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Reimbursement Recommendation

Risperidone In Situ Microparticle Long-Acting Injection (Okedi)

Indication: For the treatment of schizophrenia in adults
Sponsor: Bausch Health, Canada Inc.
Final Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Okedi?

Canada's Drug Agency (CDA-AMC) recommends that Okedi should be reimbursed by public drug plans for the treatment of schizophrenia if certain conditions are met.

Which Patients Are Eligible for Coverage?

Okedi should only be covered by public drug plans for the treatment of adult patients with schizophrenia.

What Are the Conditions for Reimbursement?

Reimbursement for Okedi should be based on the criteria used by each of the public drug plans for the initiation and renewal of other long-acting injection (LAI) atypical antipsychotic drugs for the treatment of adults with schizophrenia, and the cost of Okedi should not exceed that of the least costly LAI atypical antipsychotic reimbursed for the treatment of schizophrenia.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a bioequivalence study showed that exposures to the active moiety of risperidone were only slightly higher following repeat Okedi injections compared to once daily oral risperidone. Evaluation of similar bioavailability between risperidone ISM and oral risperidone by Health Canada supports that the clinical effects of risperidone in situ microparticle (ISM) are expected to be similar to comparable doses of oral risperidone. In addition, supportive evidence from a clinical trial demonstrated improvements in symptoms and disease severity with Okedi when compared to placebo.
- Based on the CDA-AMC assessment of the health economic evidence, Okedi may represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Okedi compared with other atypical LAI antipsychotics; therefore, the cost of Okedi should not exceed the drug program cost of treatment with the least costly atypical LAI antipsychotic reimbursed for the treatment of schizophrenia.
- Okedi addresses some needs identified by patients, including offering an LAI antipsychotic option that does not require a loading dose or supplementation with oral antipsychotic medication and that involves less frequent administration and office visits, which may be more suitable for some patients.

Summary

- Based on public list prices, Okedi is estimated to save the public drug plans approximately $793,000 over the next 3 years.

Additional Information

What Is Schizophrenia?

Schizophrenia is a complex and chronic mental health condition involving a broad range of symptoms and fluctuating severity over time. Symptoms of schizophrenia are categorized as positive symptoms that involve reality distortion (such as hallucinations, delusions, and disorganized thoughts and behaviours), negative symptoms that impact emotional expression and motivation (such as diminished functioning and social withdrawal), and cognitive symptoms (such as impairments in attention and memory). Affective symptoms, such as depression and anxiety, are also often experienced by people with schizophrenia. In 2022 to 2023, the incidence of schizophrenia in people in Canada aged 10 years and older was estimated to be 53 cases per 100,000.

Unmet Needs in Schizophrenia

Although there are many antipsychotic medications available to treat schizophrenia, there is still a need for treatments that improve negative and cognitive symptoms, improve function and quality of life, have minimal side effects, and are convenient and improve adherence.

How Much Does Okedi Cost?

Treatment with Okedi is expected to cost approximately $6,088 or $8,117 per patient per year, depending on dose.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that risperidone in situ microparticle (ISM) long-acting injection (LAI) (Okedi) be reimbursed for the treatment of schizophrenia in adults only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase I, open-label, multicentre, 1-sequence bioequivalence study (BORIS, N = 58) in patients with schizophrenia whose disease was stabilized on oral risperidone showed that steady-state total (AUC_{tau}) and peak ($C_{max,ss}$) plasma exposures to the active moiety of risperidone were only slightly higher following repeat 100 mg risperidone ISM injections compared to once daily 4 mg oral risperidone. CDEC noted that evaluation of similar bioavailability between risperidone ISM and oral risperidone by Health Canada supports that the clinical effects of risperidone ISM are expected to be similar to comparable doses of oral risperidone. In addition, CDEC discussed evidence from the randomized, double-blind trial (PRISMA-3) in adult patients experiencing acute exacerbation of schizophrenia, which was considered as supportive evidence. The PRISMA-3 trial showed that 12 weeks of treatment with risperidone ISM resulted in greater improvements in symptoms and disease severity compared to placebo. However, the clinical relevance of these results is uncertain, and placebo is not considered an appropriate comparator. In both risperidone ISM treatment groups (75 mg and 100 mg), improvements in the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression–Severity (CGI-S) total scores exceeded the within-group minimally important differences (MIDs); however, in the absence of estimated between-group MIDs for both measures, there is uncertainty regarding the clinical meaningfulness of the advantage of risperidone ISM over placebo. CDEC maintained that there is also uncertainty in the clinical applicability of these results given that the selected population within the trial comprised a patient population that may not be representative of the population of patients with this condition in Canada (i.e., those who were experiencing acute exacerbation of symptoms and whose disease was stabilized on oral risperidone and would be more likely to respond to treatment with risperidone ISM). However, at reconsideration, CDEC acknowledged that although the eligibility criteria limit the patient population suitable for treatment with risperidone ISM, there remain some patients for whom risperidone ISM would be an appropriate treatment option.

Patient group input expressed a need for treatments that improve adherence and allow for the highest level of daily functioning and symptom reduction while managing side effects. The clinical expert consulted by Canada's Drug Agency (CDA-AMC) for this review stated that there remains an unmet need for treatments that improve function and quality of life (QoL), that improve negative and cognitive symptoms, and that have minimal adverse effects. CDEC indicated that no conclusions could be made regarding the effects of risperidone ISM on health-related quality of life (HRQoL) in patients with schizophrenia in the PRISMA-3 trial due to missing data and study design limitations, so there was insufficient evidence to demonstrate that some of the important needs identified by patients and the clinical expert were met by risperidone ISM. Likewise, improved adherence was identified as an outcome of importance to patients and clinicians, but no evidence was submitted that assessed this outcome for risperidone ISM. During the reconsideration meeting,

CDEC discussed additional feedback from the patient group on the draft recommendation, stating that the need for flexible and accessible LAI treatment options remains significant. CDEC concluded that risperidone ISM meets some of the needs identified by patients, including offering an LAI antipsychotic option that does not require a loading dose or supplementation with oral antipsychotic medication, and that less frequent administration and office visits may be more convenient for some patients.

At the sponsor-submitted price for risperidone ISM and publicly listed prices for other LAI antipsychotics and oral risperidone, risperidone ISM was within the range of other LAIs and more costly than oral risperidone. Given there is insufficient evidence to suggest risperidone ISM is more effective than other LAIs, the total drug cost of risperidone ISM should not exceed the total drug cost of the least costly LAI antipsychotic.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of q.4.w. IM risperidone ISM injection should be based on the criteria used by each of the public drug plans for the initiation and renewal of other LAI atypical antipsychotic drugs for the treatment of adults with schizophrenia.	There are no clinical data to support clinical benefit for risperidone ISM for the treatment of schizophrenia compared with other LAIs. Therefore, risperidone ISM should not be treated differently than other LAI atypical antipsychotics for the treatment of adults with schizophrenia.	—
Prescribing		
2. Risperidone ISM injection should not be used in combination with other LAI antipsychotics.	The PRISMA-3 trial did not combine risperidone ISM injection with other LAI antipsychotics, and CDEC did not review any evidence regarding the efficacy and safety of risperidone ISM injection when combined with other LAI antipsychotics.	—
Pricing		
3. Risperidone ISM should be negotiated so that it does not exceed the drug program cost of treatment with the least costly atypical LAI antipsychotic reimbursed for the treatment of schizophrenia.	The comparative efficacy and harms of risperidone ISM relative to relevant comparators, including other LAI antipsychotics used in clinical practice, remain unknown. Therefore, there is insufficient evidence to justify a cost premium for risperidone ISM over the least costly LAI antipsychotic reimbursed for the treatment of schizophrenia.	—

CDEC = Canadian Drug Expert Committee; IM = intramuscular; ISM = in situ microparticle; LAI = long-acting injection; q.4.w. = every 4 weeks.

