5.06 RISPERIDONE, Subcutaneous injection (modified release) 50 mg in 0.14 mL pre-filled syringe, Subcutaneous injection (modified release) 75 mg in 0.21 mL pre-filled syringe, Subcutaneous injection (modified release) 100 mg in 0.28 mL pre-filled syringe, Subcutaneous injection (modified release) 125 mg in 0.35 mL pre-filled syringe, Uzedy®, Teva Pharma Australia Pty Ltd

1 Purpose of Application

1.1 The Category 2 submission requested the General Schedule (section 85) Authority Required (Streamlined) listing of risperidone modified release subcutaneous (MRSC) injection (Uzedy®) for the treatment of adult patients with schizophrenia.

1.2 The submission presented a cost-minimisation approach and nominated paliperidone 1-monthly intramuscular (IM) long-acting injection (LAI, PP1M) and aripiprazole 1-monthly IM LAI (A1M) as primary comparators, and risperidone 2-weekly IM LAI (R2WIM) and risperidone 4-weekly in-situ microparticles (ISM) IM LAI (R4WIM) as secondary comparators.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adult patients with schizophrenia
Intervention	Risperidone extended-release suspension for injection, 50 mg, 75 mg, 100 mg, 125 mg
Comparator	**Primary**: PP1M and A1M **Secondary**: R2WIM and R4WIM
Outcomes	Time to impending relapse, relapse rate, change from baseline in positive and negative syndrome scale (PANSS) total score and adverse events.
Clinical claim	MRSC risperidone is non-inferior to PP1M and A1M. Indirectly via PP1M, RMSC risperidone is non-inferior to R2WIM and R4WIM.
Economic claim	MRSC risperidone is cost-minimised to the least expensive cost comparator (PP1M).
Financials	The listing is expected to be cost saving to the PBS and MBS.

Source: Table 1.1, p16 of the submission.
MRSC = modified release subcutaneous; PP1M = paliperidone 1-monthly injection; A1M = aripiprazole 1-monthly injection; R2WIM = risperidone 2-weekly intramuscular injection; R4WIM = risperidone 4-weekly intramuscular injection; PBS = Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Schedule.

2 Background

Registration status

2.1 MRSC risperidone was Therapeutic Goods Administration (TGA) registered on 18 February 2025 for the prevention of relapse of schizophrenia in adults, following stabilisation with oral risperidone. The submission noted that MRSC risperidone has also been registered in the US, Korea, Canada, and Brazil.

2.2 The TGA approved Product Information (PI) stated that after stabilisation with oral risperidone, no loading dose or supplementation with oral risperidone (oral bridging) is required to initiate treatment with MRSC risperidone.

Previous PBAC consideration

2.3 The PBAC considered and listed the IM LAI form of 4 drugs for the treatment of schizophrenia prior to this consideration: aripiprazole, olanzapine, paliperidone, and risperidone.

2.4 The PBAC had not considered MRSC risperidone or any subcutaneous (SC) LAI for the treatment of schizophrenia previously.

2.5 The PBAC considered risperidone most recently in March 2024 and recommended the listing of R4WIM 75 mg and 100 mg (Okedi®). Okedi was renamed to Risvan® prior to listing on 1 January 2025.

2.6 In its consideration of R4WIM, the PBAC considered that PP1M and R2WIM were appropriate comparators but noted that any of the following PBS listed antipsychotic LAIs are alternative therapies: R2WIM, paliperidone LAIs, and A1M (Paragraph 7.3, risperidone Public Summary Document [PSD], March 2024). The PBAC did not consider olanzapine LAI as an alternative therapy because post-injection syndrome requires monitoring after administration (Paragraph 7.3, Risperidone PSD, March 2024 PBAC Meeting).

2.7 The PBAC previously considered the equi-effective doses for R4WIM as:

- R4WIM 75 mg = R2WIM 37.5mg every 2 weeks
- R4WIM 75 mg = PP1M 75 mg
- R4WIM 100 mg = R2WIM 50 mg every 2 weeks
- R4WIM 100mg = PP1M 100 mg

2.8 The PBAC previously considered the equi-effective doses for A1M as:

- A1M 390 mg = PP1M 83 mg

(Paragraph 2.2, aripiprazole PSD, July 2025 PBAC Meeting)

2.9 The PBAC considered that the clinical need for R4WIM was low (Paragraph 7.2, Risperidone PSD, March 2024 PBAC Meeting) and recommended listing on a cost-minimisation basis to the lowest-cost alternative therapy (Paragraph 7.1, Risperidone PSD, March 2024 PBAC Meeting).

2.10 The PBAC has previously considered that prescribers would be unlikely to initiate patients on a LAI without prior oral treatment and therefore a listing for "schizophrenia" without specifying maintenance treatment is appropriate (Paragraph 3.2, Risperidone PSD, March 2024 PBAC Meeting). The PBAC also noted that R4WIM does not require oral bridging nor loading doses due to the ISM formulation, however, initiation of PP1M requires loading doses on day 1 and 8 in paliperidone naïve patients, and initiating R2WIM requires 3 weeks of oral bridging (Paragraph 4.4, 5.2 and 5.3, Risperidone PSD, March 2024 PBAC Meeting).

2.11 When the PBAC considered R4WIM for maintenance treatment (relapse prevention), it accepted the relevance of efficacy data from studies enrolling patients with acute schizophrenia on the basis that efficacy in acute psychosis supports efficacy for relapse prevention, which it considered consistent with usual practice and the clinical place of antipsychotics (Paragraph 6.10, 6.15, Risperidone PSD, March 2024 PBAC Meeting).

