Agents				
Aripiprazole monohydrate	ABILIFY MAINTENA	IM	4 weeks	Continue oral dose for 14 days after initial injection
Aripiprazole lauroxil	ARISTADA INITIO	IM	Single initiation dose: not for repeated dosing	Must be administered in conjunction with aripiprazole 30mg oral dose
Aripiprazole lauroxil	ARISTADA	IM	4, 6, or 8 weeks (dose dependent)	Give 21 days of stabilized oral aripiprazole in conjunction with Aristada injection. (Conversion of oral aripiprazole to IM aripiprazole is based on current oral aripiprazole dose.)
Aripiprazole monohydrate	ABILIFY ASTIMTUFII	IM	8 weeks	Establish tolerability with oral aripiprazole prior to initiating extended-release injection. Give with oral aripiprazole 10 to 20 mg per day for 14 consecutive days after initial injection.
Olanzapine pamoate	ZYPREXA RELPREVV	IM	2 or 4 weeks (dose dependent)	Not required
Paliperidone palmitate	INVEGA SUSTENNA	IM	4 weeks	Not required
Paliperidone palmitate	INVEGA TRINZA	IM	12 weeks	Not applicable: change to Trinza after at least 4 maintenance doses of Sustenna
Paliperidone palmitate	INVEGA HAFYERA	IM	24 weeks	Not applicable: establish dose with 4- and 12-week IM preparations prior to conversion to 6-month regimen
Risperidone microspheres	RISPERDAL CONSTA	IM	2 weeks	Continue oral risperidone for 3 weeks after initial injection.
Risperidone	PERSERIS	SC	4 weeks	Establish tolerability with oral risperidone prior to initiating long-acting injection.
Risperidone	UZEDY	SC	4-8 weeks	Establish tolerability with oral risperidone prior to initiating long-acting injection.
Risperidone	RYKINDO	IM	2 weeks	Establish tolerability with oral risperidone prior to initiating long-acting injection. Continue oral risperidone for 7 days after initial injection.
Abbreviations: IM = intramuscular; mg = milligram; SC = subcutaneous				

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Long-Acting Injectable Versus Oral Antipsychotics for Maintenance Treatment of Schizophrenia
A 2021 systematic review and meta-analysis evaluated comparative evidence for LAI antipsychotics and oral antipsychotics.[2] Three study designs were included in the analysis: RCTs, cohort trials, and pre-post studies.[2] The authors identified 137 studies (n=397,319) which met the inclusion criteria (32 RCTs, 65 cohort studies, and 40 pre–post studies).[2] The quality of studies in terms of risk of bias varied across study designs and within each study design from low to high.[2] Long acting injectable antispychotics were associated with a lower risk of hospitalization or relapse than oral antipsychotics in each of the three study designs (RCTs: 29 studies, 7,833 patients, RR 0.88, 95% CI 0.79 to 0.99; p=0.033; cohort studies: 44 studies, 106,136 patients, RR 0.92, 95% CI 0.88 to 0.98, p=0.0044; pre–post studies: 28 studies, 17,876 patients, RR 0.44, 95% CI 0.39 to 0.51, p<0.0001).[2] In all other outcomes related to effectiveness, efficacy, safety, quality of life, and cognitive function, LAIs were more beneficial than oral antipsychotics in 60 (18.3%) of 328 comparisons, not different in 252 (76.8%) comparisons, and less beneficial in 16 (4.9%) comparisons when analyzed by study design.[2] Significant heterogeneity was observed across all 3 study designs.[2] Publication biases were apparent in cohort and pre-post studies.[2]