Discussion Points

- **Clinical benefit:** During the initial and reconsideration meetings, CDEC considered the uncertainty in the clinical trial evidence regarding the clinical benefit of risperidone ISM compared to placebo. Estimated between-group MIDs were not available for PANSS and CGI-S measures of disease symptoms, and severity and study limitations precluded the ability to determine the impact of risperidone ISM on HRQoL. At reconsideration, CDEC discussed feedback from the clinical expert

and the clinician group, which noted that the PRISMA-3 trial for risperidone ISM used an alignment of design and end points with other trials of schizophrenia treatments. The clinician group noted that the PRISMA-3 trial demonstrated robust changes in PANSS and CGI-S that exceeded within-patient MIDs and macro level response rates that were significantly greater than placebo. This includes overall response rates at day 85 that were [redacted]. At reconsideration, CDEC discussed the results of the sponsor-submitted bioequivalence study and considered it as the main rationale to support their recommendation, noting that the results of the BORIS study support the assertion that the clinical effects of risperidone ISM are expected to be similar to comparable doses of oral risperidone. Results of the PRISMA-3 trial were considered supportive evidence.

- **Unmet need:** During the initial and reconsideration meetings, CDEC considered the needs identified by patients, which included access to a wide range of new and convenient treatments that improve adherence and allow for the highest level of daily functioning and symptom reduction while managing side effects. CDEC also considered input from the clinical expert consulted by CDA-AMC regarding the need for treatments that improve function and QoL, improve negative and cognitive symptoms, and have minimal adverse effects. CDEC acknowledged that risperidone ISM would offer an additional risperidone treatment option for patients. Although risperidone ISM does not require a loading dose or supplemental treatment with oral medication, CDEC initially concluded that there was insufficient evidence to demonstrate that the needs identified by patients and the clinical expert were met by risperidone ISM. During the reconsideration meeting, CDEC reviewed feedback on the draft recommendation received from 1 patient group, which stated that the need for flexible and accessible LAI treatment options remains significant. The patient group added that many patients experience challenges with medication adherence and treatment continuity and that LAIs help mitigate these challenges. CDEC also acknowledged the clinical expert's input that reduced injection frequency is preferable for patients and from a health care resources perspective.
- **Generalizability to patients in clinical practice:** During the initial meeting, CDEC noted that the patient population in the PRISMA-3 trial consisted of patients experiencing acute exacerbations who had previously demonstrated a clinically significant beneficial response to an antipsychotic, who had not had a previous inadequate clinical response to risperidone or paliperidone, and who do not have a history of treatment resistance. CDEC also noted that patients with substance use disorders were not represented in the PRISMA-3 trial. Therefore, CDEC believed that the trial population does not reflect the range of patients in clinical practice, including those for whom a history of treatment response may not be known, those who have a history of no or partial response to previously tried antipsychotics, and those who have comorbidities, including experience with substance use. In addition, CDEC noted that patients requiring treatment in an acute setting for an acute exacerbation of symptoms may have a different profile than patients whose symptoms are stabilized on oral risperidone, who may benefit or desire to transition from daily oral treatment to monthly treatment with an LAI for chronic management of symptoms of schizophrenia. Therefore, the results of the

PRISMA-3 trial were believed to be limited to patients experiencing acute exacerbations and requiring treatment in an acute setting whose symptoms are stabilized on oral risperidone, and not the general population of patients with schizophrenia. During the reconsideration meeting, CDEC acknowledged the sponsor's point that a substantial proportion of patients with schizophrenia experience acute exacerbations and that these are associated with poor outcomes. CDEC also reviewed feedback on the draft recommendation from the clinician group, which noted that concerns about generalizability related to exclusion of patients whose disease did not to respond to treatment, who experienced treatment resistance, or who were actively using substances reflect standard safeguards in antipsychotic trials and do not diminish clinical applicability to common scenarios in practice in Canada, such as relapse following prior response due to partial adherence. The clinical expert consulted by CDA-AMC also noted that the exclusions in the PRISMA-3 trial are in line with other clinical trials, and although the evidence may not be generalizable to all patients with schizophrenia, this would be the case with other efficacy trials in this setting. CDEC also acknowledged that the trial for risperidone ER (Perseris), reviewed previously, had a largely similar patient population to that of the PRISMA-3 trial for risperidone ISM.

- **Relevant comparators:** During the initial and reconsideration meetings, CDEC discussed that oral risperidone and LAI antipsychotic medications are currently available for the treatment of schizophrenia, and those would have been appropriate comparators, but the PRISMA-3 trial compared risperidone ISM to placebo. CDEC reiterated the ethical concern with conducting a placebo-controlled trial among patients with acute exacerbations of schizophrenia needing urgent treatment, when several effective treatments are available. During the reconsideration meeting, the clinical expert reconfirmed that placebo is an inappropriate comparator and does not represent the standard of care for the treatment of patients with schizophrenia who are experiencing an acute exacerbation. CDEC initially concluded that, in the absence of direct or indirect evidence, the comparative efficacy and harms of risperidone ISM relative to relevant comparators, including oral risperidone and other LAI antipsychotics, remain unknown. While this remains correct, in the reconsideration meeting, CDEC acknowledged that under CDA-AMC procedures, tailored reviews cannot include indirect comparisons. CDEC also noted that the reimbursement review of Perseris did not include direct or indirect comparisons with other LAIs and that the clinical expert for that review had said it is generally accepted that all LAIs are of similar efficacy and that a lack of comparative data would be unlikely to influence the prescribing of risperidone ER because the efficacy and safety profile of oral risperidone and risperidone LAIs has been well established. At the reconsideration meeting, CDEC reiterated the importance of comparative data in enabling informed judgments about the efficacy and safety of drugs relative to relevant comparators. CDEC noted that some of their concerns were mitigated by consideration of the bioequivalence data of risperidone ISM and oral risperidone within the context of this tailored review and the established place in therapy of risperidone LAIs and risperidone more broadly.
- **Dosing restriction of oral risperidone:** During the initial meeting, CDEC discussed the differences between the dosing of oral risperidone in the PRISMA-3 OLE trial and the dosing recommendations in the Okedi product monograph. According to the product monograph, risperidone ISM 75 mg is

similar to oral risperidone 3 mg/day and risperidone ISM 100 mg is similar to oral risperidone 4 mg/day (to maintain similar plasma concentrations), and patients whose symptoms are stable on oral risperidone doses outside this range may not be suitable candidates for risperidone ISM. CDEC noted that, in clinical practice, a significant proportion of patients whose symptoms are stabilized when on oral risperidone would be receiving doses greater than 4 mg/day and thus may not be eligible for treatment with risperidone ISM. Input from the clinical expert consulted by CDA-AMC also highlighted concerns about initiating patients on a therapy with limited dosing flexibility, particularly when other antipsychotics offer a broader therapeutic range. The clinical expert echoed CDEC's concern that the dosing restrictions outlined in the product monograph would significantly limit patient eligibility and the clinical utility of risperidone ISM in practice. During the reconsideration meeting, CDEC reviewed feedback on the draft recommendation received from the clinician group, which stated that, with 2 monthly strengths available, clinicians can select patients within the labelled exposure range, whereas other patients can continue alternative risperidone or nonrisperidone options. The clinician group feedback also asserted that the limitation of dose range should not on its own negate reimbursement when similar or narrower ranges were accepted for other products. CDEC acknowledged that similar products previously reviewed (i.e., Perseris) had similar dose restrictions. The committee also noted that although dosing restrictions may render risperidone ISM unsuitable for many patients, there remain individuals for whom it would be an appropriate treatment option.

