Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Antipsychotics, Parenteral

Date of Review: February 2022

Date of Last Review: August 2020
Literature Search: 03/12/20 – 11/30/2021

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

Conclusions:

- Since the last Pharmacy and Committee review, 1 systematic review[1] and 2 guidelines[2,3] have been published.
- The objective of a Cochrane systematic review published in August 2020 was to review the effects of maintaining antipsychotic drugs for people with schizophrenia compared to withdrawing these agents.[1] Any antipsychotic dose or mode of administration (oral or by injection) was included in the search strategy. When all eligible studies were combined, antipsychotic drugs were more effective than placebo at preventing relapse (drug 22% versus placebo 58%, 71 randomized controlled trials [RCTs], n=8666, risk ratio [RR] 0.35, 95% confidence interval [CI] 0.30 to 0.40, number needed to obtain beneficial outcome [NNTB] 3).[1] Antipsychotic drugs were associated with more participants experiencing movement disorders (drug 14% versus placebo 8%, 29 RCTs, n = 5276, RR 1.52, 95% CI 1.25 to 1.85, number needed to treat for an additional harmful outcome [NNTH] 20), sedation (drug 8% versus placebo 5%, 18 RCTs, n=4078, RR 1.52, 95% CI 1.24 to 1.86, NNTH 50), and weight gain (drug 9% versus placebo 6%, 19 RCTs, n=4767, RR 1.69, 95% CI 1.21 to 2.35, NNTH 25).[1]
- In November 2021, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a review of extended-release (ER) injectable risperidone (PERSERIS).[2] The primary outcome was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score after 8 weeks of treatment.[4] A 20% improvement in the PANSS total score is considered a clinical meaningful response to treatment in schizophrenia patients.[5] The PANSS total score change for participants receiving ER risperidone 90 mg, ER risperidone 120 mg, and placebo was reported as a least squares mean [LSM] of −15.37, −16.46 , and −9.22 respectively.[2] Compared with placebo, both ER risperidone doses demonstrated statistically significant improvements in the PANSS score (ER risperidone 90 mg versus placebo: least squares mean difference [LSMD] of −6.15, 95% CI, −9.98 to −2.31; P=0.0004 and ER risperidone 120 mg versus placebo: LSMD −7.24, 95% CI, −11.05 to −3.43; P<0.0001).[2] However, a 20% improvement in PANSS score was not achieved for either ER risperidone dose.[2] The proportion of the patients who experienced at least 1 treatment-emergent adverse event (TEAE) was reportedly higher for the ER risperidone 120 mg group (77.8%) compared with the ER risperidone 90 mg (70.4%) and placebo groups (68.6%).[2]
- The American Psychiatric Association (APA) updated guidance for the treatment of patients of schizophrenia in 2021.[3] The APA recommends patients receive treatment with a long-acting injectable (LAI) antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence (Strong Recommendation, Moderate-Quality Evidence).[3] Dosing recommendations for LAI antipsychotics included in the APA 2021 guidance are presented in **Table 1**.

Author: Deanna Moretz, PharmD, BCPS

Recommendations:

- No changes to the Preferred Drug List (PDL) are recommended based on clinical information.
- After review of costs in executive session paliperidone palmitate (Invega Hafyera™) was made preferred on the PDL.

Summary of Prior Reviews and Current Policy

Evidence for the comparative effectiveness of first-generation antipsychotics, second-generation antipsychotics, and parenteral antipsychotic products was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in August 2020. The efficacy and safety of lumateperone, an oral second-generation antipsychotic which received Food and Drug Administration (FDA) approval in 2019 for treatment of adults with schizophrenia, was also reviewed at this meeting.

In the Oregon Health Plan, antipsychotic medications are exempt from traditional preferred drug list (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 Preferred Drug List. During the second quarter of 2021, the majority of antipsychotic use in the Oregon Medicaid population was for oral second generation antipsychotics including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 5% of antipsychotic medication claims were for parenteral formulations. Paliperidone, aripiprazole, and haloperidol decanoate are 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) and that 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.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, 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 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 Food and Drug Administration (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:

Cochrane Collaborative

The objective of a Cochrane systematic review published in August 2020 was to review the effects of maintaining antipsychotic drug therapy for people with schizophrenia compared to withdrawing these agents.[1] This was an update of a previous Cochrane review published in 2012. Literature was searched through September 2019. Any antipsychotic dose or mode of administration (oral or by injection) was included in the search strategy. The primary outcome of interest was relapse at 1 year as defined by the original studies or by a deterioration in mental state requiring further treatment.[1] Overall, 75 studies involving 9,145

participants met inclusion criteria.[1] Of the included studies, 17 had a duration up to three months.[1] Twenty-six studies lasted up to 6 months and 25 studies up to 12 months.[1] Seven studies lasted more than 12 months.[1] The longest study had a duration of 3 years.[1] Twenty-nine studies were conducted in hospitals (at least at the start of the trial) and 34 studies in outpatients.[1] Seven studies included both inpatients and outpatients.[1] Seventy-three studies compared maintenance treatment with antipsychotic drugs and inactive placebo; two open-label RCTs compared antipsychotic drugs with no treatment.[1] No data on active placebo as a comparator were available.[1] Relapse definition varied between studies. The main relapse criteria in 25 studies was clinical judgement,[1] while 24 studies used various rating-scale-based definitions, 16 studies defined relapse as need of medication, 4 studies defined relapse as admission to hospital, 2 studies described relapse as dropout due to worsening of symptoms, and 4 studies did not indicate the criteria for relapse.[1] Most studies had either a neutral sponsor or sponsorship was not indicated.[1] Twenty-five studies were industry sponsored.[1] In many studies the methods of randomization, allocation and blinding were poorly reported.[1] Most trials had an unclear risk of bias.[1]

When all eligible studies were combined, antipsychotic drugs were more effective than placebo at preventing relapse (drug 22% versus placebo 58%, 71 RCTs, n=8666, RR 0.35, 95% CI 0.30 to 0.40, NNTB 3, 95% CI 2 to 3).[1] The outcomes were analyzed for different lengths of follow-up: up to 3 months, 4 to 6 months, 7 to 12 months, and more than one year. Antipsychotic medication was more effective than placebo in preventing relapse in studies lasting up to 3 months (percentage of participants who relapsed despite receiving antipsychotic medication was 12% compared with 35% of participants who received placebo and relapsed, 44 RCTs, n=6362, RR 0.34, 95% CI 0.28 to 0.40, NNTB 4, 95% CI 3 to 5).[1] These results were also seen in studies lasting 4 to 6 months (drug 18% versus placebo 49%, 49 RCTs, n=7599, RR 0.36, 95% CI 0.31 to 0.42, NNTB 3, 95% CI 3 to 4).[1] High certainty evidence was provided in studies lasting 7 to 12 months (primary outcome: drug 24% versus placebo 61%, 30 RCTs, n=4249, RR 0.38, 95% CI 0.32 to 0.45, NNTB 3) and more than 12 months (drug 31% versus placebo 68%, 10 RCTs, n=1786, RR 0.46, 95% CI 0.33 to 0.64, NNTB 3).[1]

Antipsychotic drug use (as a group and irrespective of duration) was associated with more participants experiencing movement disorders (e.g. at least one movement disorder: drug 14% versus placebo 8%, 29 RCTs, n=5276, RR 1.52, 95% CI 1.25 to 1.85, NNTH 20), sedation (drug 8% versus placebo 5%, 18 RCTs, n=4078, RR 1.52, 95% CI 1.24 to 1.86, NNTH 50), and weight gain (drug 9% versus placebo 6%, 19 RCTs, n=4767, RR 1.69, 95% CI 1.21 to 2.35, NNTH 25).[1] For people with schizophrenia, the evidence suggests that maintenance on antipsychotic drugs prevents relapse to a much greater extent than placebo for approximately up to two years of follow-up.[1] This effect must be weighed against the adverse effects of antipsychotic drugs.[1]

After review, 2 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[6,7]

New Guidelines:

High Quality Guidelines:

Canadian Agency for Drugs and Technologies in Health

In November 2021 CADTH published a review of ER injectable risperidone (PERSERIS).[2] Extended-release risperidone subcutaneous (SC) injection was approved by Health Canada in November 2020[2] and by the FDA in July 2018.[8] It is indicated for the treatment of schizophrenia in adults.[8] The recommended dose is 90 mg or 120 mg once monthly by SC injection.[8] Extended-release subcutaneous risperidone does not require a loading dose or supplementation with oral risperidone.[8] Extended-release risperidone 90 mg injection corresponds to 3 mg per day oral risperidone, and ER risperidone 120 mg injection corresponds to 4 mg per day oral risperidone.[8]