Canadian Agency for Drugs and Technologies in Health: Clinical Effectiveness of Second-Generation Injectable Antipsychotics
A 2022 CADTH systematic review evaluated evidence for safety and efficacy of second-generation LAI antipsychotic medications versus first-generation LAI antipsychotics or second-generation oral antipsychotics in patients with schizophrenia and/or bipolar disorders.[1] Eight publications met inclusion criteria and were comprised of 7 international systematic reviews (Italy, Mexico, Canada, Australia, Germany, South Korea, United States) and 1 RCT conducted in China.[1] The primary outcomes of interest were clinical effectiveness (e.g., adherence to therapy, quality of life, reduction in symptoms, hospital readmission), time to relapse, and safety (e.g. tolerability, adverse effects, relapse).[1] All of the evidence evaluated in the systematic reviews were conducted in adults; 5 focused on populations with schizophrenia and 2 focused on populations with either schizophrenia or bipolar disorder.[1] Long-acting injectable antipsychotics included in the systematic reviews were aripiprazole, olanzapine, paliperidone, risperidone, haloperidol, and fluphenazine. Oral antipsychotics included in the reviews were olanzapine, quetiapine, risperidone, ziprasidone, and paliperidone. Study durations ranged from 2.5 months to 2.5 years.[1] Limitations to the body of evidence identified by the CADTH authors included: very few comparisons of second-generation LAI antipsychotics with first-generation LAI antipsychotics; a lack of statistical findings to form conclusions; unclear comparability across studies due to use of different outcome measures to determine safety and efficacy; and unclear quality of evidence.[1] The conclusions from the CADTH review are as follows:

- When comparing second-generation paliperidone palmitate LAIs and first-generation haloperidol decanoate LAIs, there was no difference in treatment success or adverse events (low quality of evidence).[1]
- When comparing risperidone LAI versus haloperidol decanoate and fluphenazine decanoate injections given together, there was no difference in whether patients discontinue treatment early (low quality of evidence).[1]
- Hospitalization appeared higher for patients who receive haloperidol decanoate LAI compared to those who received risperidone or aripiprazole LAI (low quality of evidence; no statistical comparison was reported).[1]
- There was no difference in hospitalization rates when comparing risperidone LAI versus haloperidol decanoate and fluphenazine decanoate given together (low quality of evidence; no statistical comparison was reported).[1]
- There was no difference between patients who discontinued treatment early when comparing risperidone LAI to any oral second-generation antipsychotics, olanzapine LAI compared to oral olanzapine, or aripiprazole LAI compared to oral aripiprazole (low quality of evidence). There was no difference in adverse events between patients given aripiprazole LAI compared to those given oral aripiprazole(low quality of evidence).[1]
- Patients had a shorter number of hospital days when given olanzapine LAI compared to those who received oral olanzapine (low quality of evidence).[1]

After review, 8 systematic reviews were excluded due to poor quality,[7-9] wrong study design of included trials (e.g., observational),[10-13] comparator (e.g., no control or placebo-controlled),[14] or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Department of Veterans Affairs and the Department of Defense: Management of First-Episode Psychosis and Schizophrenia

In 2023, the VA/DoD updated their guideline for management of schizophrenia.[3] The clinical practice guideline was developed after a systematic review of recent evidence.[3] One systematic review from 2021 (32 RCTs, n=8,577) was identified since the publication of their 2021 guideline.[2] Findings from this systematic review suggest that patients receiving LAI antipsychotics demonstrate higher levels of adherence rates than patients receiving oral antipsychotics, as indicated by statistically significant differences in the mean Medication Adherence Rating Scale and the proportion of patients with at least 75% days of adherence during the treatment period.[2] Of note, only two RCTs with fewer than 100 patients each contributed data to adherence outcomes.[3] Among important outcomes, LAI antipsychotics were associated with fewer hospitalizations than oral antipsychotics; however, no difference occurred in outcomes, such as symptom reduction, quality of life, functional status, and treatment discontinuation.[3]