- **Place in therapy:** At the reconsideration meeting, CDEC indicated that given that the efficacy and safety of risperidone ISM relative to other antipsychotic LAIs remains unknown, the place in therapy for risperidone ISM should be the same as other antipsychotic LAIs used in the treatment of schizophrenia.

Background

Schizophrenia is a complex and chronic mental health condition involving a broad range of symptoms and fluctuating symptom severity over time. Symptoms of schizophrenia are grouped into domains. The positive domain involves symptoms of reality distortion (hallucinations and delusions, including impaired insight into the illness) and disorganized thoughts and behaviours. Negative symptoms impact emotional expression and motivation and include reduction in spontaneous speech, diminished functioning, and social withdrawal. Cognitive symptoms may involve impairments in attention, memory, and verbal comprehension. Affective symptoms, such as depression and anxiety, are often experienced by people with schizophrenia. The course of illness in schizophrenia is heterogeneous and influenced by various factors. Schizophrenia significantly affects patients' QoL due to its impacts on physical, mental, and social well-being. Schizophrenia is characterized by higher mortality compared to the general population, with predominant causes being comorbid illnesses (e.g., cardiovascular disease) and death due to unnatural causes, including suicide. In 2022 to 2023, the prevalence of schizophrenia in people in Canada aged 10 years and older was approximately 1%, and the incidence rate in the same population was estimated to be 53 cases per 100,000.

The treatment of schizophrenia is multimodal and includes antipsychotic medications, which are classified as first-generation antipsychotics or second-generation antipsychotics (which are also known as atypical antipsychotics). Second-generation antipsychotics are less likely than first-generation antipsychotics to cause extrapyramidal symptoms. According to the clinical expert consulted by CDA-AMC for this review, the choice of antipsychotic medication is mainly determined by side effect profile, patient preference, and availability, noting that an atypical antipsychotic medication is typically used as initial therapy because this class carries less risk of side effects. Clinical practice guidelines in Canada include the use of LAI antipsychotics as a strategy to address nonadherence and note the potential place for LAIs earlier in the course of treatment and not only for patients for whom suboptimal adherence is a concern. According to the clinical expert consulted by CDA-AMC, LAIs are considered a first-line option in the treatment of schizophrenia, including during an acute exacerbation or as maintenance therapy. The clinical expert also commented that, for the minority of patients with schizophrenia who have good or partial insight into their illness and are adherent to an oral antipsychotic, the choice of either an oral or injectable treatment may be appropriate. Psychosocial interventions, such as specialty care programs, cognitive behavioural therapy, support for the development of self-management skills, family interventions, psychoeducation, access to safe and affordable housing, and supportive employment services, are also recommended as components of effective treatment for patients with schizophrenia. The clinical expert consulted by CDA-AMC stated that, in the treatment of schizophrenia, there remains an unmet need for treatments that improve function and QoL as well as negative and cognitive symptoms and have minimal (if not any) adverse effects.

Risperidone LAI (Okedi, also referred to as risperidone ISM) has been approved by Health Canada for the treatment of schizophrenia in adults. Risperidone is an atypical antipsychotic medication. Okedi is available as a prefilled syringe of powder for extended-release suspension for intramuscular deltoid or gluteal injection and is available in 75 mg and 100 mg strengths. The dosage recommended in the product monograph is 75 mg or 100 mg administered once every 4 weeks.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 multicentre, randomized, double-blind, placebo-controlled study in adult patients with schizophrenia who were experiencing acute exacerbation, and 1 long-term extension study
- patients' perspectives gathered by 1 patient group, the Institute for Advancements in Mental Health (IAM), which was received for a previous CDA-AMC review on risperidone for extended-release injectable suspension for the same indication
- input from public drug plans that participate in the reimbursement review process
- 1 clinical specialist with expertise in diagnosing and treating patients with schizophrenia
- input from 1 clinician group, the Canadian Consortium for Early Intervention in Psychosis (CCEIP)
- a review of the pharmacoeconomic model and report submitted by the sponsor

- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

No patient input was received for this review. Patient input received for a previous CDA-AMC review (November 2021) on risperidone for extended-release injectable suspension (SR0671 Perseris) for the treatment of schizophrenia in adults is included in this report. Therefore, the available input may not accurately reflect patients' current unmet needs.

Patient group input was provided by IAM and was obtained based on the institute's 40-year history of serving adults with schizophrenia. Its submission also draws some information from a survey of members of IAM's client network that was conducted in 2018. Respondents to that survey self-described as personally diagnosed (12%), a caregiver (50%), a family member or friend of someone diagnosed (63%), or working in social services (18%).

Respondents indicated that many patients experience symptoms of psychosis, which have a significant impact on day-to-day functioning. Patient experiences vary widely but typically involve some levels of cognitive impairment, delusions, and hallucinations. A large number of patients also experience a lack of insight into their illness, which often impacts their ability and motivation to access treatment and supports. This symptom can cause significant strain in relationships, including those with caregivers and family members, ultimately leading to social isolation and a lack of supports for the individual with the illness.

Patients indicated the most common side effects of antipsychotic drugs were drowsiness (reported by 58%), dry mouth (50%), restlessness (50%), dizziness (45%), muscle stiffness (45%), constipation (43%), and anxiety (43%).

Twenty-three percent of patients identified the cost of medications as a significant barrier to access; 63% of respondents indicated that it is difficult to pay for health care bills, including for medication, visits to specialists, counselling, and so forth; 20% of patients indicated that not having their preferred medication covered by public drug programs is a challenge.

Patients expect new, quick, simple, convenient, and affordable access to a wide range of treatments and medications to suit their unique needs, which can improve adherence and allow for the highest level of daily functioning and symptom reduction while managing side effects.

Clinician Input

Input From the Clinical Expert Consulted for This Review

The clinical expert stated that there remains an unmet need for treatments that improve function and QoL as well as negative and cognitive symptoms, and that have minimal (if any) adverse effects.

The clinical expert stated that risperidone ISM (Okedi) would be suitable for patients who are experiencing an acute exacerbation of schizophrenia and those who may benefit from transitioning from a stable oral risperidone dose to an LAI. Given that atypical LAI antipsychotics are currently available that can be administered less frequently than risperidone ISM (i.e., up to every 3 months), the clinical expert expected that risperidone ISM would be used for patients who are already receiving an LAI and are experiencing an inadequate response but who are not willing to take clozapine. The clinical expert also expected that risperidone ISM may be used for patients who are responding well on oral risperidone but for whom an LAI would be preferred. The clinical expert commented that participants in the PRISMA-3 pivotal trials included patients who were known to have previously experienced a clinically significant response to an antipsychotic and that the overall population in the trials was healthier than patients in clinical practice. The clinical expert acknowledged the dosing information from the Okedi product monograph, noting that risperidone ISM would not be suitable for patients who are receiving oral risperidone doses greater than 4 mg per day (or an equivalent).

According to the clinical expert, the outcome measures used in the PRISMA-3 pivotal trials are not typically used by physicians in clinical practice. The clinical expert noted that the Brief Psychiatric Rating Scale and CGI-I tools may be used in certain clinical settings, and many hospitals use the Resident Assessment Instrument–Mental Health (RAI-MH) version 2.0 tool to evaluate progress in practice; however, others may assess progress based on clinical interviews rather than an assessment scale. The clinical expert commented that a clinically meaningful response to treatment can vary across physicians and patients and that the following would all be considered important responses to treatment: reduction in the frequency or severity of symptoms, improvement in symptoms, stabilization of symptoms, and the ability to perform activities of daily living. According to the clinical expert, patients in inpatient settings receive frequent monitoring for treatment response, and in outpatient settings, patients initiating treatment with an LAI antipsychotic would initially be assessed in person every 2 weeks. Once a patient's symptoms are stable, assessments with a psychiatrist may occur every 1 to 3 months.