One phase 3, randomized, double-blind, placebo-controlled study that was performed at 33 sites in the United States was included in the summary of the CADTH clinical evidence.[4] The objective of the RCT was to evaluate the efficacy and safety of ER risperidone compared with placebo in patients (n=354) aged 18 to 55 years with moderate-to-severe schizophrenia in an acute exacerbation phase.[4] Participants could be either receiving treatment or not receiving treatment for schizophrenia. At the first visit, all participants received 0.25mg oral risperidone for 2 days to assess medication tolerability. If they were receiving antipsychotic medication, they were admitted into an inpatient setting and tapered off their current oral antipsychotic medication over 3 to 8 days. Patients were randomized to 1 of 3 treatment groups: ER risperidone 90 mg SC, ER risperidone 120 mg SC, or placebo injection SC for 8 weeks.[4] The primary outcome was the change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at end-of-treatment. The secondary outcome was change from baseline to end of treatment on the Clinical Global Impression–Severity of Illness (CGI-S). [2] The majority of patients included in the study were Black (> 70%) and male (> 73.5%).[2] The mean age ranged from 40.5 to 42.4 years across the 3 groups.[2]

The PANSS total score change from baseline for participants receiving ER risperidone 90 mg, ER risperidone 120 mg, and placebo was reported as a least squares mean [LSM] of −19.86, −23.61, and −13.37 respectively.[8] A 20% improvement in the PANSS total score is considered a clinical meaningful response to treatment in schizophrenia patients.[5] Compared with placebo, both ER risperidone doses demonstrated statistically significant improvements in PANSS score from baseline (ER risperidone 90 mg vs. placebo: LSMD −6.15, 95% CI, −9.98 to −2.13; P=0.0004 and ER risperidone 120 mg vs placebo: LSMD −7.24, 95% CI, −11.045 to −3.43; P<0.0001).[4] It is uncertain whether the difference between the ER risperidone treatment groups and placebo group was clinically meaningful, as a 20% improvement in PANSS score was not achieved.[8]

In terms of change from baseline in CGI-S score, all 3 groups demonstrated a change at Day 57 (LSM of −0.87, −0.91, and −0.52 in the ER risperidone 90 mg and 120 mg groups and placebo group, respectively).[2] Compared with placebo, both ER risperidone doses demonstrated a statistically significant improvement in CGI-S score (LSMD −0.35, 95% CI, −0.56 to −0.14; P = 0.0002 for risperidone ER 90 mg versus placebo and LSMD −0.40, 95% CI, −0.60 to −0.19; P < 0.0001 for risperidone ER 120 mg versus placebo).[4] However, neither the change from baseline for either ER risperidone treatment group, nor the treatment group difference between the ER risperidone groups and placebo, met the minimal important difference (i.e., a reduction of 1 point in the CGI-S).[2] Therefore, the clinical significance of the observed findings in CGI-S score changes is unclear.[2]

The proportion of the patients who experienced at least 1 TEAE was reportedly higher for the ER risperidone 120 mg group (77.8%) compared with the ER risperidone 90 mg (70.4%) and placebo groups (68.6%).[2] Overall, the most frequently reported TEAEs that occurred at higher rates in the ER risperidone groups compared with the placebo group were weight gain (13%, 12.8%, and 3.4% in the ER risperidone 90 mg and 120 mg groups and the placebo group, respectively) and somnolence (5.2%, 4.3%, and 0% in the ER risperidone 90 mg and 120 mg groups and placebo group, respectively).[2] There were no deaths reported during the treatment periods.[2] The incidence of serious TEAEs was infrequent (0%, 0.9%, and 0.8% in the ER risperidone 90 mg and 120 mg groups and the placebo group, respectively).[2] The proportion of patients who withdrew due to adverse events (AEs) was reportedly low (0%, 1.7%, and 2.5% in the ER risperidone 90 mg and 120 mg groups and placebo group, respectively).[2] Regarding the AEs of special interest, more patients (13%) in the ER risperidone groups experienced weight gain compared with patients who received placebo (3.4%), which was an expected AE that has been reported in all other atypical antipsychotic drugs.[2]

