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Reimbursement Recommendation

Risperidone (Longavo)

Indication: For the treatment of schizophrenia in adults
Sponsor: Teva Canada Innovation
Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Longavo?

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

Which Patients Are Eligible for Coverage?

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

What Are the Conditions for Reimbursement?

Longavo should only be reimbursed when prescribed by clinicians experienced in using long-acting injectable (LAI) atypical antipsychotic drugs to treat adult patients with schizophrenia. Reimbursement for Longavo should follow the same criteria that each public drug plan uses for other LAI atypical antipsychotic drugs approved for the condition. Longavo should only be reimbursed if the total cost does not exceed the drug program cost of treatment with the least costly LAI atypical antipsychotic drugs for the treatment of schizophrenia.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Longavo improved the time to impending relapse compared with placebo.
- Longavo addresses some needs identified by patients, such as fewer injections and clinic visits, and some people may find it more convenient because it is injected under the skin (i.e., subcutaneous injection).
- Based on the CDA-AMC assessment of the health economic evidence, Longavo does not 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 Longavo compared with the least costly LAI antipsychotic reimbursed for the treatment of schizophrenia.
- Based on public list prices, Longavo is estimated to be cost-saving to the public drug plans by approximately $11.7 million over the next 3 years. However, whether there will be cost savings realized by the drug plans, and the extent of any savings, is highly uncertain.

Additional Information

What Is Schizophrenia?

Schizophrenia is a severe, chronic psychiatric disorder that may vary in presentation, course, treatment response, and outcome. Symptoms of

Summary

schizophrenia may include hallucinations, delusions, cognitive impairment, and disorganized thoughts (which are categorized as positive symptoms), as well as social withdrawal and lack of motivation (which are categorized as negative symptoms). In 2016, the incidence of schizophrenia in Canada was estimated to be 49 per 100,000 people, with 58 per 100,000 males and 41 per 100,000 females.

Unmet Needs in Schizophrenia

Although there are many antipsychotic medications available to treat schizophrenia, there is still a need for treatments that minimize the negative and cognitive symptoms of schizophrenia, provide an additional option for those who do not experience a response to existing treatments, are administered less often, and have fewer side effects.

How Much Does Longavo Cost?

Treatment with monthly Longavo is expected to cost approximately $5,930 per patient annually, with an annual administration cost of $51.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that monthly risperidone extended release (ER) by subcutaneous (SC) injection be reimbursed for the treatment of adult patients with schizophrenia, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multicentre, randomized, double-blind, placebo-controlled study (the RISE study, N = 544) demonstrated that treatment with risperidone ER, given monthly by subcutaneous injection (SC) for maintenance therapy for patients who are stabilized on oral risperidone, resulted in added clinical benefit compared with placebo for patients with schizophrenia aged 13 to 65 years. The primary outcome, time to impending relapse, improved statistically significantly with monthly SC risperidone ER compared with placebo. The proportion of patients meeting the criteria for impending relapse was lower in the monthly SC risperidone ER group compared with the placebo group (7% versus 29%, respectively), with a hazard ratio (HR) for relapse of 0.200 (95% confidence interval [CI], 0.109 to 0.367; $P < 0.0001$). Monthly SC risperidone ER also demonstrated a statistically significant improvement over placebo in the secondary outcomes of impending relapse rate at week 24 (7% versus 28%, respectively; $P < 0.0001$) and percentage of patients who maintained stability at end point (87% versus 61%, respectively; $P < 0.0001$). In the absence of direct evidence assessing the comparative efficacy and safety of risperidone ER compared to other active treatment options, the sponsor submitted a network meta-analysis (NMA) indirectly comparing long-acting injectable (LAI) antipsychotics. Results from the NMA suggested that relapse rates at 6 months, as well as change in personal and social performance, were similar with SC risperidone ER compared with other atypical LAI antipsychotics used in Canada.

Patient group input identified a need for treatments that are simple, convenient, and affordable, and which reduce symptoms, promote the highest level of daily functioning, have minimal adverse events (AEs), improve adherence, and suit their unique needs. CDEC concluded that monthly SC risperidone ER met some of the needs identified by patients, including less frequent administration and office visits and an SC formulation, which may be more convenient for some patients.