3 Requested listing

3.1 The submission requested a General Schedule (Section 85) Authority Required (STREAMLINED) listing for MRSC risperidone, supplied as a pre-filled syringe in four strengths (50 mg/0.14 mL, 75 mg/0.21 mL, 100 mg/0.28 mL, 125 mg/0.35 mL), for the treatment of schizophrenia in adults with a maximum quantity (1) and repeats (5) to permit up to 6 months' supply per prescription.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
RISPERIDONE					
Risperidone 50 mg/0.14 mL subcutaneous modified release injection prefilled syringe drug	Published: $[redacted] Effective: $[redacted]	1	1	5	Uzedy
Risperidone 75 mg/0.21 mL subcutaneous modified release injection prefilled syringe drug	Published: $[redacted] Effective: $[redacted]	1	1	5	Uzedy
Risperidone 100 mg/0.28 mL subcutaneous modified release injection prefilled syringe drug	Published: $[redacted] Effective: $[redacted]	1	1	5	Uzedy
Risperidone 125 mg/0.35 mL subcutaneous modified release injection prefilled syringe	Published: $[redacted] Effective: $[redacted]	1	1	5	Uzedy

Category / Program: General Schedule Section 85
Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Condition: Schizophrenia
Indication: Schizophrenia
Administrative Advice: For a patient switching from oral risperidone, the prescriber must determine the patient dosage of this drug based on the current dose of oral risperidone according to the dose transition table in the Therapeutic Goods Administration (TGA) approved Product Information.

SPA Criteria

3.2 The submission requested PBAC advice to demonstrate special pricing arrangement (SPA) eligibility should MRSC risperidone be recommended for listing. The submission requested a published list price that [redacted] and advised that a SPA would enable a lower, cost-effective effective price.

3.3 In support of SPA eligibility, the submission sought that the PBAC consider that at the very least, compared to placebo, MRSC risperidone generates substantial incremental benefit for the intended patient population, and that it, compared to any available alternative therapies, exhibits the following unique characteristics:

- **The subcutaneous administration route**: The submission stated that avoiding an IM injection using a longer and thicker needle is expected to significantly reduce pain and discomfort as well as allowing patients to be injected without the need to undress (all likely to improve adherence). The submission referenced 2022 survey data from Healthcare Providers (HCPs) and patients with direct experience which indicated high ease-of-use (89% of patients; 92% of providers), with 70% of patients reporting a better injection experience relative to their prior LAI and 65% of HCPs preferring SC over IM administration. The Pre-Sub-Committee Response (PSCR) added that the use of smaller 26–27G needles and avoidance of IM administration significantly reduce injection-related pain and discomfort, with therapeutic levels achieved within 6–24 hours, removing the need for oral supplementation or booster doses.

- **The monthly administration schedule**: The submission referenced R4WIM (28 days) and R2WIM (14 days) as alternative therapies that do not share the same dosing frequency. The ESC noted A1M and PP1M are administered monthly and were considered by the submission as alternative therapies to MRSC risperidone.
- **The employment of MedinCell's proprietary BEPO® technology, licensed to Teva as SteadyTeq**: The submission stated that this technology delivers risperidone over an extended period through a small, bioresorbable depot formed in situ via a solvent exchange mechanism. The submission claimed that MRSC risperidone pre-filled syringe is superior to other LAI antipsychotics due to its drug loading, release control, duration, and ready-to-use formulations that simplify administration processes and reduce the potential for preparation errors. The submission considered the reconstitution processes of other risperidone LAIs to be complex.

3.4 The ESC acknowledged the arguments provided by the submission and PSCR and agreed that MRSC risperidone was demonstrated to have a substantial incremental benefit versus placebo. The ESC noted the submission claimed non-inferior effectiveness compared to PP1M, A1M, R2WIM and R4WIM and non-inferior safety compared to PP1M and A1M. The ESC also noted the submission did not claim any significant improvement in efficacy nor reduction in toxicity over any of the alternative therapies yet has claimed substantial incremental benefit over these therapies due to the way in which MRSC risperidone is administered. The ESC considered advice on the relative benefit versus relevant comparators (PP1M, A1M, R2WIM and R4WIM) and agreed that MRSC risperidone has characteristics that were unique. Noting that SPA eligibility requires that the PBAC advises the medicine generates substantial incremental benefit for the intended patient population, the ESC advised that it is unclear whether the SPA criteria has been met.

Prior oral risperidone stabilisation

3.5 The ESC noted that absence of a prior oral risperidone stabilisation/tolerability criterion in the proposed restriction and noted this as a requirement of both the TGA PI and RISE study. The ESC agreed with the PBAC's previous consideration of R4WIM that it is unlikely prescribers would initiate a LAI without first initiating oral risperidone (Paragraph 3.2, Risperidone PSD, March 2024 PBAC Meeting) and therefore considered that specifying beyond simply "schizophrenia" is not required.

Oral-MRSC switching

3.6 The ESC noted the dose form switching administrative advice of the requested listing. The ESC considered it appropriate to align the MRSC restriction with that of A1M (PBS item codes 14790K and 14824F) and considered that explicit guidance on switching from oral to MRSC risperidone would be unnecessary.

Definition of schizophrenia

3.7 The ESC noted that 'schizophrenia' was not defined in the proposed restriction but was added by the Department to the restriction of all PBS listings for this indication to

reduce prescriber correspondence to Services Australia about patient eligibility under DSM-5 criteria. The ESC considered it appropriate to include this administrative advice in the MRSC risperidone restriction.