The clinical expert commented that there are no specific parameters to define loss of response, absence of clinical benefit, and disease progression in clinical practice; these would be determined on an individual basis, typically based on the patient's symptoms, ability to function, and other factors.

The clinical expert stated that LAI antipsychotics are initially prescribed and monitored by psychiatrists (and in some cases, family physicians with specialized practices). Once a patient's symptoms are stable, the patient may continue to see a psychiatrist or may be followed by a family physician and receive injections in the family practice setting.

Clinician Group Input

Two clinicians from CCEIP provided input for this review, and information was gathered from a literature review of risperidone ISM, comparison of risperidone LAI formulations, data concerning the use of long-acting antipsychotic injections in schizophrenia and first 5 years of illness, clinical experience, and a conference presentation by the author of the submission.

CCEIP also noted that atypical LAI antipsychotic medications all require some type of titration or loading protocol to ensure therapeutic levels are achieved as quickly as possible, highlighting that early attainment of therapeutic levels is correlated with more positive outcomes and better persistence with treatment. According to the clinician group, the desired outcomes of early intervention during the critical period are to improve the course of psychosis and lead to a period of stability, return to the social and occupational levels of functioning that existed before the onset of illness, result in a better outcome compared with the intervention after the critical period, and decrease the risk of suicide.

CCEIP commented that risperidone ISM allows for achievement of therapeutic levels within 24 hours of administration and that it would be recommended to try early and as monotherapy (rather than as a last option or in polypharmacy) for the majority of patients. In selecting the best drug for an individual patient, considerations include achieving a balance between efficacy and tolerability, ease of use, QoL, functionality, and patient acceptance. According to CCEIP, patients are likely to demonstrate adherence issues at some point in treatment, and it is recommended that LAIs be considered at the appropriate place in therapy per Canadian guidelines.

Regarding determining response to treatment, CCEIP commented that outcomes in clinical practice are mainly determined by multidisciplinary clinical observation supplemented by reports from patients and caregivers. CCEIP identified differences between clinical trial outcomes (e.g., PANSS) and patients compared to those in clinical practice, noting that, in clinical practice, the more relevant goals include symptom control, improvement in QoL, and functionality and that patients have significant psychiatric and physical comorbidity and experience greater variability in treatment response. CCEIP noted that measures of successful treatment include gaining stability of illness and preventing recurrences and/or relapses, and that symptom and functional response to treatment is a priority in the population with early-phase psychosis.

CCEIP suggested that factors for discontinuing or switching treatment with risperidone ISM would be the same as with other treatments and would include nonresponse or suboptimal response to treatment, or intolerability to side effects.

CCEIP stated that the inpatient (hospital) and outpatient (hospital outpatient and community clinic) settings are appropriate for administration of risperidone ISM, including in acute care settings and early in the course of hospitalization, given the rapid onset of the medication's effect. According to CCEIP, risperidone ISM would typically be administered by nurses (and pharmacists in certain jurisdictions) under the supervision of a physician (specialist or general practitioner). CCEIP noted that most early intervention for psychosis programs are specialty teams located in community outpatient settings and that, given the ease of use and rapid onset of action of risperidone ISM, it is ideally suited for initiation in the community for any type of program.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for risperidone ISM:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- care provision issues
- system and economic issues.

The clinical expert consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Issues with the choice of comparator in the submitted trial(s) PRISMA-3: 12-week placebo-controlled trial in patients with schizophrenia experiencing an acute exacerbation. Eligible patients received risperidone ISM 75 mg, risperidone ISM 100 mg, or placebo injected into the gluteal or deltoid muscle every 4 weeks on days 1, 29, and 57. What is an appropriate comparator for patients with schizophrenia, given that there are other long-acting antipsychotics on the market in Canada?	The clinical expert stated that the most appropriate comparators to risperidone ISM would be risperidone LAI q.2.w. (Risperdal Consta), aripiprazole LAI q.1.m. (Abilify Maintena), and the paliperidone LAIs. CDEC acknowledged the clinical expert's input, noting that appropriate comparators to risperidone LAI would be any LAI or oral antipsychotic. CDEC commented that the use of a placebo in an acutely decompensated patient population with schizophrenia whose symptoms had responded to previous antipsychotics does not align with current clinical practice.
Other implementation issues regarding relevant comparators (e.g., access and/or funding, population with coverage for prescription drugs) Abilify Maintena received a positive reimbursement recommendation from CDA-AMC (2014), which concluded with an LOI. Invega Sustenna received a negative reimbursement recommendation from CDA-AMC (2011). Invega Trinza concluded with an LOI. Risperdal Consta has not been reviewed by CDA-AMC. **CDEC:** There is a variability in listing status across the federal, provincial, and territorial jurisdictions and, therefore, not consistent access and funding.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Considerations for initiation of therapy	
Other patient characteristics for eligibility (e.g., age restrictions, comorbidities) The inclusion criteria for the PRISMA-3 trial include: • aged 18 to 65 years • current diagnosis of schizophrenia as per the *DSM-5* • BMI 18.5 kg/m^2 to 40.0 kg/m^2 • currently experiencing an acute exacerbation or relapse with a total score between 80 and 120 on the PANSS and a score ≥ 4 points for ≥ 2 of the following positive symptom items: delusions, conceptual disorganization, hallucinatory behaviour, and suspiciousness and/or persecution • a score of ≥ 4 (moderately ill or worse) on the CGI-S • a previous clinically significant beneficial response after treatment with an antipsychotic other than clozapine. The exclusion criteria for the PRISMA-3 trial include: • an improvement in PANSS total score of ≥ 20% between the screening visit and baseline or with active suicidality, indicated by having answered "yes" on item 4 or 5 of the C-SSRS in the most recent episode (within the past 2 months) • having answered "yes" to any of the 5 items (suicidal behaviour) with an episode occurring within the last year • the presence of a clinically significant comorbid neuropsychiatric disorder, lifetime history of schizoaffective or bipolar disorder, lifetime history of schizoaffective or bipolar disorders, or a history of any unstable medical condition or laboratory abnormality that could interfere with the conduct of the study or compromise the well-being of the patient. • pregnancy or breastfeeding. The inclusion criteria for de novo patients for the PRISMA-3 OLE trial include: • aged 18 to 65 years • current diagnosis of schizophrenia • on a stable dose of PO risperidone from 4 mg to 6 mg daily as maintenance therapy for at least the last 4 weeks prior and/or before screening and/or baseline and would potentially benefit from conversion to an extended-release injectable in the opinion of the investigator • BMI between 18.5 kg/m^2 and 40.0 kg/m^2 • PANSS total score < 70 • CGI-S score ≤ 3 (mild). **Question for the clinical expert:** Should the CDEC reimbursement criteria align with inclusion and/or exclusion criteria as described in the PRISMA-3 trial? Please elaborate, especially given the age and BMI thresholds. (That is, can patients aged < 18 years and aged > 65 years access this medication, and can patients < 18.5 kg/m^2 and > 40.0 kg/m^2	The clinical expert could not comment on the use of Okedi in patients younger than 18 years. Regarding patients older than 65 years, the clinical expert commented that many patients with schizophrenia would belong to this age group and that reimbursement should extend to these patients (noting that a higher risk of side effects would be a clinical consideration in this group). According to the clinical expert, reimbursement should not necessarily be limited to patients who fall within the BMI range of patients included in the PRISMA-3 pivotal trials. The clinical expert stated that LAIs would be considered a first-line option for most patients diagnosed with schizophrenia, including during an acute exacerbation or as maintenance therapy. The clinical expert stated that Okedi would be suitable for patients who are experiencing an acute exacerbation of schizophrenia and also for patients who may benefit from transitioning from a stable oral risperidone dose to a long-acting antipsychotic injection. CDEC stated that no conclusion can be made for risperidone LAI other than for the patient population studied in the PRISMA-3 trial, which was narrow and likely very different than the patient population that would be prescribed risperidone LAI in practice if it were listed in a manner similar to other LAIs.