At the sponsor-submitted price for risperidone ER and publicly listed prices for other LAI antipsychotics and oral risperidone, risperidone ER was similar in cost to LAI aripiprazole, within the range of costs for various doses of LAI risperidone and LAI paliperidone, and more costly than oral risperidone. As risperidone ER is considered similarly effective compared to other LAI antipsychotics, the total drug cost of risperidone ER should not exceed the total drug cost of other LAI antipsychotics.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of monthly SC risperidone ER 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 is insufficient or no evidence that monthly SC risperidone ER should be treated differently than other long-acting injectable atypical antipsychotic drugs for the treatment of adults with schizophrenia.	—
Prescribing		
2. Monthly SC risperidone ER should be prescribed by clinicians with expertise in managing LAI antipsychotics in patients with schizophrenia.	This ensures that monthly SC risperidone ER is prescribed for appropriate patients and that adverse effects are managed optimally and in a timely manner.	CDEC recommended aligning the prescribing condition of monthly SC risperidone ER with those used by each of the public drug plans for other LAI atypical antipsychotics for the treatment of adults with schizophrenia.
3. Monthly SC risperidone ER should not be used in combination with other LAI antipsychotics.	The RISE trial did not combine monthly SC risperidone ER with other LAI antipsychotics, and CDEC did not review any evidence regarding the efficacy and safety of monthly SC risperidone ER when combined with other LAI antipsychotics.	—
Pricing		
4. Risperidone ER should be negotiated so that it does not exceed the drug program cost of treatment with the least costly LAI antipsychotic reimbursed for the treatment of schizophrenia.	Results of the sponsor-submitted indirect treatment comparisons indicate that risperidone ER will have similar clinical benefits compared to other LAI antipsychotics. As such, there is insufficient evidence to justify a cost premium for risperidone ER over the least expensive LAI antipsychotic reimbursed for the treatment of schizophrenia.	—
Feasibility of adoption		
5. The feasibility of adoption of risperidone ER must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—

CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; ER = extended release; LAI = long-acting injectable; SC = subcutaneous.

Discussion Points

- **Unmet needs:** CDEC discussed the patient-identified unmet needs, acknowledging that symptoms have a significant impact on day-to-day functioning. CDEC also noted the clinical expert input that patients may experience different responses to treatment for reasons that are not yet clear. CDEC noted that other formulations of risperidone are currently approved in Canada, including tablets for once-daily oral administration and an LAI formulation for intramuscular (IM) administration every 2 weeks. The committee determined that monthly SC risperidone ER demonstrates the known efficacy and safety profile of other risperidone formulations, offers the convenience of less frequent administration, and provides an additional maintenance therapy option for patients with schizophrenia. CDEC noted that another LAI monthly SC risperidone ER (Perseris) was recommended for reimbursement with conditions in September 2021; however, pan-Canadian Pharmaceutical Alliance (pCPA) negotiations were concluded without a listing agreement and risperidone ER (Perseris) has since been cancelled postmarket.
- **Health-related quality of life:** CDEC noted that health-related quality of life (HRQoL) was an important outcome identified by the patient group. However, in the RISE study, HRQoL was assessed as an exploratory outcome only. Therefore, CDEC concluded that while monthly SC risperidone ER may offer convenience to some patients compared to other existing LAI treatments for schizophrenia (such as IM treatments that require office visits, and/or oral therapies), there is insufficient evidence for a definitive conclusion regarding the impact of this new formulation of risperidone on patients' HRQoL.
- **Indirect evidence:** CDEC noted that evidence from the NMA submitted by the sponsor for the treatment of schizophrenia was limited by the heterogeneity in patient populations across the included studies and by the uncertainty in the indirect estimates of effect. While acknowledging these limitations, CDEC discussed the consistency of the results with the clinical expert's suggestion that monthly SC risperidone ER is likely to be similar in effect to maintenance treatment for schizophrenia with other LAI options.
- **Economic considerations:** There is uncertainty about the displacement that monthly SC risperidone ER may have on other antipsychotics, including oral therapy. The sponsor noted that LAI atypical or second-generation antipsychotics are underused in Canada due to limitations related to complex initiation regimens; preparation steps, such as reconstitution; the mode of administration; and limited dosing, administration, and injection site flexibility. Additionally, the sponsor noted that some Canadian jurisdictions limit the reimbursement of LAI atypical antipsychotics to patients with adherence issues or who have not experienced a response to, or have intolerances or contraindications to, other antipsychotic options. The sponsor further stated that monthly SC risperidone ER was designed to facilitate acceptance of LAIs, improve adherence, and ease the transition from oral to LAI therapy. Clinical expert feedback noted that monthly SC risperidone ER is intended to — and likely will — displace the use of some oral antipsychotic drugs currently reimbursed in Canada, particularly oral risperidone. However, no evidence was provided comparing the efficacy and safety of risperidone ER to oral risperidone (or other oral atypical antipsychotics).