For more detail on PBAC's view, see section 7 PBAC outcome

4 Clinical place for the proposed therapy

4.1 Schizophrenia is a chronic disorder with profound effects on the quality of life of patients and their families, adverse effects on education and employment, and reduced life expectancy. The 2010 Survey of High Impact Psychosis (SHIP) estimated that, in Australia, over one year, 5 per 1000 individuals required treatment for psychotic illness, of whom about half had schizophrenia.[1]

4.2 Antipsychotic medications are the first-line treatment for psychosis due to schizophrenia. LAI forms of antipsychotics have been proposed to address problems of non-adherence and thereby improve outcomes. The benefit of LAI vs oral treatment in trials appears modest; a recent systematic review showed a 0.88 (0.79-0.99) pooled relative risk (95% CI) of hospitalisation or relapse across 29 randomised controlled trials with 7,833 patients.[2]

4.3 The technologies used to achieve the stable release of a drug differ across the various LAIs, including those with the same active ingredient. MRSC risperidone is suspended in a biodegradable co-polymer solution which solidifies after injection and releases the drug as the co-polymer degrades.

4.4 The submission proposed no change in the treatment algorithm. The submission considered MRSC risperidone would mainly displace R2WIM and R4WIM because patients who show initial response to a drug by reduction in acute psychotic symptoms typically continue maintenance treatment with the same drug but may also displace A1M and PP1M.

5 Comparator

5.1 The submission nominated PP1M and A1M as primary comparators, which the evaluation considered was appropriate. The PSCR agreed with the evaluation that the risperidone LAIs would also be appropriate comparators and considered that if the PBAC recommended MRSC risperidone as non-inferior to the nominated comparators, by extension it would also be considered non-inferior to the risperidone LAIs noting PBAC advice that risperidone, paliperidone and aripiprazole, but not olanzapine,

[1] Morgan V, Waterreus A, Saw S, et al. People living with psychotic illness in 2010: The second Australian national survey of psychosis. ANZ J Psych 2012; 46:735-752.

[2] Kishimoto T, Hagi K, Kurokawa S, et al. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre–post studies. *Lancet Psych* 2021; 8:387-404.

should be treated as interchangeable on an individual patient basis (Paragraphs 7.3 and 7.14, Risperidone PSD, March 2024 PBAC Meeting).

For more detail on PBAC's view, see section 7 PBAC outcome

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed Uzedy as a subcutaneous long-acting antipsychotic that was described as potentially more acceptable to some patients due to less invasive administration, and simpler administration compared with IM formulations, and a safety profile broadly consistent to oral therapy with more stable drug exposure than existing LAIs.

6.2 The clinician outlined the current LAI landscape, noting that established long-acting antipsychotics (e.g. risperidone, paliperidone PP1M, olanzapine LAI) are effective but are typically administered intramuscularly and may be perceived as more intrusive by some patients. Uzedy was presented as a novel subcutaneous LAI formulation that may be perceived as less intrusive than IM LAIs.

6.3 SC administration was described as less intrusive, potentially better tolerated, and aligned with established use of SC injectables in other therapeutic areas, with reduced clinic time due to a pre-filled formulation and no requirement for reconstitution. The clinician noted that while the product does not require a loading dose or oral bridging, initiation in practice would typically follow oral risperidone stabilisation, consistent with the TGA-approved PI.

6.4 The clinician expected initial administration to be clinician-led, and stated that home or self-administration may be feasible in motivated patients. The clinician noted that the main impediment to self-administration is patient willingness, and that LAIs are commonly used in patients on community treatment orders. The safety profile was described as comparable to oral formulations, with the clinician commenting that differences in metabolic effects between LAIs and oral therapy are generally minor.

Consumer inputs

6.5 The PBAC noted and welcomed the input from health care professionals (4) and organisations (1) via the Office of Health Technology Assessment Consultation Hub. The inputs described a range of perceived benefits with MRSC risperidone, noting that SC administration was considered less painful, less embarrassing, and less invasive than existing LAIs, with the potential to improve adherence, sustain treatment engagement, and increase overall patient acceptability.

6.6 The PBAC noted the joint advice received from Psychosis Australia and the Mental Illness fellowship of Australia clarifying the likely use of MRSC risperidone in clinical practice. Psychosis Australia advised that the use of MRSC risperidone may reduce the pain, stigma, and intrusion associated with treatment, which may improve treatment

adherence and patient engagement compared to the IM LAIs.

6.7 The PBAC agreed that the introduction of MRSC risperidone may support more consistent use of antipsychotic therapy for patients with schizophrenia. The PBAC considered that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.8 The submission relied on:

- Study 30072 (RISE) placebo-controlled randomised trial with MRSC risperidone
- Hough (2010) placebo-controlled randomised trial with PP1M
- Kane (2012, ASPIRE) placebo-controlled randomised trial with A1M
- A formal indirect treatment comparison (ITC) of MRSC risperidone vs PP1M and A1M via placebo

6.9 None of these studies were among those noted by the PBAC in its March 2024 consideration of R4WIM.

6.10 The submission identified trials for inclusion using a prespecified search strategy that required studies to include a stabilisation period, to enrol patients with a diagnosis of schizophrenia for at least one year, and to include patients with at least one episode of relapse in the preceding two years. All trials incorporated extended open-label conversion and stabilisation phases prior to randomisation, with eligibility criteria requiring patients to be clinically stable before entering the double-blind phase. Trials were further excluded if they did not study patients with schizophrenia during the maintenance phase, that is, once stabilised on an antipsychotic. Patients who withdrew due to lack of efficacy or adverse events during these preliminary phases were excluded from randomisation. The evaluation noted that these design features were likely to result in a selected trial population enriched for treatment-responsive and treatment-tolerant patients, potentially leading to overestimation of efficacy and underestimation of harms compared with routine clinical practice. The evaluation interpreted this as the submission implying that efficacy demonstrated in other clinical contexts (such as acute treatment) could not be assumed to translate to maintenance treatment.

6.11 The evaluation noted that the application of these criteria raised internal inconsistencies. While the search strategy sought to restrict inclusion to patients with a clear history of relapse, 43 of 408 patients (10.5%) in the Hough (2010) paliperidone trial had never been hospitalised for schizophrenia. The evaluation also observed that no rationale was provided to explain why the specified design features were considered sufficiently critical to preclude comparison with other risperidone LAI trials, or why those same considerations were not applied consistently across all included studies.