A recently added recommendation in the guideline is a weak recommendation to offer long-acting injectable antipsychotics to improve medication adherence in individuals with schizophrenia (quality of evidence = very low.[3] The body of evidence for adherencehad some limitations, including a small sample size, imprecision, and risk of bias because of the lack of blinding of personnel and participants.[3] The benefits of LAIs, including greater adherence and lower rates of hospitalization, slightly outweighed the potential harm of any adverse events, or training needed to administer LAIs.[3]

After review, one guideline was excluded due to poor quality.[15]

New Formulations:

- In January 2023, the FDA approved a new extended-release IM formulation of risperidone (RYKINDO) injection.[4] Extended-release risperidone injection is indicated for treatment of schizophrenia and as monotherapy, or as an adjunctive therapy, to lithium or valproate for the maintenance of bipolar I disorder

in adults.[4] Tolerance to oral risperidone should be established prior to initiating extended-release injections of risperidone.[4] Oral risperidone should be continued for 7 days when initiating RYKINDO.[4] The recommended dose is 25 mg IM every 2 weeks administered in the gluteal muscle by a healthcare provider.[4] Patients not responding to 25 mg may benefit from 37.5 mg or 50 mg.[4] The maximum recommended dose is 50 mg every 2 weeks.[4] In patients with renal or hepatic impairment, a starting dose of 12.5 mg may be appropriate.[4] As with all second generation antipsychotics, the medication has a black boxed warning regarding the risk of increased mortality in elderly patients with dementia-related psychosis.[4] Safety and efficacy of extended-release risperidone were based on clinical trials of risperidone long-acting IM injection (RISPERIDAL CONSTA) and oral risperidone.[4] Safety and effectiveness of RYKINDO have not been established in pediatric patients.[4] RYKINDO as supplied as a refrigerated vial, which contains powder that must be reconstituted with the supplied diluent prior to administration.

- The FDA approved a new extended-release IM formulation of aripiprazole monohydrate (ABILIFY ASIMTUFII) in April 2023.[5] This product is indicated for treatment of schizophrenia and as maintenance monotherapy treatment of bipolar I disorder in adults.[5] For patients naïve to aripiprazole, tolerance should be established with oral aripiprazole for 14 consecutive days prior to initiating treatment with the extended-release injection.[5] The recommended dose is 960 mg IM once every 2 months in the gluteal muscle by a healthcare professional.[5] The dose can be reduced to 720 mg IM in patients with adverse reactions, or poor CYP2D6 metabolizers.[5] As with all second generation antipsychotics, the medication has an FDA black boxed warning regarding the risk of increased mortality in elderly patients with dementia-related psychosis.[5] The safety and efficacy of ABILIFY ASIMTUFII are based on studies of ABILIFY MAINTENA (once monthly IM dosing).[5] Safety and effectiveness of ABILIFY ASIMTUFII have not been established in pediatric patients.[5] ABILIFY ASIMTUFII is supplied as single-dose, prefilled syringe.

- In April 2023, the FDA approved a new extended-release SC formulation of risperidone (UZEDY) injection.[6] This medication is indicated for treatment of schizophrenia in adults.[6] Tolerance to oral risperidone should be established prior to initiating extended-release injections of risperidone.[6] Dosing ranges from 50 mg to 125 mg SC once a month or 100 mg to 250 mg SC every 2 months administered in the abdomen or upper arm by a healthcare professional.[6] Subcutaneous dosing is determined by the established dose of the oral risperidone regimen. In patients with renal or hepatic impairment, the maximum recommended dose is 50 mg SC once monthly.[6] As with all second generation antipsychotics, the medication has a black boxed warning regarding the risk of increased mortality in elderly patients with dementia-related psychosis.[6] The safety and efficacy of UZEDY in adults was based on clinical trials of oral risperidone.[6] Safety and effectiveness of UZEDY have not been established in pediatric patients.[6] UZEDY is supplied as a refrigerated, single-dose, prefilled syringe.

New FDA Safety Alerts: No new FDA safety alerts were issued since the last class review of these medications.