Implementation issues	Response
access this medication?) The Health Canada indication states "treatment of schizophrenia." In the PRISMA trial, the mean time since acute exacerbation or relapse days was approximately 3 days. Clinical practice suggests offering LAIs as an option in all phases of illness, including the first episode, after first establishing tolerability with oral formulations. **Question for the clinical expert:** Would you be able to elaborate on patient selection and place in therapy of Okedi? Is Okedi to be used **only** in the setting of an acute exacerbation in patients with schizophrenia? Can Okedi be used in patients who may benefit from transitioning from a stable oral risperidone dose to a long-acting antipsychotic injection?	
Prior therapies required for eligibility Also, patients who had never taken risperidone had a brief trial of oral risperidone 2 mg/day for 3 days during the screening period to ensure lack of any hypersensitivity reactions before the first dose of the study drug. **Question for the clinical expert:** Should a trial of oral antipsychotic (any) be initiated before the administration of Okedi be a part of the CDEC reimbursement criteria? Or can the patient receive Okedi for the acute episode without this trial?	According to the clinical expert, it would be reasonable for the reimbursement criteria to require a safety trial of oral risperidone to ensure lack of any hypersensitivity reaction or severe side effects before administration of risperidone ISM, including in patients being treated for an acute episode. CDEC agreed with the clinical expert's feedback
Consistency with initiation criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space Abilify Maintena (2014): Positive reimbursement recommendation from CDA. "... recommends that aripiprazole long-acting injection (LAI) be listed for the maintenance treatment of schizophrenia in adult patients who are stabilized on oral aripiprazole, if the following condition is met: List in a manner similar to other long-acting atypical antipsychotic drugs." **Question for the clinical expert:** Should there be a requirement in the criteria for patients to be stabilized on PO risperidone at a specific dose range before accessing Okedi? Noted as per product monograph: • Okedi 75 mg once every 4 weeks is similar to PO risperidone 3 mg/day • Okedi 100 mg once every 4 weeks is similar to PO risperidone 4 mg/day • Patients prescribed higher or lower PO risperidone doses may not be candidates for Okedi. **Question for the clinical expert:** If the dose of PO risperidone is not in the range provided in the product monograph to transition over to Okedi, what other options do patients have?	The clinical expert stated that there should not necessarily be a requirement in the criteria for patients to be stabilized on oral risperidone at a specific dose range before accessing risperidone ISM; however, it might be reasonable to be consistent with other medications. According to the clinical expert, for patients whose dose of oral risperidone is not in the range provided in the product monograph to transition to risperidone ISM, the other options would be other atypical LAI antipsychotics (risperidone, paliperidone, or aripiprazole) or, for patients who have tried these without adequate response, first-generation antipsychotic injections. CDEC acknowledged the clinical expert's input.
Considerations for continuation or renewal of therapy	
Challenges related to assessment and monitoring of therapeutic response	The clinical expert stated that the outcome measures used in the PRISMA-3 pivotal trials (PANSS, CGI-S, CGI-I) are not typically used by physicians in clinical practice. For example,

Implementation issues	Response
The efficacy in the PRISMA-3 trial was assessed by PANSS, CGI-S, and CGI-I. **Question for the clinical expert:** Is the assessment and monitoring of therapeutic response for LAI performed through PANSS, CGI-S, and CGI-I in clinical practice? Please include comments on feasibility and other tools used for consideration in this population context. **Question for the clinical expert:** How often in clinical practice do you assess and/or monitor therapeutic response for LAI? This may help inform the approval period for the initial period and renewal period.	PANSS is a research tool that lacks feasibility in clinical practice because it takes considerable time to complete. The clinical expert noted that the BPRS and CGI-I may sometimes be used in certain clinical settings. The clinical expert also commented that the RAI-MH version 2.0 is a mandatory tool that is used in psychiatric admissions in Ontario to capture data. The clinical expert noted that many hospitals may use the RAI-MH tool to evaluate progress; however, others may assess progress based on clinical interviews rather than an assessment scale. According to the clinical expert, the frequency of assessment for treatment response in clinical practice depends on the treatment setting. Inpatients receive frequent monitoring for treatment response. On an outpatient basis, patients initiating treatment with an LAI antipsychotic would initially be assessed in person every 2 weeks (with phone consultations in between as needed); once a patient's symptoms are stable, assessments with a psychiatrist may occur every 1 to 3 months (although patients may see the nurse in the injection clinic more frequently than this). CDEC acknowledged the clinical expert's input.
Considerations for discontinuation of therapy	
Definition of loss of response, absence of clinical benefit, or disease progression **Question for the clinical expert:** What definition would you use for loss of response, absence of clinical benefit, and disease progression in clinical practice? Based on what parameters? Noted: If a dose is delayed by a week, the median trough concentration decreases by ~50% during that week. **Question for the clinical expert:** If the patient is nonadherent, is this a consideration for discontinuation? How is the treatment of these patients managed?	According to the clinical expert, there are no specific parameters to define loss of response, absence of clinical benefit, and disease progression in clinical practice. These would be determined on an individual patient basis and would typically be based on the patient's symptoms (e.g., delusions, hallucinations), ability to function, and other factors (e.g., threatening behaviour, eviction, hospitalization). The clinical expert stated that management of nonadherence is dependent on its cause. Nonadherence due to adverse effects would be managed by changing the medication. Nonadherence due to lack of insight into the illness may result in a detailed assessment of the individual's ability to consent to treatment and, as needed, a community treatment order. CDEC acknowledged the clinical expert's input.
Considerations for prescribing of therapy	
Dosing, schedule/frequency, dose intensity **Question for the clinical expert:** Is there any evidence to increase or reduce the frequency of medication administration for this indication (i.e., from every 4 weeks to every 3 weeks, and so forth)?	The clinical expert noted that this occurs in clinical practice for other antipsychotics; however, no comment could be made regarding risperidone ISM. CDEC acknowledged the clinical expert's input.
Drug administration Note: There is a cost of administration given that Okedi is to be administered by a health care professional. It is not self-administered.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Concerns related to accessing clinical specialists and/or special settings **Question for the clinical expert:** Please describe which specialists will be seeing these patients and in which setting Okedi would be administered?	LAI antipsychotics are initially prescribed and monitored by psychiatrists (and in some cases, family physicians with specialized practices). Once a patient's symptoms are stable, they may continue to see a psychiatrist or may be followed by a family physician and receive injections in the family practice setting. When prescribed by a psychiatrist, an LAI would typically be administered by a nurse working with the psychiatrist in a clinic setting but may also be administered at home in the case of mental health outreach teams. CDEC acknowledged the clinical expert's input.
Care provision issues	
Drug preparation, storage, administration, or dispensing **Question for the clinical expert:** Where would Okedi be initiated for administration (e.g., specialist's office) and where would it be maintained for administration (e.g., primary care office)?	LAI antipsychotics are initially prescribed and monitored by psychiatrists (and in some cases, family physicians with specialized practices). Once a patient's symptoms are stable, they may continue to see a psychiatrist or may be followed by a family physician and receive injections in the family practice setting. When prescribed by a psychiatrist, an LAI would typically be administered by a nurse working with the psychiatrist in a clinic setting, but it may also be administered at home in the case of mental health outreach teams. CDEC acknowledged the clinical expert's input.
System and economic issues	
Presence of confidential negotiated prices for comparators Abilify Maintena and Invega Trinza have successfully gone through price negotiations for the same indication.	Comment from the drug programs to inform CDEC deliberations.

BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; *DSM-5* = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ISM = in situ microparticle; LAI = long-acting injection; LOI = letter of intent; OLE = open-label extension; PANSS = Positive and Negative Syndrome Scale; PO = oral; q.1.m. = once monthly; q.2.w. = every 2 weeks; RAI-MH = Resident Assessment Instrument–Mental Health.

Clinical Evidence

Pivotal Studies

The PRISMA-3 Trial

Description of the Study

The PRISMA-3 trial (N = 438) was a multicentre, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of risperidone ISM in treating adult patients with schizophrenia who were experiencing acute exacerbation. Both the PRISMA-3 trial and its extension study, PRISMA-3 OLE, were conducted at 26 centres in the US and Ukraine. In the PRISMA-3 trial, patients were randomized 1:1:1 to receive risperidone ISM 75 mg, risperidone ISM 100 mg, or matched placebo by intramuscular injection every 4 weeks for a total of 3 injections during the 12-week treatment phase. The primary end point was the PANSS total score mean change from baseline at day 85, and the key secondary end point was the CGI-S score mean change from baseline at day 85. The PANSS is a 30-item scale with total scores ranging from 30

to 210 and higher scores representing greater symptom severity; PANSS subscales include the positive (7 items), negative (7 items), and general psychopathology (16 items) subscales. The CGI-S is a clinician-rated severity-of-illness scale with overall scores ranging from 0 (not assessed) to 7 (among the most extremely ill patients). Other secondary end points included overall response rate (defined as PANSS total score ≥ 30% decrease from baseline or CGI-I score of 2 [much improved] or 1 [very much improved]) at day 85; PANSS positive subscale score mean change from baseline and PANSS negative subscale score mean change from baseline, each at day 85; and HRQoL at the end of the trial, as measured by the Subjective Well-Being Under Neuroleptics-Short Form (SWN-20) total score change from baseline. The CGI-I is a clinician-rated global improvement scale with overall scores ranging from 1 (very much improved) to 7 (very much worse). The SWN-20 is a scale asking patients to rate well-being items that have been identified as related to antipsychotic treatment, with total scores ranging from 20 to 120, and higher scores indicating better HRQoL. Harms outcomes were also assessed.

Patients eligible for participation in the PRISMA-3 trial were aged 18 to 65 years, with a current diagnosis of schizophrenia, and who were actively experiencing acute exacerbation or relapse with a PANSS total score between 80 and 120 and a score of greater than or equal to 4 points for 2 or more of the following positive symptom items: delusions, conceptual disorganization, hallucinatory behaviour, and suspiciousness and/or persecution. All patients had a CGI-S score of greater than or equal to 4 (moderately ill or worse). Patients previously had a clinically significant beneficial response after treatment with an antipsychotic other than clozapine and had no history of inadequate clinical response to treatment with risperidone or paliperidone and no history of treatment resistance. The mean age of patients in the PRISMA-3 trial was 42.0 years. Approximately one-third of patients were female (33.0%) and two-thirds of patients were male (67.0%). Approximately half of patients were Black or African American (49.9%) and half were white (48.5%). The majority of patients were in the US (61.1%) and the remainder were in Ukraine (38.9%). The mean body mass index (BMI) of patients was 28.33 kg/m^2. The mean time since acute exacerbation or relapse was 0.4 weeks and the mean years since schizophrenia diagnosis was 15.5 years.

Efficacy Results

PANSS Total Score Change From Baseline to Day 85 (Primary End Point)

The mean change from baseline to day 85 was −11.0 (95% confidence interval [CI], −14.1 to −8.0) for the placebo group, −24.6 (95% CI, −27.5 to −21.6) for the risperidone ISM 75 mg group, and −24.7 (95% CI, −27.7 to −21.6) for the risperidone ISM 100 mg group. The Lawrence and Hung mean difference from the placebo group was −13.0 (95% CI, −17.3 to −8.8) for the risperidone ISM 75 mg group, and −13.3 (95% CI, −17.6 to −8.9) for the risperidone ISM 100 mg group (Hommel adjusted P value < 0.0001 for both groups). The within-group changes for risperidone ISM exceeded the PANSS within-group MID estimate of 15 points; however, in the absence of an estimated between-group MID, there is uncertainty as to whether the advantage of risperidone ISM over placebo is clinically meaningful.

CGI-S Score Change From Baseline to Day 85 (Key Secondary End Point)

The mean change from baseline at day 85 was −0.6 (95% CI, −0.8 to −0.4) for the placebo group, −1.3 (95% CI, −1.5 to −1.2) for the risperidone ISM 75 mg group, and −1.3 (95% CI, −1.5 to −1.2) for the risperidone

ISM 100 mg group. The Lawrence and Hung mean difference from the placebo group was −0.7 (95% CI, −1.0 to −0.5) for the risperidone ISM 75 mg group and −0.7 (95% CI, −1.0 to −0.5) for the risperidone ISM 100 mg group (Hommel adjusted P value < 0.0001 for both groups). The within-group changes exceeded the 1-point improvement on the CGI-S that is considered clinically meaningful; however, in the absence of an estimated between-group MID, there is uncertainty as to whether the advantage of risperidone ISM over placebo is clinically meaningful.

PANSS Positive and Negative Subscale Score Change From Baseline to Day 85

The PANSS positive subscale score mean change from baseline at day 85 was −4.1 (95% CI, −5.1 to −3.1) for the placebo group, −8.0 (95% CI, −9.0 to −7.1) for the risperidone ISM 75 mg group, and −8.7 (95% CI, −9.7 to −7.8) for the risperidone ISM 100 mg group. The least squares means difference from placebo was −3.9 (95% CI, −5.3 to −2.5; P < 0.0001) for the risperidone ISM 75 mg group and −4.6 (95% CI, −6.0 to −3.2; P < 0.0001) for the risperidone ISM 100 mg group. At day 85, the PANSS negative subscale score mean change from baseline was −1.7 (95% CI, −2.5 to −0.9) for the placebo group, −3.8 (95% CI, −4.5 to −3.0) for the risperidone ISM 75 mg group, and −3.7 (95% CI, −4.4 to −2.9) for the risperidone ISM 100 mg group. The least squares means difference from placebo was −2.1 (95% CI, −3.1 to −1.0; P < 0.001) for the risperidone ISM 75 mg group and −2.0 (95% CI, −3.1 to −0.9; P < 0.001) for the risperidone ISM 100 mg group. These end points were not part of the multiple testing procedure and are considered as supportive evidence. In the absence of MID estimates, the clinical meaningfulness of the between-group differences is uncertain.

Overall Response Rate at Day 85

At day 85, the overall response rate was [redacted] This end point was not part of the multiple testing procedure and is considered as supportive evidence. In the absence of MID estimates, the clinical meaningfulness of the between-group differences is uncertain.

SWN-20 Total Score Change From Baseline

The mean change in SWN-20 total score from baseline to the end of the PRISMA-3 trial was [redacted]) for the placebo group; for the comparison of risperidone ISM versus placebo, [redacted]. This end point was not part of the multiple testing procedure and is considered as supportive evidence. The clinical meaningfulness of the between-group differences is uncertain because no MID has been established for the SWN-20 scale and the clinical expert could not comment on the clinical meaningfulness of these results.