6.12 The evaluation further considered that the emphasis on maintenance-phase populations and specific stabilisation requirements implied a rejection of the PBAC's longstanding position that antipsychotic efficacy demonstrated in one clinical setting can be informative for others, particularly where the same active ingredient is used. In this context, the evaluation questioned whether the exclusion of trials of other risperidone LAIs was justified, or whether a formal ITC should have been attempted.

6.13 Concerns were also raised about outcome selection. While the submission relied on impending relapse and change in positive and negative syndrome scale (PANSS) total score to support non-inferiority, the evaluation noted that differences in baseline PANSS scores, relapse definitions, and assessment timing across trials limited the comparability of these outcomes and complicated any extension of the results beyond the nominated comparators.

6.14 On this basis, the evaluation suggested that the PBAC may wish to consider whether a formal ITC with other risperidone LAIs should be provided, or, alternatively, whether population criteria in the restriction should be included to restrict usage to patients who reflected the specific features of the MRSC risperidone trial program that were said to preclude such comparisons.

6.15 In response, the PSCR stated that a risperidone-to-risperidone ITC had been explored but was not feasible. The PSCR argued that heterogeneity in trial populations, study designs, and outcome measures, including the absence of comparable impending-relapse endpoints in studies of other risperidone LAIs, meant that any such analysis would lack validity and would not meaningfully inform decision-making.

6.16 The ESC agreed with the evaluation that the evidentiary basis for directly comparing MRSC risperidone with other risperidone LAIs was limited. However, the ESC considered differences in baseline symptom severity across trials, as reflected by PANSS scores, to be relevant to the feasibility of an ITC. The ESC noted that studies of other PBS-listed risperidone LAIs generally enrolled patients with higher PANSS scores, consistent with more symptomatic populations, whereas the MRSC risperidone trial program enrolled a comparatively lower PANSS score population following stabilisation. The ESC considered that these differences in baseline disease severity and clinical context limited the comparability of outcomes across trials and further reduced the validity of a formal risperidone-to-risperidone ITC. The ESC therefore accepted that a formal ITC would be unfeasible and advised that further analyses were unlikely to provide additional value. In forming this view, the ESC had regard to the PBAC's established position that, if MRSC risperidone were considered non-inferior to paliperidone and aripiprazole, it would, by extension, be regarded as non-inferior to other risperidone LAIs, consistent with prior PBAC reasoning.

6.17 The trials and the associated reports and publications (excluding conference abstracts) included in the submission are shown in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
TV46000-CNS-30072 RISE **NCT03503318**	A Multicenter, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia (The RISE Study - The Risperidone Subcutaneous Extended-release Study) **Kane JM, Harary E, Eshet R, et al. Efficacy and safety of TV-46000, a long-acting, subcutaneous, injectable formulation of risperidone, for schizophrenia: a randomised clinical trial in the USA and Bulgaria.**	**2021** ***Lancet Psych* 2023; 10:934–943.**
TV-46000-CNS-30078 SHINE NCT03893825	A Study to Evaluate the Safety, Tolerability, and Effect of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients With Schizophrenia. Kane, JM, Eshet R, Harary E, et al. A long-term safety and tolerability study of TV-46000 for subcutaneous use in patients with schizophrenia: a Phase 3, randomized, double-blinded clinical trial.	2019 *CNS Drugs* 2024; 38:625-636.
Hough, 2010 NCT00111189	A Randomized Double-blind Placebo-controlled Parallel Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Patients With Schizophrenia. Hough D, Gopal S. Vijapurkar U, Lim P, Morozova M, Eerdekens M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomised, double-blind, placebo-controlled study.	2005 *Schizophr Res* 2010; 116:107-117.
ASPIRE US NCT00705783 Kane, 2012	A 52-week, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular Depot Formulation of Aripiprazole as Maintenance Treatment in Patients With Schizophrenia. Kane JM, Sanchez R, Perry PP, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomised, double-blind, placebo-controlled study.	2008 *J Clin Psychiatry* 2012; 73:617-624

Source: Table 2-5, pp52-55 of the submission.

6.18 Details of the trials are shown in **Error! Reference source not found.**.

Table 3: Key features of the trials included in the submission.

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
MRSC RIS vs Placebo						
RISE	544	Randomised, double-blind (but see comment), multicentre; open label transition then randomised 1:1:1 placebo, MRSC risperidone q1m, MRSC risperidone q2m, maximum treatment duration 24 months but study ended when 90 impending relapses accrued.	High	Schizophrenia >1 year, ≥1 relapse last 2 years, responsive to antipsychotic last year with PANSS <100; after 12-week conversion to oral RIS PANSS ≤80	Time to impending relapse.	Used
SHINE	336	Randomised, double-blind (but see comment) multicentre; patients from RISE not relapsed continued MRSC risperidone (172) or if on placebo (55) randomised to MRSC risperidone q1m or q2m; new patients (109) went through oral stabilisation and then randomised to MRSC risperidone q1m or q2m. Double-blind treatment 56 weeks.	High	Same as RISE	Adverse events	Not used
PP1M vs Placebo						
Hough, 2010	410	Randomised, double-blind, multicentre; open label transition then open label maintenance then double blind 1:1 PP1M vs placebo until 136 relapses accrued.	Low	Schizophrenia >1 year, PANSS <120	Time to first relapse in double-blind phase.	Used
A1M vs Placebo						
ASPIRE US	403	Randomised, double-blind, multicentre; transition to oral aripiprazole, if stable went to single-blind A1M 12-36 week if stable; randomised 2:1 double blind A1M vs placebo; double-blind phase 52 week but trial terminated early for efficacy.	Low	Schizophrenia >3 years and relapse when off antipsychotic	Time to impending relapse.	Used.