The 8-week duration of the double-blind randomized controlled trial was considered short to assess the long-term maintenance effect of treatment.[2] There was no direct or indirect treatment comparison evidence to compare ER risperidone with oral risperidone or risperidone LAI (IM every 2 weeks) or other relevant atypical antipsychotic LAIs currently marketed in Canada.[2] Based on the summary of clinical evidence, ER risperidone 90 mg and 120 mg (SC once monthly) showed statistically significant improvements in schizophrenia symptoms compared with placebo after 8 weeks, as measured by PANSS total scores and CGI-S scores; however, given that improvements in these outcomes were also observed in the placebo group, the clinical importance of these results is uncertain.[2] The

safety of the once-monthly formulation appears to be consistent with the safety profile of risperidone (both oral and LAI every 2 weeks).[2] Key evidence gaps include the short duration of the trial; ER risperidone is intended to be used as a chronic treatment and longer trials comparing it with the existing oral risperidone or LAI atypical antipsychotic drugs available in Canada for the maintenance treatment of schizophrenia are needed to adequately assess the long-term outcomes, including mortality, relapse, remission, and hospitalization.[2]

The CADTH recommendations state adult patients with well-diagnosed schizophrenia or schizoaffective disorder who have responded to oral risperidone are candidates for ER risperidone SC injection.[2] Geriatric and pediatric patients are not good candidates for risperidone, given the lack of data on these groups and the risk of stroke and increased mortality in older adults.[2] In addition, patients with appropriately diagnosed treatment-resistant illness are unlikely to benefit.[2] Risperidone ER has not undergone adequate study in pregnant patients to determine whether it is safe, especially in the first trimester of pregnancy.[2] The benefits may outweigh the risks of ER risperidone ER for certain patients, and close monitoring would be necessary if it is prescribed to a pregnant patient.[2]

American Psychiatric Association

The APA published updated guidance for the treatment of patients of schizophrenia in 2021.[3] Since publication of the last APA practice guideline in 2004 and guideline watch on schizophrenia in 2009, there have been many studies on new pharmacological and nonpharmacological treatments for schizophrenia.[3] The updated guidance was based on an AHRQ systematic review completed in 2017.[9] The APA recommends patients receive treatment with a LAI antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence (Strong Recommendation, Moderate-Quality Evidence).[3] Dosing recommendations for LAI antipsychotics included in the APA 2021 guidance are presented in **Table 1**.

Long acting injectable formulations of antipsychotic medications can provide a number of benefits for patients, families, and clinicians, yet they are often underutilized.[3] Racial differences also exist in the proportion of individuals who are treated with LAI antipsychotic medications, with greater use of these formulations in Black patients than in White patients.[3] Presumably due to improved adherence, advantages of LAI antipsychotics include the potential for a decreased risk of mortality, reduced risk of hospitalization, and decreased rates of treatment discontinuation.[3] Other benefits for patients include a subjective sense of better symptom control, greater convenience as a result of needing to take fewer medications daily, and reduced conflict with family members or other persons of support related to medication-related reminders.[3] Although some patients may not wish to experience the discomfort associated with receiving injections of medications, this is not a major barrier for most patients.[3] In addition, discomfort can often be minimized by using second generation LAIs rather than first generation LAIs, which have sesame oil based vehicles, or by using an LAI with a small injection volume or lower administration frequency.[3]

Table 1. Long-acting injectable antipsychotic medications[3]

Generic Name	Brand Name	Maintenance Dose	Frequency	Need for Initial Oral Supplementation
First-generation Agents				
Fluphenazine	PROLIXIN DECANOATE	12.5 mg to 50 mg IM	Every 2-4 weeks	Decrease oral dose by half after first injection, then discontinue with second injection
Haloperidol	HALDOL DECANOATE	50 mg to 450 mg IM	Every 4 weeks	Taper and discontinue after 2 to 3 injections
Second-generation Agents				
Aripiprazole monohydrate	ABILIFY MAINTENA	200 mg to 400 mg IM	Every 4 weeks	Continue oral dose for 14 days after initial injection