References:

1. Canadian Agency for Drugs and Technologies in Health (CADTH) Clinical Effectiveness Review. Second Generation Injectable Antipsychotics. May 2022. https://www.cadth.ca/clinical-effectiveness-second-generation-injectable-antipsychotics Accessed August 9, 2023.
2. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *The lancet Psychiatry*. 2021;8(5):387-404.

3. VA/DoD Clinical Practice Guideline. (2023). Management of First-Episode Psychosis and Schizophrenia Work Group. Washington, DC: U.S. Government Printing Office. https://www.healthquality.va.gov/guidelines/MH/scz/VADoDCPGSchizophreniaCPG_Final_508.pdf. Accessed August 9, 2023.
4. RYKINDO (risperidone) extended-release subcutaneous injection. Yantai, Shandong Province, China; Shandong Luye Pharmaceutical Co., Ltd. January 2023.
5. ABILIFY ASIMTUFII (aripiprazole) extended-release intramuscular injection. Rockville, MD; Otsuka America Pharmaceutical, Inc. April 2023.
6. UZEDY (risperidone) extended-release subcutaneous injection. Parsippany, NJ; Teva Neuroscience, Inc. April 2023.
7. Okoli CTC, Kappi A, Wang T, Makowski A, Cooley AT. The effect of long-acting injectable antipsychotic medications compared with oral antipsychotic medications among people with schizophrenia: A systematic review and meta-analysis. *Int J Ment Health Nurs.* 2022;31(3):469-535.
8. Schneider-Thoma J, Chalkou K, Dörries C, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *Lancet (London, England).* 2022;399(10327):824-836.
9. Huang MW, Gibson RC, Jayaram MB, Caroff SN. Antipsychotics for schizophrenia spectrum disorders with catatonic symptoms. *Cochrane Database Syst Rev.* 2022;7:CD013100.
10. Baeza I, Fortea A, Ilzarbe D, Sugranyes G. What Role for Long-Acting Injectable Antipsychotics in Managing Schizophrenia Spectrum Disorders in Children and Adolescents? A Systematic Review. *Paediatric drugs.* 2023;25(2):135-149.
11. Lian L, Kim DD, Procyshyn RM, et al. Efficacy of long-acting injectable versus oral antipsychotic drugs in early psychosis: A systematic review and meta-analysis. *Early intervention in psychiatry.* 2022;16(6):589-599.
12. Cristarella T, Castillon G, Nepveu JF, Moride Y. Impact of schizophrenia relapse definition on the comparative effectiveness of oral versus injectable antipsychotics: A systematic review and meta-analysis of observational studies. *Pharmacol Res Perspect.* 2022;10(1):e00915.
13. Benarous X, Cottin G, Lahaye H, et al. Efficacy, Tolerability, and Acceptance of Long-Lasting Antipsychotics in Children and Adolescents: A Systematic Review. *Journal of Child & Adolescent Psychopharmacology.* 2022;32(6):312-327.
14. Wang D, Schneider-Thoma J, Siafis S, et al. Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials. *Schizophr Bull.* 2023.
15. Janas-Kozik M, Dudek D, Heitzman J, et al. Polish Psychiatric Association diagnostic and therapeutic management guidelines for patients with early-onset schizophrenia. *Psychiatria Polska.* 2022;56(4):675-695.
16. Xiao L, Zhao Q, Li AN, et al. Efficacy and safety of aripiprazole once-monthly versus oral aripiprazole in Chinese patients with acute schizophrenia: a multicenter, randomized, double-blind, non-inferiority study. *Psychopharmacology.* 2022;239(1):243-251.
17. Najarian D, Sanga P, Wang S, et al. A Randomized, Double-Blind, Multicenter, Noninferiority Study Comparing Paliperidone Palmitate 6-Month Versus the 3-Month Long-Acting Injectable in Patients With Schizophrenia. *Int J Neuropsychopharmcol.* 2021;25(3):238-251.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
aripiprazole	ABILIFY ASIMTUFII	SUSER SYR	IM	Y
aripiprazole	ABILIFY MAINTENA	SUSER SYR	IM	Y
aripiprazole	ABILIFY MAINTENA	SUSER VIAL	IM	Y
aripiprazole lauroxil	ARISTADA	SUSER SYR	IM	Y
aripiprazole lauroxil, submicr.	ARISTADA INITIO	SUSER SYR	IM	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	AMPUL	IJ	Y
chlorpromazine HCl	THORAZINE	AMPUL	IJ	Y
fluphenazine decanoate	FLUPHENAZINE DECANOATE	VIAL	IJ	Y
fluphenazine HCl	FLUPHENAZINE HCL	VIAL	IJ	Y
haloperidol decanoate	HALDOL DECANOATE 100	AMPUL	IM	Y
haloperidol decanoate	HALDOL DECANOATE 50	AMPUL	IM	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	AMPUL	IM	Y
haloperidol decanoate	HALOPERIDOL DECANOATE 100	AMPUL	IM	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	VIAL	IM	Y
haloperidol lactate	HALOPERIDOL LACTATE	SYRINGE	IM	Y
haloperidol lactate	HALOPERIDOL LACTATE	VIAL	IJ	Y
paliperidone palmitate	INVEGA HAFYERA	SYRINGE	IM	Y
paliperidone palmitate	INVEGA SUSTENNA	SYRINGE	IM	Y
paliperidone palmitate	INVEGA TRINZA	SYRINGE	IM	Y
risperidone	PERSERIS	SUSER SYR	SQ	Y
risperidone microspheres	RISPERDAL CONSTA	VIAL	IM	Y
olanzapine	OLANZAPINE	VIAL	IM	V
olanzapine	ZYPREXA	VIAL	IM	V
olanzapine pamoate	ZYPREXA RELPREVV	VIAL	IM	V
risperidone	UZEDY	SUSER SYR	SQ	V
ziprasidone mesylate	GEODON	VIAL	IM	V
ziprasidone mesylate	ZIPRASIDONE MESYLATE	VIAL	IM	V