Source: Constructed during the evaluation from published reports or CSRs.
A1M = aripiprazole once-monthly; MRSC = modified release subcutaneous injection; PANSS = positive and negative syndrome scale; PP1M = paliperidone once-monthly intramuscular injection; q2m = 2-monthly; q1m = 1-monthly.

6.19 Although RISE was described as a double-blind study, the placebo pre-filled syringes, which were administered to patients allocated to 2-monthly treatment on alternate months, were noticeably different in appearance from the active pre-filled syringes. Furthermore, all injections were given by an unblinded study nurse (p44, p50, RISE). As a result, the risk of unblinding and the overall risk of bias have been rated as High. Importantly, the information that led to this high risk of bias assessment in RISE was available only from the Clinical Study Report (CSR), not from the published report.

Therefore, it cannot be ruled out that similar issues may have occurred in other trials where published reports are the only available source of data.

6.20 All patients in SHINE received MRSC risperidone and were blinded only to their allocation to monthly or 2nd monthly treatment. The difference in the appearance of active and placebo pre-filled syringes meant the risk of unblinding was high. The risk of bias in SHINE would have been High in any case because all patients received MRSC risperidone.

6.21 When the United States Food and Drug Administration (FDA) reviewed the results of RISE and SHINE in 2021 "deficiencies were identified related to IP [investigational product] dosing errors, lack of documentation of IP administration and dually or triply enrolled patients" (SHINE Addendum 02). In response, the sponsor performed a review of source documents for treatment administration, an audit of the study database, and a re-analysis of the data to determine whether there were material impacts of the data deficiencies on the trial results. The results of these supplementary analyses are presented in the submission as Attachments 5 and 6 for RISE and Attachment 8 for SHINE. The evaluation considered the supplementary analyses do not materially affect the trial results but do have implications for study procedures.

6.22 There were eight dually enrolled patients (in both RISE and SHINE, in four cases allocated to placebo in RISE but receiving risperidone in SHINE) and one triply enrolled patient (once in RISE and twice in SHINE). The evaluation considered these patients did not materially affect the reported results.

6.23 Dosing errors or failure to document the dose occurred most often when placebo injections were given 66 (36%) of 181 patients randomised to placebo had errors of dosing or documentation in 340 (25%) of 1,374 treatments, compared to 53 (29%) of 183 of patients and 298 (16%) of 1,909 treatments among patients randomised to MRSC risperidone. Errors of dosing or documentation occurred in patients randomised to 2nd monthly injections (monthly injections alternating active and placebo) in 206 (23%) of 904 risperidone treatments and 376 (47%) of 801 placebo treatments (RISE CSR Addendum 2).

6.24 The most common dosing errors were injection volumes that were too high or too low, which occurred in 328 (15%) of 2,175 placebo injections across all treatment groups, compared to 69 (2.5%) of 2,813 active injections across all treatment groups (RISE CSR Addendum 2).

6.25 The evaluation considered these findings indicate that active and placebo injections were not treated in the same manner, supporting its notion that there was a High risk of unblinding.

6.26 In RISE, Hough (2010) and ASPIRE, patients were only randomised after complex and prolonged preliminary phases.

6.27 Patients in RISE entered an open-label oral conversion phase, lasting up to 12 weeks, in which they stopped their current treatment, including other brands of risperidone LAI, and changed to oral risperidone 2-5 mg/day. Patients had to stabilise on oral risperidone for at least four consecutive weeks before baseline to be eligible for

randomisation. Patients requiring less than 2 mg/day or more than 5 mg/day were not randomised because they could not be treated with the lowest or highest dose of MRSC risperidone, respectively. Of 183 patients randomised to monthly MRSC risperidone, 47 (26%) were stabilised on an oral dose of 2 mg/day and received 50 mg monthly, 46 (25%) were stabilised on 3 mg/day and received 75 mg monthly, 68 (37%) were stabilised on 4 mg/day and received 100 mg monthly, and 22 (12%) were stabilised on 5 mg/day and received 125 mg monthly. These doses were relatively low, the recommended dose in the risperidone oral PIs being 4-6 mg/day and the highest approved dose 16 mg/day.

6.28 Patients in Hough (2010) who had not been treated previously with PP1M, or risperidone were given two oral doses of PP1M, and those who tolerated those doses or had been previously treated with PP1M or risperidone entered a 9-week open-label transition phase, switching from their previous medication to paliperidone LAI. Those who were stable at week 9 entered a 12-week open-label dose adjustment phase, and then a 12-week open-label phase of treatment at the dose established in the preceding phase. Stable patients were randomised 1:1 to PP1M at their established dose or placebo.

6.29 Patients in ASPIRE were converted from their previous medication to oral aripiprazole 10 mg/day over 4-6 weeks. Patients were then titrated to an oral dose of 10-30 mg/day over 4-12 weeks. Stable patients transitioned to single-blind A1M at 300 mg or 400 mg monthly for 12-36 weeks. Patients who were stable for 12 consecutive weeks were randomised 2:1 to continue A1M or placebo for 52 weeks.

6.30 The flows of patients through the trials are shown in the CONSORT diagrams in Attachment 2. Withdrawals due to adverse events or lack of efficacy were common in all trials during the preliminary phases:

- In Hough (2010), 541 of 951 patients enrolled were excluded before randomisation, of whom 108 chose to withdraw and 103 were excluded for adverse events or failure to meet stability criteria.
- In ASPIRE, 440 of 843 enrolled were excluded before randomisation, of whom 82 withdrew consent and 87 were excluded for adverse events or lack of efficacy.
- In RISE 319 of 863 patients enrolled were excluded or withdrew before randomisation, of whom 114 withdrew consent and 75 were excluded for adverse events or not meeting stability criteria. This is likely to have led to over-estimation of efficacy and under-estimation of adverse events during the double-blind phases.