Harms Results

The proportion of patients who experienced at least 1 treatment-emergent adverse event (TEAE) was [redacted]

[redacted]. The most common TEAEs were blood prolactin increase ([redacted]), headache ([redacted]), hyperprolactinemia ([redacted]), akathisia ([redacted]), and weight increase ([redacted]). The proportion of patients who experienced at least 1 serious adverse event was 1.4% in the risperidone ISM 75 mg group, 3.4% in the risperidone ISM 100 mg group, and 3.4% in the placebo group, and the proportion of patients who discontinued risperidone ISM due to a TEAE were 4.2%, 6.2%, and 6.8%, respectively. No patient died during the PRISMA-3 trial.

Critical Appraisal

The PRISMA-3 trial was a randomized double-blind, placebo-controlled study. Methods of randomization and treatment allocation were adequate for limiting risk of bias in the randomization process. The reported baseline characteristics were generally balanced across the groups, and the clinical expert consulted for this review did not identify any imbalances that would be expected to impact the interpretation of the results. Because unblinded individuals prepared and administered the study drug, there is potential risk that patients and/or outcome assessors could have become aware of the treatment group assignment, which could introduce risk of bias in the measurement of subjective outcomes (including PANSS, CGI-S, SWN-20, and adverse events); however, the magnitude and direction of this risk cannot be predicted. Multiplicity of testing was accounted for in the primary and key secondary end points and included hierarchical ordering. Analyses of other secondary end points (and SWN-20) were not adjusted for multiplicity and were considered as supportive evidence. Study completion rates were low with imbalances noted between groups; however, loss to follow-up was generally low and similar among treatment groups. The clinical expert consulted for this review stated that the discontinuation rates and reasons for discontinuation in the PRISMA-3 trial reasonably aligned with rates that would be expected for patients receiving LAI antipsychotics for treatment of schizophrenia in clinical practice. For the SWN-20 end point, the proportion of patients with missing data increased over time, with a greater proportion of patients in the risperidone ISM group having completed the SWN-20 than in the placebo group; therefore, the HRQoL results could be biased as a result of missing outcome data; the direction of bias is uncertain. Evidence is available to support the psychometric properties of the PANSS and SWN-20 outcome measures (evidence regarding the responsiveness of PANSS was not available); however, there is limited information available on the validity, reliability, and responsiveness of the CGI-S and CGI-I measures in patients with schizophrenia.

Patients in the PRISMA-3 trial had a diagnosis of schizophrenia and were experiencing an acute exacerbation. Eligibility criteria included that patients have a history of clinically significant beneficial response to an antipsychotic other than clozapine and that patients not have a history of inadequate clinical response to risperidone or paliperidone nor a history of treatment resistance. The clinical expert commented that these criteria are not reflective of patients in clinical practice for whom a history of treatment response may not be known and who often have a history of no or partial response to previously tried antipsychotics. All patients in the PRISMA-3 trial had a history of receiving an antipsychotic, which included risperidone. The clinical expert highlighted that the trial includes a highly selected population of patients who would be more likely to respond to treatment with risperidone ISM. The clinical expert also noted that the average patient

with schizophrenia would have a high degree of comorbidities, often including substance use; however, these patients were excluded from the trial. According to the clinical expert, the age of patients randomized in the trial is reflective of the indicated population in clinical practice and the sex of the participants was slightly skewed toward male patients. The clinical expert noted that the race of patients in the trial is not representative of the population in Canada because people of Asian ancestry are under-represented. An important limitation of the PRISMA-3 trial is that risperidone ISM was compared to placebo, which does not represent the standard of care for treatment of patients with schizophrenia who are experiencing an acute exacerbation. As identified by the clinical expert, appropriate comparators to risperidone ISM would be risperidone LAI every 2 weeks, aripiprazole LAI once monthly, and the paliperidone LAIs. Although many of the outcomes assessed in the PRISMA-3 trial align with key outcomes of importance to patients and clinicians, the clinical expert stated that the outcome measures used in the PRISMA-3 trial are not typically used in clinical practice, and physician assessment of response to treatment may be based on clinical interviews rather than an assessment scale. The clinical expert also highlighted that a clinically meaningful response to treatment can vary across physicians and patients.

The PRISMA-3 OLE Trial

Description of the Study

PRISMA-3 OLE (N = 215) was an OLE study of the PRISMA-3 trial evaluating the long-term efficacy and safety of risperidone ISM in adult patients with schizophrenia. All patients received either risperidone ISM 75 mg or risperidone ISM 100 mg by intramuscular injection every 4 weeks over 12 months. End points from the PRISMA-3 OLE trial included those for the PRISMA-3 trial (but at the end point for the OLE [i.e., day 365 or the last postbaseline OLE assessment]) and also relapse (defined as PANSS total score increase of ≥ 30% from baseline, or rehospitalization for psychotic symptoms or use of adjunctive antipsychotic medication after stabilization) and remitters (defined as the simultaneous attainment of a score of ≤ 3 for 6 months or more on 8 main items of the PANSS [delusions, conceptual disorganization, hallucinations, blunted affect, passive apathetic social withdrawal, lack of spontaneity and flow of conversations, mannerisms and posturing, unusual thought content]).

Patients eligible for participation in the PRISMA-3 OLE trial included rollover patients who had completed the PRISMA-3 trial; those who had been receiving placebo (patients with “unstable” symptoms) were randomly assigned to receive either risperidone ISM 75 mg or 100 mg and patients who had been treated with risperidone ISM received risperidone ISM at the same dose as during the double-blind phase (patients with “stabilized” symptoms). In addition, newly eligible de novo patients were aged 18 to 65 years with a current diagnosis of schizophrenia with symptoms that were clinically stable at screening (“stable” symptoms) with a PANSS total score of less than 70 and a CGI-S score of 3 or less (mild). De novo patients previously had a clinically significant beneficial response after treatment with an antipsychotic other than clozapine and had no history of inadequate clinical response to treatment with risperidone or paliperidone and no history of treatment resistance. De novo patients were also on a stable dose of 4 mg/day to 6 mg/day of oral risperidone; patients taking 4 mg/day received risperidone ISM 75 mg, and those taking more than 4 mg/day and up to 6 mg/day received risperidone ISM 100 mg. The mean age of patients in the PRISMA-3 OLE trial was 39.3 years. Female and male patients comprised 39.1% and 60.9% of participants, respectively, and

the majority (84.7%) of patients were white, whereas 14.9% of patients were Black or African American. The majority of patients were in Ukraine (81.4%), and the remainder were in the US (18.6%); all de novo patients were in Ukraine. The mean BMI was 26.88 kg/m^2 and the mean years since schizophrenia diagnosis was 10.9 years.

Efficacy Results

At OLE end point, the mean PANSS total score change from baseline in the open-label population (OLP) was −11.2 (standard deviation [SD] = 14.67) and the positive and negative subscale score mean changes from baseline in the OLP were −3.4 (SD = 5.11) and −2.2 (SD = 4.00), respectively. Also at OLE end point, the mean CGI-S score change from baseline in the OLP was −0.5 (SD = 0.91). The overall response rate was 45.1% in the OLP (42.2% [95% CI, 33.1 to 51.8] in the 75 mg group and 48.5% [95% CI, 38.3 to 58.7] in the 100 mg group).

Relapse during the OLE phase occurred in 11.2% (95% CI, 6.1 to 18.4) of patients in the risperidone ISM 75 mg group and 10.1% (95% CI, 5.0 to 17.8) of patients in the risperidone ISM 100 mg group. The relapse rate in the OLP was 10.7% (95% CI, 6.9 to 15.6).