Appendix 2: New Comparative Clinical Trials

A total of 86 citations were manually reviewed from the initial literature search. After further review, 84 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Endpoint	Results	Notes/Limitations
Xiao L, et al.[16] DB, MC, NI RCT 12 weeks	1. Aripriprazole 400 mg IM once monthly Vs. 2. Aripiprazole 10-20 mg oral tablet once daily	-Adults aged 18 to 65 yo with an acute psychotic episode from 15 clinical sites across China -PANSS score ≥ 70 points N=436 (218 in each arm)	Change in PANSS and CGI-S scores from baseline to week 10. Prespecified NI margin: lower bound of 95% CI < -7.5	Change in PANSS from baseline to week 10: 1. -33.6 2. -34.8 LSM Difference = -1.2 (95% CI -4.1 to 1.7; NS) NI met due to lower CI of -4.1 Changes in CGI-S score from baseline to week 10 1. -2.2 2. -2.3 LSM Difference = -0.1 (95% CI -0.3 to 0.1; P=0.357)	-Limited to patients of Chinese descent, cannot generalize results to other races/ethnicities -Noninferiority trial design is not as robust as superiority trial design -Short trial duration This study confirmed the non-inferiority of once monthly aripiprazole to oral aripiprazole based on PANSS score in patients experiencing an acute schizophrenia episode
Najarian D, et al.[17] DB, NI, MC RCT 12 months	1. Paliperidone 350 mg or 525 mg IM every 3 months Vs. 2. Paliperidone 700 mg or 1000 mg IM every 6 months	-Patients aged 18 to 70 yo -Diagnosis of schizophrenia ≥ 6 months prior to study enrollment -Stabilized on maintenance IM paliperidone 1 or 3 months -PANSS score < 70 points N=702, randomized 2:1	-Percent of patients who did not relapse (hospitalized for psychiatric reason, change in PANSS* score > 25%, patient demonstrated self-harm) over 12 months Prespecified NI margin: lower bound of 95% CI < 10%	Percent of patients who did not relapse over 12 months: 1. 94.8% 2. 91.9% Difference -2.9% (95% CI -6.8% to 1.1%; NS) NI met due to lower CI of -6.8%	-Noninferiority trial design is not as robust as superiority trial design This study demonstrated the noninferiority of 6-month paliperidone injection at 700 and 1000 mg equivalent doses in patients with schizophrenia, suggesting comparable efficacy with its 3-monthly equivalent formulation for patients who remained relapse free at the end of the 12-month DB phase.