6.31 In all three trials the primary outcome was time to relapse. Relapse was defined as hospitalisation for psychosis, violent behaviour, suicidality, or worsening of manifestations of schizophrenia as assessed by the PANSS score. Details were the same for RISE and ASPIRE (which had the same chief investigator), but they differed in Hough (2010) in that a relapse based on PANSS scores required the scores to be

increased at two consecutive assessments. Details of the relapse criteria are provided in Attachment 2, Table A2.1.

6.32 The baseline characteristics of the randomised patients in the trials are shown in Table A2.2 in Attachment 2. Little data on the characteristics of patients excluded during the open-label phases were reported. Only data for patients in RISE randomised to monthly MRSC risperidone was included.

6.33 Important differences in the baseline characteristics of age and race among the studies were that the patients in RISE were older and much more likely to be Black than in either of the other two studies. Since there were 480 patients enrolled in the USA and 63 enrolled in Bulgaria (RISE CSR), the over-representation of Black patients in the US cohort would be slightly greater than in the study overall.

6.34 No reason for the over-representation of Black patients was provided in the study reports. Black populations are more likely to be diagnosed with schizophrenia than white populations: e.g., in a recent meta-analysis of US data OR (95% CI) was 2.07 (1.64, 2.61).[3] About 14% of the US population self-identifies as Black, so about 25% of US patients with a diagnosis of schizophrenia would be Black.

6.35 The PSCR disagreed with the evaluation's view that the overall risk of bias of RISE was High. The PSCR argued that the key outcomes within the trials (time to impending relapse and relapse rate) are objective, hospital-based events, which were not influenced by blinding/unblinding. The PSCR asserted that blinded outcome assessors were used for all the study outcome assessments, and that the unblinded nurse was not involved in the outcome assessment.

6.36 The PSCR stated that withdrawal rates during the open-label run-in phases were comparable across the trials, noting that 48% of eligible patients in both Hough (2010) and ASPIRE progressed to randomisation, compared with 69% in RISE, and argued that this supports the appropriateness of the comparative evidence base. The PSCR argued that RISE's 12-week oral risperidone stabilisation period aligns with accepted LAI trial methodology, clinical guidelines, and PBS practice, with 96% of Australian patients initiating treatment with oral antipsychotics prior to LAI use and PBS criteria explicitly requiring prior oral stabilisation. The PSCR also stated that PBAC precedent, specifically the aripiprazole LAI July 2014 consideration, supports the assumption that prescribers typically introduce LAIs only after oral therapy.

6.37 The ESC noted these concerns but broadly considered that the evidence was indicative of non-inferiority and did not indicate concern that the limitations of the evidence were strongly reflective of the efficacy in clinical practice.

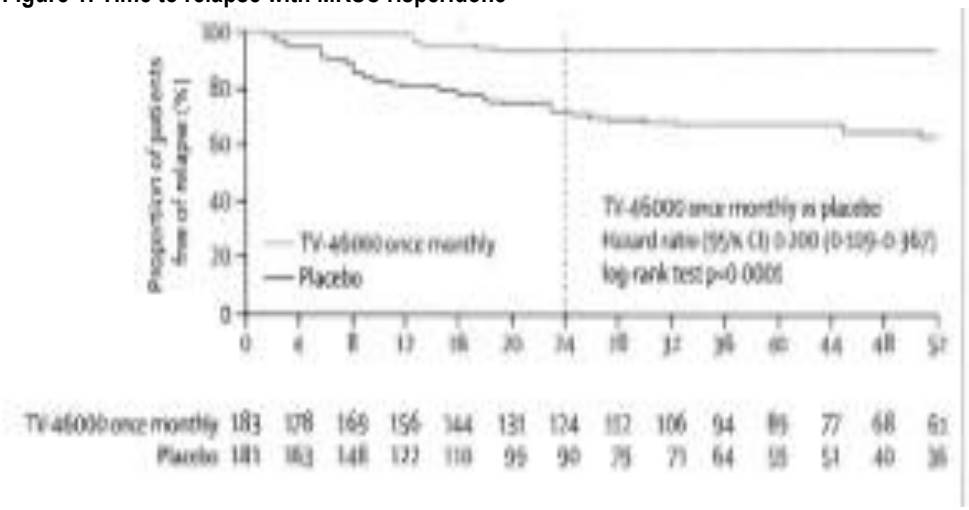
[3] van der Ven E, Olino TM, Diehl K, et al. Ethnoracial risk variation across the psychosis continuum in the US: A systematic review and meta-analysis. *JAMA Psych* 2024; 81(5):447-455.

