Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

risperidone (Okedi)

(Bausch Health, Canada Inc.)

Indication: For the treatment of schizophrenia in adults.

March 31, 2025

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0879-000

Generic Drug Name (Brand Name): Risperidone ISM

Indication: Schizophrenia

Name of Clinician Group: The Canadian Consortium for Early Intervention in Psychosis

Author of Submission: Dr. Pierre Chue.

1. About Your Clinician Group

The Canadian Consortium for Early Intervention in Psychosis (https://www.epicanada.org) is a national and bilingual not-for-profit organization of clinicians and researchers who are associated with early psychosis programs. With 55 members nation-wide, the CCEIP represents 22 early phase psychosis (EPP) programs and is a national leader in EPP service delivery, research, and education.

VISION: Towards a healthy future for Canadians in the early phase of psychosis.
MISSION: To enhance optimum care for Canadians in the early phase of psychosis through improved service models, the generation and translation of knowledge, and engagement and partnership with multiple stakeholders.

CCEIP's overall objectives include:

- Effective advocacy for development, implementation, and improvement of early intervention services
- Clinical research across the spectrum of biological, psychological and social determinants of illness and interventions, including studies of service delivery models to effect evidence-based care and policy
- Training across programs for clinicians, researchers, and trainees from all disciplines
- Development of standards for service delivery
- Engagement, partnership, and support of stakeholders in the early psychosis intervention community
- Promotion of equity, diversity and inclusion in our leadership, membership, and activities

2. Information Gathering

- Literature review specific to Risperidone ISM.
- Data concerning the use of long-acting antipsychotic injections (LAIs) in schizophrenia and first five years of illness (early phase of psychosis).
- Comparison of risperidone long-acting injection formulations (Consta, Perseris, Uzedy)
- Clinical experience: Frontline multidisciplinary Canadian and international in hospital and community, and specialized programs – early psychosis, assertive community treatment, intensive case management, complex psychosis, community treatment orders, forensic, neuropsychiatric and geriatric.
- Conference presentation (Chue P, Eighth Schizophrenia International Conference. Abu Dhabi 2025).

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3. Current Treatments and Treatment Goals

Schizophrenia is a complex, heterogeneous, disabling and for many, a progressively deteriorating psychiatric disorder, that impairs multiple domains of cognitive, perceptual, emotional, and behavioral functioning. Typically, life-long treatment is required but non-adherence rates for oral antipsychotics are in the 60- 70% range, particularly when partial adherence, defined as “not taking the medication as prescribed” (self-adjusted changes in dose, timing, duration, etc.,) is considered (Chue P, Eighth Schizophrenia International Conference. Abu Dhabi 2025). It should be noted that the most common symptom in acute schizophrenia is “lack of insight”, which is arguably the primary factor the drives partial and non-adherence.

LAI formulations were developed in the 1960s from the 1st generation antipsychotics, ”depots”, to address this issue. These formulations incorporated a pro drug dissolved in a viscous vegetable oil which following IM

(gluteal only) administration allowing for slow release over the ensuing two to four weeks. However, the oil-based injections were associated with injection site complications such as induration and required a specific injection technique, “Z-tracking”.

The atypical antipsychotics were also developed as long-acting formulations beginning with Risperdal Consta, Invega Sustenna, Invega Trinza, Abilify Maintena, and most recently Abilify Asimtufii. These newer medications incorporate the advantages of atypicality together with aqueous-based vehicles. However, all of these formulations because of their complexity required some type of titration or loading protocol to ensure the achievement of therapeutic levels as quickly as possible. Early attainment of therapeutic levels is correlated with more positive outcomes and better persistence with treatment. These titration or loading protocols range from simultaneous or spaced double injections to oral supplementation to a combination of the two.

Risperidone ISM is a long-acting formulation of risperidone administered into either the deltoid or gluteal muscle. Unlike Risperdal Consta, it does not require refrigeration, a complex mixing and administration process or oral loading, and has a duration of action of 4 weeks. Further, unlike any of the other atypical LAIs as listed above it does not require any specific titration or loading protocol as the formulation provides therapeutic levels within several hours of injection.