- **Budget impact considerations:** Due to the uncertainty associated with the comparative clinical efficacy assumptions, whether risperidone ER would increase LAI market size and/or displace some use of oral risperidone, and the confidential negotiated prices of comparator products, the overall budget impact of reimbursing monthly SC risperidone ER for the treatment of schizophrenia in adults is uncertain at the submitted price.

Background

Schizophrenia is a severe, chronic, and disabling psychiatric syndrome, which represents a heterogeneous group of disorders that may differentially affect presentation, course, treatment response, and outcome. The positive symptoms reflect a distortion or abundance of normal functioning (e.g., delusion, conceptual disorganization, hallucinatory behaviour); the negative symptoms reflect a loss or restriction of normal functioning (e.g., blunted affect, emotional withdrawal, poor rapport). Patients with schizophrenia are at an increased risk for suicide, substance use, homelessness, and unemployment. The prevalence of schizophrenia in Canada was estimated to be approximately 0.95% of the population in 2016, with 1.08% for males and 0.82% for females. The incidence of schizophrenia in Canada was estimated to be approximately 49 per 100,000 in 2016, with 58 per 100,000 males and 41 per 100,000 females.

Antipsychotic medications form the cornerstone of treatment for schizophrenia, as they target the characteristic symptoms of schizophrenia. The underlying principles for the administration of pharmacotherapy include the individualization of medication (including patient preferences); simple medication regimens; appropriate dosing; attention to side effect profiles; regular evaluation of responses (including AEs); and short-term and long-term clinical efficacy, safety, and tolerability. One major obstacle to the effective treatment of schizophrenia is nonadherence to medication, resulting in cycles of relapse. Studies have found that continuing treatment with LAI antipsychotic preparations in clinical practice outperforms oral antipsychotic medication in preventing rehospitalization.

Health Canada issued a Notice of Compliance for risperidone ER on June 18, 2025, for the treatment of schizophrenia in adults. It is available as a prefilled syringe (50 mg, 75 mg, 100 mg, and 125 mg) given once monthly.

Sources of Information Used by the Committee

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

- a review of 2 phase III, multicentre, randomized, double-blind clinical studies in adult and adolescent patients with schizophrenia (1 study was placebo-controlled and 1 study had a parallel-group design)
- patients' perspectives gathered by a patient group (the Institute for Advancements in Mental Health [IAM]) from a previous CADTH review on risperidone ER for the same indication
- input from public drug plans that participate in the reimbursement review process

- input from 1 clinical specialist with expertise diagnosing and treating patients with schizophrenia
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

No patient input was received for this review. Patient input received for a previous CADTH review (from November 2021) on risperidone for ER injectable suspension for the same indication is reported here.

Patient group input was provided by IAM and was obtained based on IAM's 40-year history of serving adults with schizophrenia. Its submission also drew 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%), caregiver (50%), family member or friend of someone diagnosed (63%), or working in social services (18%).

Respondents indicated that many patients experience symptoms of psychosis, which has a significant impact on day-to-day functioning. Patient experiences vary widely but typically involve some level 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 support. This symptom can cause significant strain in relationships, including those with caregivers and family members, ultimately leading to social isolation and a lack of support for the individual with the illness.

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

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

The clinical expert noted that there are many aspects of schizophrenia treatment that constitute an unmet need. These include the 15% to 20% of patients whose disease does not respond to currently available treatments, and patients whose disease becomes refractory to current treatment options. Furthermore, no treatments are available that reverse the course of disease or improve negative or cognitive symptoms,

which are correlated with poor functional outcomes. The clinical expert highlighted the need for better tolerated treatments, noting the significant side effects (including but not limited to sedation, weight gain and metabolic dysfunction, sexual side effects, motor side effects, and cognition- and motivation-related problems). The clinical expert noted the need for treatments that improve adherence, including more convenient formulations, noting that many patients forget to take their oral medications.