Comparative effectiveness

Kaplan-Meier curves for time to relapse are shown in Figure 1,

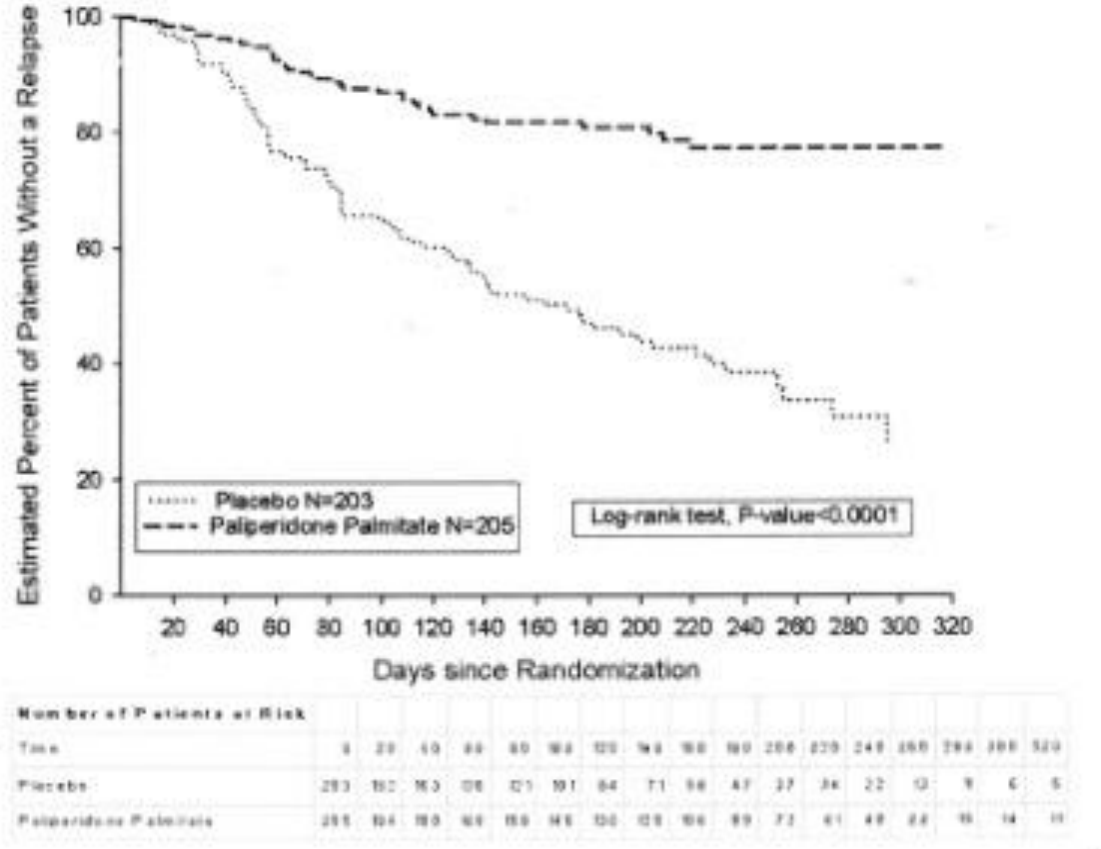
6.38 Figure 2 and Figure 3.

Figure 1: Time to relapse with MRSC risperidone



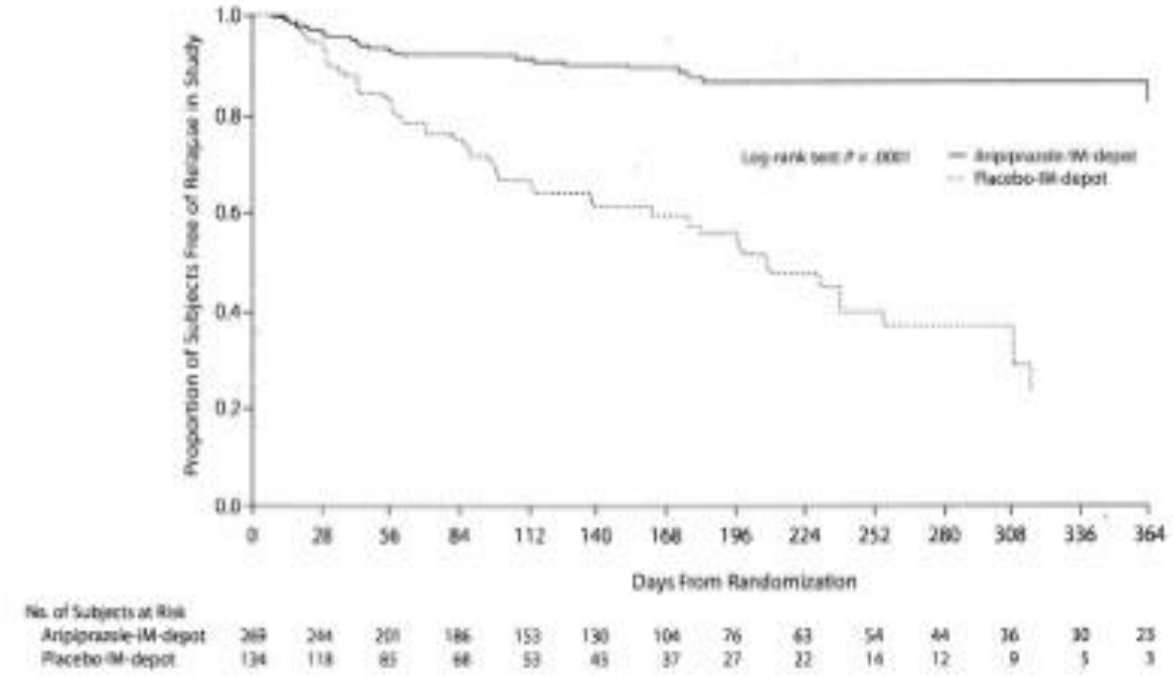
Source: Figure 2-8, p130 of the submission.

Figure 2: Time to relapse with PP1M



Source: Figure 2-9, p131 of the submission.
PP1M = paliperidone.

Figure 3: Time to relapse with A1M



Source: Figure 2-10, p131 of the submission.
A1M = aripiprazole.

6.39 The active treatment arms had longer time to event than the placebo arms. However, the number of events was small in the active treatment arms, especially in the RISE trial (Table 4).

6.40 The event rate in the placebo arm was much lower in RISE than in the other trials.

6.41 Table 4 shows the secondary efficacy results in patients randomised to monthly MRSC risperidone in RISE and other trials where similar outcomes were reported.

6.42 A large majority of patients who met the criteria for relapse also satisfied the clinical global impression (CGI) and PANSS criteria. Events of suicidality and violence were uncommon and not clearly different between placebo and MRSC risperidone.