		1. n=224 2. n=478			

Abbreviations: CGI-S = Clinical Global Impressions – Severity; CI = confidence interval; DB = double blind; IM = intramuscular; LSM = least squares mean; MC = multi-center; NI = noninferiority; NS = not statistically significant; OL = open-label; PANSS = Positive and Negative Syndrome Scale*; RCT = randomized clinical trial; YO = years old

*The neuropsychiatric symptoms of schizophrenia were assessed using the 30-item PANSS scale, which provides a total score (sum of the scores for all 30 items) and scores for 3 subscales: the 7-item positive-symptom (P) subscale, the 7-item negative-symptom (N) subscale, and the 16-item general-psychopathology symptom (G) subscale. Each item is rated on a scale from 1 (absent) to 7 (extreme). The PANSS total score ranges from 30 (absent disease)-210 (more severe neuropsychiatric symptoms of schizophrenia).[17]

Appendix 3: Abstracts of Comparative Clinical Trials

Efficacy And Safety Of Aripiprazole Once-Monthly Versus Oral Aripiprazole In Chinese Patients With Acute Schizophrenia: A Multicenter Randomized, Double Blind, Non-Inferiority Study.[16]

OBJECTIVE: The present study aimed to evaluate the efficacy and safety of aripiprazole once-monthly (AOM) compared to oral aripiprazole in treating acute schizophrenia.

METHODS: This randomized, double blind, non-inferiority study recruited patients from 15 trial sites across China from May 2017 to April 2019. Patients with an acute psychotic episode received AOM at 400 mg or oral aripiprazole at 10-20 mg for 12 weeks. The primary and secondary efficacy endpoints were the difference in scores from baseline to week 10, as assessed on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S) scores, respectively.

RESULTS: A total of 436 patients were randomized. Among them, 159/218 (72.9%) and 165/218 (75.7%) in the AOM and oral aripiprazole groups completed 10 weeks of treatment, respectively. The least squares (LS) mean changes from baseline to endpoint (week 10) in PANSS were - 33.6 for the AOM group and - 34.8 in the oral aripiprazole group, respectively, with a difference of - 1.2 (95% CI: - 4.1, 1.7). The non-inferiority margin of AOM to oral aripiprazole was - 4.1, which was above the lower limit of the pre-defined margin. The altered CGI-S score was - 2.2 and - 2.3 in the AOM and oral aripiprazole groups, respectively. The incidence of treatment-emergent adverse events (TEAEs) was similar in both groups. The rate of discontinuation due to TEAEs was 2.3% and 3.2% in the AOM and oral aripiprazole groups, respectively.

CONCLUSIONS: This study confirmed the efficacy and safety of AOM for the treatment of Chinese patients with acute schizophrenia. The non-inferiority of AOM to oral aripiprazole was established, with comparable efficacy and tolerability. These findings suggested that AOM could be used as a treatment option for patients experiencing an acute episode of schizophrenia.

TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT03172871.