The clinical expert noted that risperidone LAI is not unique versus other LAI antipsychotics in reducing positive symptoms of schizophrenia, and that it does not have a unique mechanism of action. Therefore, the clinical expert suggested that risperidone LAI would be used similarly to other LAI antipsychotics, often in the first-line or second-line setting.

The clinical expert suggested that all adult patients with schizophrenia would be suitable for treatment with risperidone LAI and that it should be prescribed in a manner similar to that of other LAI antipsychotics for schizophrenia.

The clinical expert noted that a 20% reduction in standard rating scales is usually considered adequate for a response; however, it was noted that most clinicians do not use standardized measures when assessing patients. Once symptoms have stabilized, the clinical expert suggested that relapse prevention is a key goal and noted that there is less variability in what constitutes a clinical relapse.

The clinical expert suggested that response should be assessed every 3 months initially, and then yearly or at key decision points thereafter.

The clinical expert noted that a lack of efficacy in treating symptoms of psychosis, or intolerable side effects including neurologic, metabolic, or sexual side effects that do not respond to corrective treatment strategies, would result in discontinuation of treatment. Prolonged stability can suggest dose reduction and, in rare cases, discontinuation as an option.

The clinical expert suggested that it is appropriate for clinicians with experience in prescribing LAI antipsychotics for schizophrenia to prescribe risperidone LAI, noting that it should not require another specialist. The clinical expert highlighted that treating psychosis early is paramount and that all clinicians with experience in prescribing LAI antipsychotics for schizophrenia should be able to prescribe risperidone LAI without the supervision of another specialist, to ensure wide access to all medication options.

The clinical expert highlighted that increasing the number of treatment and formulation options available to patients is beneficial. The clinical expert noted that LAI antipsychotics have been shown to be superior to oral antipsychotics in relapse prevention. However, they are painful to receive, as all of them are deep IM injections. The clinical expert highlighted that longer-term LAI formulations are not available for risperidone, reducing options for patients who have been stabilized on oral risperidone. A formulation that eliminates or reduces these barriers would be helpful.

Clinician Group Input

No clinician group input was received for this review.

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 ER:

- considerations for initiation 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
Considerations for initiation of therapy	
Other LAI antipsychotics that are currently listed vary with regard to covered indications under the public drug plans. Some specifically state that they are covered for schizophrenia, plus or minus related psychotic disorders, and others do not specify the diagnosis needed for coverage. The sponsor's request is for this drug to be covered for adult patients with schizophrenia. As alluded to in the submission, this requires that the patient meet the diagnostic criteria for schizophrenia, as detailed in the DSM-5. A diagnosis requires that the patient has continuous signs over a period of at least 6 months. • Would consideration be given to patients who have a probable diagnosis of schizophrenia, or would it require a definite diagnosis? • In the case of requiring a definite diagnosis, would the recommendation provide implementation guidance specifying a 6-month minimum duration of symptoms or refer to the DSM-5 criteria? • Should patients with other related psychotic disorders be eligible for coverage? Related psychotic disorders could include schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-induced psychotic disorder, and others, as per the DSM-5. Should patients with a diagnosis of bipolar disorder with psychotic features be eligible for this drug?	The clinical expert and CDEC agreed that many patients present with schizophrenia spectrum disorders, and it would therefore be beneficial to be able to prescribe to patients with schizophrenia spectrum disorders, including patients with a probable diagnosis. The clinical expert suggested that patients with brief psychotic disorder, substance-induced psychotic disorder, and bipolar disorder would be unlikely to be prescribed risperidone. CDEC noted that because patients with schizophrenia are required to be stabilized on a stable dose of oral antipsychotics before being considered for any LAI antipsychotic, it is implied that a confirmed diagnosis of schizophrenia would be made before switching from an oral formulation to an LAI formulation.
It is the sponsor's intent that this drug be available for first-line use; however, this would misalign with other LAI criteria in various jurisdictions that require nonadherence to oral agents. Should nonadherence or intolerance to other antipsychotic medications be an eligibility requirement?	The clinical expert highlighted that it is generally a treatment goal to have patients that can tolerate LAI transition onto using LAIs given the benefits of LAI drugs versus oral therapies. Therefore, the clinical expert and CDEC did not support the requirement of nonadherence or intolerance before a patient could receive LAI risperidone.