LAIs by virtue of parental administration address partial and non-adherence. They have been shown particularly in mirror image studies to reduce relapse and rehospitalization and more importantly reduce all -cause mortality in schizophrenia (Correll CU. World Psychiatry. 2022 ;21(2):248-271). It has also been shown that atypical antipsychotics may also reduce the neurodegeneration observed in the first five years of illness or critical period (Chue P, Eighth Schizophrenia International Conference. 2025).

To improve functional outcome aligned to patient goals it is ideal to have a sustained remission of illness. Early intervention during the critical period) can help achieve the following desired outcomes:

- Improve the course of psychosis and lead to a period of stability
- Return to pre-illness social and occupational levels of functioning
- Result in a better outcome compared with intervention after the critical period
- Decrease risk of suicide

These goals are best achieved with a specialized, multidisciplinary, evidence-based pharmacologic and non-pharmacologic approach.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There are many obstacles to improving outcomes, which include but are not limited to:

- Delay in obtaining adequate treatment (duration of untreated psychosis)
- Delay in treatment response (inadequate dosing, titration)
- Partial and non-adherence to treatment (use of oral medications)
- Inadequate persistence with treatment (discontinuing before an adequate trial)
- Remission not being achieved or sustained (inadequate dosing, titration)
- Poor treatment of comorbidities including substance use

The limitations of current treatments result in poor outcomes and unacceptable mortality in patients with schizophrenia. Access to and reimbursement of the full range of modern antipsychotic medications is necessary given the variability and evolution of the illness.

Early psychosis patients respond well to antipsychotic medication but also have the highest rates of discontinuation and relapse. There is a rapid period of progression of psychosis prior to and in the 3–5 years following the first presentation. The risk of relapse is high within 2 years and nearly three quarters of patients can expect to relapse within 5 years. Suicide risk is highest in the first 5 years and during the early phase following a relapse. It is clearly imperative that in a modern healthcare system that the most vulnerable be offered acceptable and effective medications that have the potential to control symptoms, improve quality of life and functioning and reduce all-cause mortality. There is no other area in medicine where we would not offer such medications first line.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Compared with other countries Canada has a limited range of atypical LAIs. Not only do our patients not have access to aripiprazole lauroxil, olanzapine LAI or indeed, the LAI with the longest duration- paliperidone six monthly, but even when medications are finally approved this is often years after approval in other countries (ironically even when the pivotal trials of those compounds have been conducted in Canada). Furthermore, other oral atypical agents for treating psychosis such as iloperidone, lumateperone and pimavanserin are still not available in Canada.

Risperidone ISM offers significant advantages over Risperdal Consta in terms of achievement of therapeutic levels within 24 hours of administration. Therefore, there is the potential for a treatment that could be offered at the start of the disease could alter the trajectory and outcome of patients.

Given this mechanism of action and results of studies, it would be recommended to try the treatment early, and as a monotherapy, rather than as a last option or in polypharmacy, for the majority of patients.

From a clinical perspective, it is important to choose the best drug for the individual patient based on patient and disease characteristics, and who will likely benefit from the medication. In many instances, this is likely to be the agent most effective at achieving a balance between efficacy and tolerability, as well as ease of use, and additionally quality of life, functionality and patient acceptance. These latter concepts are rarely considered in clinical trials yet are fundamentally important to patients in real world settings.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Numerous guidelines in Europe (where LAI use is more prevalent) discuss the use of LAIs in early psychosis (Alamo C, et al 2022):

1) France: Guidelines recommend the use of second-generation LAIs as first-line treatment in the maintenance of patients after a first psychotic episode and in recent-onset schizophrenia.

2) Spain: Guidelines recommend second-generation LAIs as a first-line strategy to improve adherence in outpatients with a recent diagnosis of psychosis with a course of less than 2 years.