A Randomized, Double-Blind, Multicenter, Noninferiority Study Comparing Paliperidone Palmitate 6-Month Versus the 3-Month Long-Acting Injectable in Patients With Schizophrenia[17]

This double blind (DB), randomized, parallel-group study was designed to evaluate efficacy and safety of paliperidone palmitate 6-month (PP6M) formulation relative to paliperidone palmitate 3-month (PP3M) formulation in patients with schizophrenia. Following screening, patients entered an open-label (OL) maintenance phase and received 1 injection cycle of paliperidone palmitate 1-month (PP1M; 100 or 150 mg eq.) or PP3M (350 or 525 mg eq.). Clinically stable patients were randomized (2:1) to receive PP6M (700 or 1000 mg eq., gluteal injections) or PP3M (350 or 525 mg eq.) in a 12-month DB phase; 2 doses of PP6M (corresponding to doses of PP1M and PP3M) were chosen. Overall, 1036 patients were screened, 838 entered the OL phase, and 702 (mean age: 40.8 years) were randomized (PP6M: 478; PP3M: 224); 618 (88.0%) patients completed the DB phase (PP6M: 416 [87.0%]; PP3M: 202 [90.2%]). Relapse rates were PP6M, 7.5% (n = 36) and PP3M, 4.9% (n = 11). The Kaplan-Meier estimate of the difference (95% CI) between treatment groups (PP6M − PP3M) in the percentages of patients who remained relapse free was −2.9% (−6.8%, 1.1%), thus meeting noninferiority criteria (95% CI lower bound is larger than the pre-specified noninferiority margin of −10%). Secondary efficacy endpoints corroborated the primary analysis. Incidences of treatment-emergent adverse events were similar between PP6M (62.1%) and PP3M (58.5%). No new safety concerns emerged. The efficacy of a twice-yearly dosing regimen of PP6M was noninferior to that of PP3M in preventing relapse in patients with schizophrenia adequately treated with PP1M or PP3M.Clinical Trials.gov identifier: NCT03345342

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1996 to July Week 3 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to July 31, 2023

1	exp CHLORPROMAZINE/	1912
2	exp HALOPERIDOL/	6489
3	exp FLUPHENAZINE/	344
4	exp ARIPIPRAZOLE/	2895
5	exp Paliperidone Palmitate/	1038
6	exp RISPERIDONE/	6529
7	ziprasidone.mp.	1883
8	Olanzapine/	6224
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	22186
10	exp Schizophrenia/	75019
11	exp Bipolar Disorder/	32276
12	10 or 11	101649
13	9 and 12	8405
14	limit 13 to (english language and humans and yr="2022 -Current")	240
15	limit 14 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	86

Risperdal® Consta® Quantity Limit

Goal(s):

- To ensure the use of the appropriate billing quantity. This is a quantity initiative, **not a clinical initiative**. The vial contains 2 mL. The dispensing pharmacy must submit the quantity as 1 vial and not 2 mL.

Length of Authorization:

- Date of service or 12 months, depending on criteria

Requires PA:

Risperdal® Consta®

Approval Criteria		
1. Is the quantity being submitted by the pharmacy expressed correctly as # syringes?	**Yes:** Go to #2	**No:** Have pharmacy correct to number of syringes instead of number of mL.
2. Is the amount requested above 2 syringes per 18 days for one of the following reasons? • Medication lost • Medication dose contaminated • Increase in dose or decrease in dose • Medication stolen • Admission to a long-term care facility • Any other reasonable explanation?	**Yes:** Approve for date of service only (use appropriate PA reason)	**No:** Go to #3
3. Is the pharmacy entering the dose correctly and is having to dispense more than 2 syringes per 18 days due to the directions being given on a weekly basis instead of every other week.	**Yes:** Approve for 1 year (use appropriate PA reason)	Note: This medication should NOT be denied for clinical reasons.

P&T Review: *10/23 (DM); 2/22 (DM); 9/18 (DM); 9/17; 9/16; 5/05*
Implementation: *10/13/16; 11/18/04*