Implementation issues	Response
	CDEC noted no evidence suggesting that monthly SC risperidone ER should be held to a different standard than other LAI drugs for the treatment of adults with schizophrenia. Therefore, monthly SC risperidone ER should be reimbursed based on similar criteria used by each of the public drug plans for other LAI atypical antipsychotics for the treatment of adults with schizophrenia.
Listing criteria should be similar to that of Risperdal Consta, Invega Sustenna, Invega Trinza, and Abilify Maintena.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
Dosing is to be done monthly or every second month. If there is relapse or inadequate symptom control with monthly dosing, would you expect that the dose frequency be increased (to every 3 weeks, for example)?	The clinical expert and CDEC noted that there is no evidence to support increasing the frequency of dosing beyond the once-monthly regimen. CDEC noted that the Health Canada indication is for monthly injection, which was the only dosing interval evaluated in the CDA-AMC review. Therefore, evidence regarding more frequent injections or injections every second month was not reviewed.
The sponsor noted that the dosing corresponds to "the full range for maintenance treatment, as per oral risperidone product monograph." Despite this, doses above 5 mg daily are seen in real-world practice, with 1 reputable reference noting a maximum dose of 10 mg daily (8 mg maximum per single dose). It is unclear if patients who require more than 5 mg oral daily will be eligible for this LAI treatment.	The clinical expert and CDEC noted that this is a small population of patients who may require more than 5 mg daily oral risperidone, further noting the lack of evidence available to determine the benefit in these cases. CDEC acknowledged the clinical expert's input.
In the case that they do receive the LAI treatment, despite a maintenance oral risperidone dose > 5 mg daily, would it be expected that the dose be supplemented with oral risperidone?	While noting the difficulty of determining the appropriate management in this case, the clinical expert suggested that they would supplement the patient with oral risperidone and then attempt to reduce the dose over time to a point where the patient was treated with the LAI therapy only. CDEC acknowledged the clinical expert's input.
The RISE trial included patients stabilized on oral risperidone for 12 weeks before switching to the new LAI formulation. Can the clinical expert comment on the appropriate duration of oral risperidone use for establishing tolerability?	The clinical expert noted that, in the real-world setting, 4 to 8 weeks is an adequate time period to determine whether the patient will tolerate the treatment. CDEC acknowledged the clinical expert's input, noting that, per RISE protocol, the oral conversion and stabilization stage of study (stage 1) was a total of 12 weeks. Patients had to be stabilized for 4 consecutive weeks.
Although the study drug comes in a prefilled SC syringe, it does still require administration by a health care provider, as preparation for injection involves some professional skills. For example, it is a viscous solution that requires forceful motions when prepping the injection, and also creates resistance during the injection administration. It is important to consider ease of access to health care professionals when determining eligibility for this medication.	This is a comment from the drug programs to inform CDEC deliberations. CDEC acknowledged the drug program input, noting that pharmacists, among many health care professionals, could administer this drug, so access to professionals to administer the drug should not be a limiting factor.
It is not uncommon to see various combinations of antipsychotic medications being used to treat patients. Would there be eligibility for the study drug in combination	The clinical expert and CDEC suggested that questions regarding the use of risperidone LAI in combination with other drugs should

Implementation issues	Response
with other drugs? If yes, would there be limitations to the combination drugs, such as yes for oral therapies but no for other LAI therapies?	be handled in a similar manner as other LAI drugs. CDEC agreed with the clinical expert's input.
Care provision issues	
This medication requires administration by a health care provider, and it also requires refrigeration 30 minutes before administration.	This is a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
The 150 mg, 200 mg, and 250 mg PFS are double the price of the lower strengths; however, these 3 doses are only intended to be administered every 2 months, making them the same overall price as the lower strengths that are administered every month. Of note, the 100 mg PFS can also be dosed every 2 months (in lieu of 50 mg monthly), making the price of dosing 100 mg every 2 months half that of the 50 mg monthly dose. The sponsor noted that the expected bimonthly use of the 100 mg dose is approximately 1%, so they only considered 100 mg monthly dosing for the purposes of their BIA. Comparably, the price of Consta increases with increased dose, despite frequency being maintained at every 2 weeks. In the sponsor's BIA, they expected that their LAI drug would displace market share differently in each province based on current usage of comparator treatments. (Note that Risperdal Consta is not a benefit in NT, and the 12.5 mg dose is not a benefit in AB.) When comparing costs of the comparators (Risperdal Consta, Invega Sustenna, Invega Trinza, and Abilify Maintena), the sponsor used dosing as recommended in each product monograph; however, in the real world, there are patients who require increased dosing or increased frequency of dosing, and these aren't accounted for in the analysis. The sponsor anticipates a cumulative cost-savings of $14,523,251 over 3 years.	This is a comment from the drug programs to inform CDEC deliberations. CDEC noted that the Health Canada indication is for a monthly injection, which was the only dosing interval evaluated in the CDA-AMC review. Therefore, evidence regarding more frequent injections or injections every second month was not reviewed.
Confidential pricing agreements are likely for Risperdal Consta, and they exist for Invega Sustenna, Invega Trinza, and Abilify Maintena. Therefore, it is difficult to directly compare the overall costs of using these previously listed options with the new risperidone LAI.	This is a comment from the drug programs to inform CDEC deliberations.