3) Britain: Guidelines recommend using LAIs in patients with first psychotic episodes in those who request it.

Given that all patients are likely to demonstrate adherence issues at some point in treatment it is recommended that LAIs be considered at the appropriate place in therapy in accordance with Canadian guidelines such as QAAPAPLE (Stip, E, et al. Can J Psychiatry. 2019).

Substance use disorders represent a frequent comorbidity that impacts negatively on adherence and outcomes, with substance exposure triggering an exacerbation of psychosis or difficulty in achieving remission. The use of an LAI can often be helpful, particularly compared to an oral medication, in achieving a degree of stability and providing protection against future decompensation. Several studies have shown this benefit with LAIs such as Risperdal Consta and Abilify Maintena.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

In clinical practice, outcomes are primarily determined by multi-disciplinary clinical observation supplemented by patient and caregiver reports.

In clinical trials, response is often defined as a pre-specified reduction in symptoms scales (e.g. PANSS), however in clinical practice, symptom control, improvement in quality of life, and functionality are the more relevant treatment goals. Unlike clinical trials which recruit select (and adherent) patients in clinical practice patients have significant physical and psychiatric comorbidity and there is much greater variability in treatment response. Gaining stability of illness and preventing recurrences/relapses are measures of successful treatment. The magnitude of the response to treatment varies between patients and at different stages and times thus it should be monitored on a regular basis as part of good clinical practice.

Treatment response in an early phase psychosis population is a priority (symptom and functional response). Clinicians in Canada will follow the Canadian Schizophrenia Guidelines (2017) for specifics and additionally through standards that exist for EPP service delivery (Nolin et al. 2016).

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Factors for discontinuing or switching treatment with Risperidone ISM would be the same as with other treatments such as treatment non (or suboptimal) response, or intolerability to side effects. It should be noted that switching to and from a medication can be a complex process that requires an evidence-based, rational and collaborative approach between care team, patient and caregivers.

5.5 What settings are appropriate for treatment with Risperidone ISM? Is a specialist required to diagnose, treat, and monitor patients who might receive Risperidone ISM?

Both inpatient (hospital) and outpatient (hospital outpatients and community clinics) settings. Given the rapid onset of action of Risperidone ISM there is a place for this treatment in acute care settings including the ED and early on in the course of hospitalization. Frequently, it is the initial treatment that is continued throughout the course of admission and at discharge even though it may not be the most appropriate medication for community maintenance. This has been shown to reflect directly in the 30- 90 day readmission rates in Canadian hospitals.

The medication is typically administered by nurses (and pharmacists in certain jurisdictions) under the supervision of a physician who can be a specialist or general practitioner. Community outpatient settings represent the environment where the majority of patients receive the most treatment During their illness journey but to be effective, LAI should ideally be started prior to discharge from inpatient units. Most early intervention for psychosis programs are specialty teams located in community outpatient settings. Risperidone ISM is ideally suited to initiation in the community for any type of program as well given its ease of use and rapid onset of action.

6. Additional Information

It is important that there are multiple treatment options given the variability of schizophrenia and idiosyncrasy of response. Risperidone ISM has been available in Europe for the last two years and is very recently approved in Australia. Canadians should have the opportunity to have access to this new treatment.

Finally, the other LAI formulations of risperidone including Consta and Perseris may be associated with more discomfort given the needle size of the former and the subcutaneous application of the latter, and this is relevant in terms of patient persistence with treatment.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Pierre Chue
Position: Member CCEIP
Date: 25th March 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen		X		
Abbvie			X	
Otsuka			X	
Boehringer-Ingelheim		X		
Teva		X		
Lundbeck			X	
Bausch	X			
HLS		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Thomas Hastings
Position: Member CCEIP
Date: 31st March 2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen			X	
Boehringer-Ingelheim		X		
Lundbeck			X	
Bausch	X			

* Place an X in the appropriate dollar range cells for each company.