Aripiprazole lauroxil	ARISTADA INITIO	675 mg IM	Single initiation dose: not for repeated dosing	Must be administered in conjunction with aripiprazole 30mg oral dose
Aripiprazole lauroxil	ARISTADA	441 mg to 1,064 mg IM	• 441, 662, or 882 mg every 4 weeks • 882 mg every 6 weeks • 1,064 mg every 8 weeks	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.)
Olanzapine	ZYPREXA RELPREVV	150 mg to 405 mg	• 300 mg every 2 weeks • 405 mg every 4 weeks	Not required
Paliperidone palmitate	INVEGA SUSTENNA	78 mg to 234 mg IM	Every 4 weeks	Not required
Paliperidone palmitate	INVEGA TRINZA	273 mg to 819 mg	Every 12 weeks	Not applicable: change to Trinza after at least 4 maintenance doses of Sustenna
Risperidone	RISPERDAL CONSTA	25 mg to 50 mg IM	Every 2 weeks	Continue oral risperidone for 3 weeks
Risperidone	PERSERIS	90 mg to 120 mg SC	Every 4 weeks	Not required
Abbreviations: IM = intramuscular; mg = milligram; SC = subcutaneous				

After review, no guidelines were excluded due to poor quality.

New Formulations:
Paliperidone palmitate (INVEGA HAFYERA) received FDA approval August 2021. This new formulation of extended-release paliperidone intramuscular injection is administered by a healthcare professional via gluteal injection every 6 months.[10] The dose of INVEGA HAFYERA ranges from 1,092 mg to 1,560 mg depending on the prior maintenance dose of INVEGA SUSTENNA (156 mg or 234 mg) or INVEGA TRINZA (546 or 819 mg).[10] Switching to INVEGA HAFYERA from other doses of INVEGA SUSTENNA (39 mg, 78 mg, and 117 mg) or INVEGA TRINZA (273 mg and 410 mg) has not been studied.[10] INVEGA HAFYERA is indicated for the treatment of schizophrenia in adults after they have been adequately treated with either:

- once-a-month paliperidone palmitate extended-release injectable suspension (INVEGA SUSTENNA) for at least 4 months or
- every-three-month paliperidone palmitate extended-release injectable suspension (INVEGA TRINZA) for at least one 3 month-cycle.[10]

The safety and efficacy of INVEGA HAFYERA were evaluated in a non-inferiority, double-blind RCT which compared INVEGA HAFYERA administered every 6 months with INVEGA TRINZA administered every 3 months over a 12 month period.[10] Patients in the INVEGA HAFYERA arm received placebo injections at every other 3 month visit to maintain blinding. All participants with schizophrenia had previously been stably treated for at least 4 months with INVEGA SUSTENNA or at least one 3-month injection cycle with INVEGA TRINZA.[10] The primary efficacy variable was time to first relapse. Relapse was pre-defined as emergence of one or more of the following: psychiatric hospitalization, ≥25% increase (if the baseline score was >40) or a 10-point increase (if the baseline score was ≤40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation: a score of ≥5 (if the maximum baseline score was ≤3) or ≥6 (if the maximum baseline score was 4) on two consecutive assessments of the specific PANSS items.[10] A relapse event was experienced by 7.5%

and 4.9% of patients in the INVEGA HAFYERA and INVEGA TRINZA treatment groups, respectively, with the Kaplan-Meier estimated difference between INVEGA HAFYERA and INVEGA TRINZA of 2.9% (95% CI -1.1 to 6.8).[10] The upper bound of the 95% CI (6.8%) was less than 10%, the prespecified non-inferiority margin.[10] The study demonstrated non-inferiority of INVEGA HAFYERA to INVEGA TRINZA. An evaluation of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.[10]

The injection volume of INVEGA HAFYERA ranges from 1.5 mL to 5 mL and must be administered as a single intramuscular injection. Induration, redness and swelling at the injection site were observed in 13% of participants in the INVEGA HAFYERA group and 9% of participants in the INVEGA TRINZA group.[10] Investigator evaluation of injection site tenderness was higher for subjects in the INVEGA HAFYERA group versus the INVEGA TRINZA group (31% vs. 19%).[10] The most commonly observed adverse reactions observed with INVEGA HAFYERA administration included upper respiratory infection, injection site reaction, increased weight, headache and parkinsonism.[10]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Clozapine	**CLOZARIL**	**4/2020**	**Warnings and Precautions**	CLOZARIL has potent anticholinergic effects. Treatment with CLOZARIL can result in central nervous system and peripheral anticholinergic toxicity, especially at higher dosages, or in overdose situations. Use with caution in patients with a current diagnosis or prior history of constipation, urinary retention, clinically significant prostatic hypertrophy, or other conditions in which anticholinergic effects can lead to significant adverse reactions. When possible, avoid concomitant use with other anticholinergic medications because the risk for anticholinergic toxicity or severe gastrointestinal adverse reactions is increased.[11] Severe gastrointestinal adverse reactions have occurred with the use of CLOZARIL, primarily due to its potent anticholinergic effects and resulting gastrointestinal hypomotility. In post marketing experience, reported effects range from constipation to paralytic ileus. Increased frequency of constipation and delayed diagnosis and treatment increased the risk of severe complications of gastrointestinal hypomotility, resulting in intestinal obstruction, fecal impaction, megacolon and intestinal ischemia or infarction. These reactions have resulted in