BIA = budget impact analysis; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ER = extended release; LAI = long-acting injectable; PFS = progression-free survival; SC = subcutaneous.

Clinical Evidence

Systematic Review

Description of Studies

The RISE study (Study TV46000-CNS-30072) was a phase III, multicentre, randomized, double-blind, placebo-controlled, relapse prevention study of TV-46000 for schizophrenia in adults and adolescents. The objective was to assess the efficacy, safety, and tolerability of 2 dose regimens of TV-46000 (risperidone ER injectable suspension [Longavo]) given subcutaneously versus placebo as maintenance therapy for patients with schizophrenia (544 patients were randomized, 181 to placebo, 183 to the risperidone ER once-monthly group, and 180 to the risperidone ER bimonthly group).

The SHINE study (Study TV46000-CNS-30078) was a phase III, multicentre, randomized, double-blind, parallel-group study to evaluate the long-term safety, tolerability, and effectiveness of TV-46000 administered once a month or once every 2 months at doses of 50 mg to 250 mg SC (comparable to 2 mg/day to 5 mg/day of oral risperidone) for up to 56 weeks in adult and adolescent patients with schizophrenia (n = 334 patients who were randomized and treated). For new patients (who did not participate in the RISE study), the SHINE study consisted of a screening period (up to 4 weeks), a conversion and stabilization stage (12 weeks on oral risperidone, stage 1), a double-blind, active-treatment maintenance stage (up to 56 weeks, stage 2), and a follow-up period (8 weeks).

The primary outcome for the RISE study was time to impending relapse, while the primary end point for the SHINE study was frequency of AEs. In the RISE study, baseline patient characteristics and demographics were generally well balanced across treatment groups. The mean age was approximately 49 years, 39% of patients were female, and 61% of patients were male. On average, patients in each group had schizophrenia for approximately 20 years, and the mean time since last relapse was approximately 10 months. In the SHINE study, the mean age was 50.6 years, 64% of patients were male, and 36% were female, and the mean length of disease was 21.1 years, with a mean of 21 months since last relapse. Only 3 adolescents were randomized and received at least 1 dose of TV-46000 in the study.

Efficacy Results (the RISE Study)

To align with the Health Canada–approved indication, only the findings regarding once-monthly dosing of risperidone ER are reported in this CDA-AMC review.

Time to Impending Relapse

The number of patients in the placebo group with impending relapse was 53 (29%), and the number of patients in the TV-46000 once-monthly group was 13 (7%), with an HR of 0.200 (95% CI, 0.109 to 0.367; P < 0.0001).

Impending Relapse Rate at Week 24

In the placebo group, the impending relapse rate at week 24 was 0.28 (95% CI, 0.205 to 0.347). The impending relapse rate at week 24 in the TV-46000 once-monthly group was 0.07 (95% CI, 0.03 to 0.109, P < 0.0001).

Percentage of Patients Who Maintain Stability at End Point

The number of patients in the placebo group who maintained stability at the end point was 110 (61%). The number of patients in the TV-46000 once-monthly group was 159 (87%; P < 0.0001).

Percentage of Patients Achieving Remission at End Point

The percentage of patients in the placebo group who achieved remission at the end point was 23%, while remission was achieved at the end point in 29% of patients in the TV-46000 once-monthly group.