Kaplan-Meier estimated remittance rates after 365 days or less of treatment [redacted]

During the OLE phase, the mean SWN-20 total score change from baseline to the end of the OLE phase was [redacted]

Harms Results

The sponsor-provided summary of the harms results presented combined data for patients who received risperidone ISM in the PRISMA-3 and PRISMA-3 OLE trials. In both phases, 68.4% experienced at least 1 TEAE. The most common TEAEs were headache ([redacted]), hyperprolactinemia ([redacted]), blood prolactin increase ([redacted]), nasopharyngitis ([redacted]), weight increase ([redacted]), insomnia ([redacted]), and akathisia ([redacted]). In both phases, [redacted]

Critical Appraisal

The PRISMA-3 OLE trial was the OLE of the PRISMA-3 trial in which all patients received either risperidone ISM 75 mg or risperidone ISM 100 mg. Results for subjective end points, including PANSS, CGI-S, SWN-20, and adverse events, may have been biased due to the patients' and investigators' knowledge of the treatment being received. No adjustments for multiplicity were made for the end points in the OLE, and the efficacy analyses were descriptive. Results for within-group comparisons (i.e., comparing baseline to the end of the OLE phase within a treatment group) are at increased risk of type I errors (false-positive results). The

lack of a control arm precludes the ability to draw conclusions regarding the magnitude of effect attributable to risperidone ISM. According to the clinical expert, the discontinuation rates and reasons for discontinuation in the PRISMA-3 OLE trial reasonably aligned with rates that would be expected for the indicated population in clinical practice. Missing data for the SWN-20 end point over time could have introduced bias.

In the PRISMA-3 OLE trial, the patient population comprised rollover patients (i.e., with “stabilized” and “unstable” symptoms) from the PRISMA-3 trial and de novo patients (i.e., with “stable” symptoms), which represents a broader population of patients with schizophrenia than in the double-blind phase. Given that the other eligibility criteria were aligned for patients between the double-blind and OLE phases, the generalizability considerations noted for the PRISMA-3 trial (e.g., a generally healthier and selected population that would be expected to have better response to risperidone) would be expected to be relevant to the PRISMA-3 OLE trial. In addition, rollover patients represent a selected population who tolerated or stayed on the study drug long enough to complete the double-blind phase. Regarding de novo patients, the clinical expert commented that the inclusion criteria reflect patients with schizophrenia whose symptoms would be considered stable. The clinical expert noted that, as in the double-blind phase, a higher proportion of patients in the PRISMA-3 OLE trial were male, and patients of Asian ancestry were under-represented. De novo patients on a stable dose of oral risperidone of 4 mg/day received risperidone ISM 75 mg and those taking a stable oral risperidone dose of greater than 4 mg/day and up to 6 mg/day received risperidone ISM 100 mg. However, the Okedi product monograph states that risperidone ISM 75 mg is similar to oral risperidone 3 mg/day and risperidone ISM 100 mg is similar to oral risperidone 4 mg/day (to maintain similar plasma concentrations), and patients who symptoms are stable on oral risperidone doses outside this range may not be candidates for risperidone ISM. The clinical expert stated that, in practice, a significant portion of patients whose symptoms were stabilized on oral risperidone would be receiving doses greater than 4 mg/day. As for the PRISMA-3 trial, many of the outcomes assessed in the extension phase align with key outcomes of importance to patients and clinicians, including relapse.

Economic Evidence

Cost and Cost-Effectiveness

The sponsor submitted a cost comparison evaluating the annual drug and administration costs associated with risperidone ISM compared to other LAI antipsychotics approved for the treatment of adults with schizophrenia, as well as to oral risperidone. At the submitted prices of $468.32 and $623.40 for the 75 mg and 100 mg vials, the annual drug cost of risperidone ISM is $6,088 or $8,117 per patient per year, with an estimated annual administration cost of $88. The incremental cost of risperidone ISM every 4 weeks compared to the recommended doses of the LAI comparators ranged from a savings of $4,746 annually to an additional cost of $4,302 annually, per patient, depending on the doses being compared. The annual drug acquisition cost of risperidone ISM is $5,644 to $7,821 more expensive than that of risperidone tablets ($222 to $445 per patient).

The sponsor's cost comparison was associated with limitations, including uncertainty in the assumption of clinical similarity, uncertainty in the equivalency of doses across comparators, and the potential confidential prices of the comparators. All incremental costs or savings are based on publicly available list prices and may not reflect actual prices paid by public drug plans in Canada.

Budget Impact

CDA-AMC identified several limitations with the sponsor's analysis:

- uncertainty with the claims-based approach, the projected number of patient-years of treatment considered, and the portion of claims for LAI antipsychotics attributable to use for schizophrenia
- uncertainty in the projected uptake of risperidone ISM, which LAI comparators it will displace, and in whether it would also displace oral risperidone
- uncertainty in the doses of comparators that would be displaced by each risperidone ISM dose
- the calculation of dispensing fees and markups may have been inappropriately conducted
- the existence of confidential pricing agreements for the comparators.

CDA-AMC conducted a base case reanalysis removing dispensing fees and markups and halving the estimated uptake of risperidone ISM. The CDA-AMC base case suggests that the reimbursement of risperidone ISM for the treatment of adult patients with schizophrenia would be associated with a 3-year budgetary savings of $792,827 (year 1 = $85,078, year 2 = $283,557, year 3 = $424,193).

CDA-AMC also conducted scenarios exploring the impact of assuming that risperidone ISM would displace some use of oral risperidone and assuming that a generic aripiprazole product would become available. Under these assumptions, risperidone was associated with an incremental budgetary cost rather than savings (range: $452,046 to $2,617,394). CDA-AMC was unable to adjust for uncertainty in which and what doses of LAI comparators would be displaced by risperidone ISM or for confidential pricing of the comparator products.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for risperidone ISM (Okedi) for schizophrenia. In their request, the sponsor identified the following issues:

- The sponsor disagreed with the assertion that acutely relapsed patients are not representative of the population of patients with schizophrenia in Canada.
- The sponsor disagreed that there is uncertainty about the clinical meaningfulness of the PRISMA-3 trial, given that it used gold standard end points and showed improvements exceeding the minimal clinically important difference. The sponsor noted that other LAIs followed the same methodology and showed less robust improvements yet were recommended for reimbursement by CDA-AMC, and that risperidone ISM should be appraised in the same manner.

- The sponsor stated that the absence of an indirect treatment comparison in the risperidone ISM review has been disproportionately emphasized, especially when contrasted with the review of Perseris, another risperidone formulation, in which similar limitations did not hinder a positive recommendation.
- The sponsor stated that prescribing realities of treatment should not negatively impact a recommendation, given that many patients will be eligible for a dose of risperidone ISM 75 mg or 100 mg (corresponding to 3 mg and 4 mg of oral risperidone, respectively). The sponsor added that the dosing range of risperidone ISM has been disproportionately emphasized in the CDA-AMC review, despite precedent from the review of Perseris, in which similar constraints were not considered a limitation.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 1 clinical specialist with expertise in diagnosing and treating patients with schizophrenia
- feedback on the draft recommendation from 1 patient group: IAM
- feedback on the draft recommendation from 1 clinician group: CCEIP
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process
- feedback on the draft recommendation from the sponsor.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Initial Meeting Date: September 24, 2025

Members of the committee: Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: Two expert committee members did not attend.

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.

Reconsideration Meeting Date: November 26, 2025

Members of the committee: Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia

McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Carla Velastegui, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: Two expert committee members did not attend.

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.