				hospitalization, surgery, and death. The risk of severe adverse reactions is further increased with anticholinergic medications (and other medications that decrease gastrointestinal peristalsis); therefore, concomitant use should be avoided when possible.[11]
			Drug Interactions	Concomitant treatment with clozapine and other drugs with anticholinergic activity (e.g., benztropine, cyclobenzaprine, diphenhydramine) can increase the risk for anticholinergic toxicity and severe gastrointestinal adverse reactions related to hypomotility. Avoid concomitant use of CLOZARIL with anticholinergic drugs when possible.[11]
			Adverse Reactions	Restless leg syndrome, myocarditis, and polyserositis added to observed adverse effects in post marketing experiences.[11]

References:

1. Ceraso A, Lin JJ, Schneider-Thoma J, et al. Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev.* 2020(8).
2. Canadian Agency for Drugs and Technologies in Health (CADTH). Risperidone for Extended-Release Injectable Suspension (Perseris). https://www.cadth.ca/sites/default/files/DRR/2021/SR0671-Perseris-Combine.pdf November 2021. Accessed December 6, 2021.
3. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. 3rd ed. Washington (DC): American Psychiatric Association;2021: https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841 Accessed December 6, 2021.
4. Nasser AF, Henderson DC, Fava M, et al. Efficacy, Safety, and Tolerability of RBP-7000 Once-Monthly Risperidone for the Treatment of Acute Schizophrenia: An 8-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Study. *J Clin Psychopharmacol.* 2016;36(2):130-140.
5. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261-276.
6. DelBello MP, Kadakia A, Heller V, et al. Systematic Review and Network Meta-analysis: Efficacy and Safety of Second-Generation Antipsychotics in Youths With Bipolar Depression. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2021.
7. Finucane AM, Jones L, Leurent B, et al. Drug therapy for delirium in terminally ill adults. *Cochrane Database Syst Rev.* 2020;1(1):Cd004770.
8. Risperidone extended-release subcutaneous injection (PERSERIS) Prescribing Information. North Chesterfield, VA; Indivior, Inc. December 2019.
9. McDonagh MS DT, Selph S, et al. Treatments for Schizophrenia in Adults: A Systematic Review. Comparative Effectiveness Review No. 198. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 17(18)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality; October 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
10. Paliperidone palmitate extended-release injectable suspension (INVEGA HAFYERA) Prescribing Information. Titusville, NJ; Janssen Pharmaceuticals, Inc. August 2021.
11. Clozapine tablets (CLOZARIL) Prescribing Information. Rosemont, PA; HLS Therapeutics (USA), Inc. February 2021.

Appendix 1: Current Preferred Drug List

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

Appendix 2: New Comparative Clinical Trials

A total of 5 citations were manually reviewed from the initial literature search. After further review, all 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).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2021 & Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 29, 2021

1 exp CHLORPROMAZINE/	1826
2 exp HALOPERIDOL/	6299
3 exp FLUPHENAZINE/	326
4 exp ARIPIPRAZOLE/	2608
5 exp Paliperidone Palmitate/	923
6 exp RISPERIDONE/	6249
7 olanzapine	5865
8 ziprasidone.mp	1836
9 Schizophrenia/th [Therapy]	6471
10 Bipolar Disorder/th [Therapy]	3301
11 9 or 10	9396
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	21064
13 11 and 12	143
14 limit 13 to humans and english language	126
15 limit 14 to (clinical trial, phase iii or comparative study, or equivalence trial, or meta-analysis or multicenter study or practice guideline or randomized controlled trial)	33
16 limit 15 to years 2020-2021	5

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