Drug Attitudes Inventory 10-Item Version

In the placebo group, the least squares (LS) mean change from baseline in Drug Attitudes Inventory 10-Item Version (DAI-10) total score at early termination (ET) was −0.55 (standard error [SE] = 0.38), and at end of treatment (EoT) was −0.59 (SE = 0.31). In the TV-46000 once-monthly group, it was 0.25 (SE = 0.42) at ET and 0.57 (SE = 0.28) at EoT.

Schizophrenia Quality of Life Scale

In the placebo group, the LS mean change from baseline in Schizophrenia Quality of Life Scale (SQLS) total score at ET was 3.20 (SE = 1.58), and at EoT was 1.14 (SE = 1.32). In the TV-46000 once-monthly group, at ET it was −3.99 (SE = 1.74) and at EoT it was −5.40 (SE = 1.12).

Harms Results (RISE and SHINE Studies)

The most commonly reported AE was injection site pain, reported by 5% of patients in the TV-46000 once-monthly group and 6% of those in the placebo group. Injection side nodules were also commonly reported (6% in the TV-46000 once-monthly group and 3% in the placebo group). Serious adverse events (SAEs) were reported by 4% of individuals in the TV-46000 once-monthly group and 8% in the placebo group. AEs leading to treatment discontinuation were reported by 11% of patients in the TV-46000 once-monthly group and 11% in the placebo group.

Critical Appraisal

The RISE and SHINE studies were phase III studies, with the RISE study being a randomized, double-blind, placebo-controlled study and the SHINE study being a phase III, randomized, parallel-group study allowing carry-over enrolment from the RISE study. Limitations included the high number of protocol deviations, although the sponsor did note that, in response to a request from the FDA regarding the protocol deviations, sensitivity analyses were conducted that indicated the original results were robust. The primary end point of time to impending relapse was met for once-monthly dosing group in comparison to placebo, as well as several secondary end points. However, due to the hierarchal statistical testing in place to reduce the risk of type I error, important outcomes like HRQoL were not statistically tested, and thus no conclusions can be drawn with regard to the effect of once-monthly risperidone ER on HRQoL.

According to the clinical expert consulted, the patient population of the RISE and SHINE studies appeared to be sufficiently similar to the expected patient population in Canada; therefore, results should be generalizable to the population in Canada. The RISE and SHINE studies were conducted with patients who were stabilized on oral risperidone. While the clinical expert did not expect this to differ from the expected

usage of risperidone ER, this is nevertheless a more restricted population than the indication, and thus the generalizability of the study results to the broader indication is uncertain.

Indirect Comparisons

Description of Studies

A systematic literature review (SLR) and 2 NMAs (1 for efficacy and 1 for safety) were conducted to synthesize relevant literature and compare the efficacy and safety of TV-46000 administered once a month or once every 2 months with atypical LAI therapies approved in Canada and used for the maintenance treatment of schizophrenia. A total of 6 studies (including the RISE study) were eligible for inclusion in the NMA. Efficacy outcomes were relapse rate, time to relapse, and change in Personal Social Performance (PSP). These outcomes were reported in 5 of the relevant studies captured and included all interventions of interest within the network. Safety outcomes were AE-related discontinuation, significant weight gain, treatment-related AEs, and injection site pain. AE-related discontinuation and significant weight gain were reported in all included studies. Treatment-related AEs and injection site pain were reported in 4 and 5 of the relevant studies, respectively. Relative risk (RR) was used for the dichotomous outcome NMAs including relapse rate at 6 months, AE-related discontinuation, significant weight gain, treatment-related AEs, and injection site pain. HRs were used for the survival data NMA of time to relapse. Lastly, the mean difference was used for the continuous outcome NMA of change from baseline in PSP score.

Efficacy Results

Relapse Rate at 6 Months

For this outcome, all active treatments (i.e., once-monthly TV-46000, aripiprazole, paliperidone palmitate 1-month [PP1M] 25 mg to 100 mg equivalent [EQ], paliperidone palmitate 3-month [PP3M], and PP1M 50 mg to 150 mg EQ) were comparable, and were significantly better than placebo.

Time to Relapse

For this outcome, all active treatments (i.e., once-monthly TV-46000, aripiprazole, PP1M 25 mg to 100 mg EQ, PP3M, and PP1M 50 mg to 150 mg EQ) were significantly better than placebo.

Change in Personal and Social Performance

For this outcome, all active treatments (i.e., once-monthly TV-46000, aripiprazole, PP1M 25 mg to 100 mg EQ, PP3M, and PP1M 50 mg to 150 mg EQ) were comparable, and were significantly better than placebo.

Harms Results

AE-Related Discontinuation

For this outcome, once-monthly TV-46000 was comparable to PP1M and placebo.

Significant Weight Gain

For this outcome, once-monthly TV-46000 and PP1M 25 mg to 100 mg EQ were comparable to placebo and significantly better than both PP3M and PP1M 50 mg to 150 mg EQ.

Treatment-Related AEs

For this outcome, PP1M 25 mg to 100 mg EQ and once-monthly TV-46000 were comparable to placebo. PP1M 25 mg to 100 mg EQ, once-monthly TV-46000, and placebo were significantly better than PP3M and PP1M 50 mg to 150 mg EQ. PP1M 25 to 100 mg EQ and placebo were significantly better than PP1M 50 mg to 150 mg EQ.

Injection Site Pain

For this outcome, all active treatments (once-monthly TV-46000, aripiprazole, PP3M, and PP1M) were comparable to placebo. Aripiprazole was significantly better than PP3M and PP1M.

Critical Appraisal

The sponsor-submitted indirect treatment comparison (ITC) was conducted from a well-described and appropriate SLR. The comparators in the included studies were appropriate to inform decision-making in the Canadian context. The outcomes included were appropriate, with the exception of HRQoL, which was excluded for data availability reasons. The studies included were similar in baseline characteristics, with the main differences being that the RISE study had both an older population on average and a slightly higher Positive and Negative Syndrome Scale (PANSS) score. However, the direction of bias introduced from these differences is unknown. Further uncertainty resulted from the unknown differences in censoring methodology among the studies and the impact of these differences on the proportional hazard assumption.

Economic Evidence

Cost and Cost-Effectiveness

The sponsor submitted a cost comparison for monthly risperidone ER (Longavo) compared with other LAI antipsychotics approved for the treatment of adults with schizophrenia, including biweekly risperidone (Risperdal Consta), another monthly risperidone ER (Perseris), monthly aripiprazole (Abilify Maintena), and monthly and trimonthly paliperidone (Invega Sustenna and Invega Trinza, respectively).

At the submitted price of $456.18 for the 50 mg, 75 mg, 100 mg, and 125 mg monthly doses, the annual drug cost of risperidone ER is $5,930 per patient, with an annual administration cost of $51. Annual drug costs for the injectable comparators ranged from $2,394 to $9,939, with annual administration costs ranging from $17 to $101. The incremental cost of monthly risperidone ER ranged from a savings of $4,060 annually to an additional cost of $3,486 annually, per patient, compared to risperidone 50 mg and 12.5 mg biweekly, respectively.

The sponsor's cost comparison was associated with limitations, including uncertainty in the assumption of clinical similarity between comparators and the exclusion of oral risperidone tablets as a comparator. The annual cost of risperidone ER is $5,486 to $5,634 more expensive than that of risperidone tablets ($297 to $444 per patient) when not considering administration costs, or $5,537 to $5,685 per patient per year more expensive when administration costs are included. All incremental costs or savings are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Budget Impact

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

- There is uncertainty with the claims-based approach and the assumption that the market shares and doses of LAI treatments used for schizophrenia can be represented by the market shares and doses used for all LAI indications.
- The Health Canada product monograph indication only includes the monthly regimen.
- There is uncertainty that risperidone ER will only displace other LAI treatments.
- There are confidential pricing agreements for the comparators.

CDA-AMC conducted a base-case reanalysis removing risperidone ER uptake associated with bimonthly dosing regimens. The CDA-AMC base case suggests that the reimbursement of monthly risperidone ER for the treatment of adult patients with schizophrenia would be associated with an incremental savings of $2,467,801 in year 1, $3,813,961 in year 2, and $5,482,072 in year 3, for a 3-year budgetary savings of $11,763,833.

CDA-AMC also conducted scenario analyses exploring the impact of assuming that the funding of risperidone ER would increase the LAI market size and displace some use of oral risperidone and assuming comparator products are less expensive than their list prices. Under these assumptions, the budgetary savings associated with the reimbursement of risperidone ER are reduced compared to the sponsor's base case, or result in incremental costs to jurisdictional drug plans (3-year total range, savings of $6,200,264 to an incremental cost of $41,915,711).

CDEC Information

Members of the Committee

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

Meeting date: June 25, 2025

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