6.43 In this context, the evaluation considered the possibility of unblinding important because placebo and active pre-filled syringes were not identical and all treatments were administered by an unblinded study nurse.

6.44 In RISE, key secondary efficacy outcomes were the proportion of patients, at study endpoint, who were stable or in remission. Stability was defined as meeting all the following for 4 consecutive weeks:

- not in hospital
- PANSS total score ≤80
- PANSS score ≤4 on all conceptual disorganisation, suspiciousness, hallucinatory behaviour, and unusual thought content

- CGI-S score ≤4 (moderately ill); and CGI-SS score ≤2 (mildly suicidal) on Part 1 and ≤5 (minimally worsened) on Part 2.

6.45 Remission was defined as not meeting the relapse criteria during the study and, for at least 6 months before the study endpoint, maintaining scores of ≤3 on each of the PANSS items delusions, unusual thought content, hallucinatory behaviour, conceptual disorganisation, mannerisms/posturing, blunted affect, social withdrawal, and lack of spontaneity.

6.46 Stability and remission at the study endpoint were more common in the risperidone-treated patients in RISE. This difference was statistically significant for stability (P<0.0001 by Cochrane-Mantel-Haenszel test) but not for remission (P=0.12).

Table 4: Secondary efficacy outcomes in the submitted trials.

	RISE	RISE	Hough, 2010	Hough, 2010	ASPIRE	ASPIRE
	MSCR risperidone q1m N = 183	**Placebo N = 181**	**PP1M N = 205**	**Placebo N = 203**	**A1M N = 269**	**Placebo N = 134**
Patients meeting the relapse criteria, n (%) CGI + PANSS Hospitalisation Suicidality Violence	**13 (7%)** **10 (5.5%)** 2 (1%) 2 (1%) 0	53 (29%) 45 (25%) 7 (4%) 2 (1%) 1 (0.5%)	36 (18%) NR	97 (48%) NR	27 (10%) 20 (7%) 7 (3%) 1 (0.4%) 1 (0.4%)	53 (39.6%) 46 (34%) 5 (4%) 1 (1%) 4 (3%)
Patients stable at study endpoint, n (%)	159 (87%)	110 (61%)	NR	NR	NR	NR
Patients in remission at study endpoint, n (%)	39 (29%)	30 (23%)	NR	NR	NR	NR
Patients meeting the relapse criteria, n/N (%) White Black	 6/72 (8%) 7/108 (6%)	 22/68 (32%) 29/104 (28%)	 NR	 NR	 NR	 NR
EQ VAS Score, baseline Mean (SD) Median (range)	 79.1 (17.2) 82.0 (3, 100)	 80.0 (17.4) 83.5 (8, 100)	 NR	 NR	 NR	 NR
EQ VAS score, end of treatment, Mean (SD) Median (range) LS mean change (SE) LS mean difference vs placebo (95% CI))	 84.0 (14.1) 89.0 (50, 100) 2.3 (1.1) 4.73 (1.5, 8.0)	 79.0 (13.4) 81.0 (25, 100) -2.5 (1.3)	 NR	 NR	 NR	 NR
PSP Scale, baseline Mean (SD)	 63.3 (11.7)	 63.7 (11.5)	 72.0 (10.6)	 72.9 (10.7)	 NR	 NR
PSP Scale, change from baseline to end of study Mean (SD) LS mean change (SE) LS mean difference vs placebo (95% CI))	 2.1 (8.9) 1.2 (0.7) 1.1 (-0.9, 3.2)	 2.1 (6.9) 0.1 (0.8)	 -1.5 (11.5) NR	 -7.2 (13.0) NR	 NR	 NR

Source: RISE CSR, Tables 15.10.2, 15.11.2; 15.11.3; 15.11.6; 15.12.4 (pp77, 88); Kane, 2023, Hough, 2010 and Kane, 2012.
Results in **bold** are statistically significant vs placebo.
A1M = aripiprazole; CGI = clinical global impression; CI = confidence interval; EQ VAS. = EuroQoL visual analogue scale, 0 = worst imaginable health, 100 = best imaginable health; LS = least squares; PANSS = positive and negative syndrome scale; PP1M = paliperidone; PSP = personal and social performance, higher scores = better performance; SE = standard error.

6.47 There was statistically and marginally clinically meaningful improvement in quality of life associated with MRSC risperidone treatment.

6.48 The EuroQoL Visual Analogue Scale asks patients for a summary estimate of their current health-related quality of life, from 0 = "worst health you can imagine" to 100 = "best health you can imagine" (the description on p121 of the submission is incorrect). EQ VAS scores increased in patients treated with MRSC risperidone and fell in placebo-treated patients, although in both groups the scores remained around the

middle of the range seen in random samples of the population. In an Australian sample, e.g., mean (SD) EQ VAS varied with age, but at the lower end of the age range studied in RISE it was 82.0 (14.1) and at the upper end it was 78.9 (16.8).[4] The minimum clinically important difference varies with baseline score, but the range seen in RISE is of the order of 5.[5]

6.49 The EuroQoL 5-dimension 5-level (EQ-5D-5L) score change from baseline to end of study also favoured MRSC risperidone: least squares mean (SE) change was -2.46 (1.32) for placebo and 2.28 (0.83) for pooled MRSC risperidone and 2nd monthly groups (RISE CSR, p124).

6.50 The Personal and Social Performance (PSP) Scale measures four areas: socially useful activities (e.g., housework, work outside the home, study); personal and social relationships; self-care (hygiene and appearance); and disturbing and aggressive behaviour. The scores did not change meaningfully during the RISE trial and there was no difference between placebo and MRSC risperidone-treated patients. The minimal clinically important difference for the PSP Scale is around 8, so although the changes in Hough (2010), were statistically significant they were probably not clinically important.[6]

6.51 Additional claims of efficacy made in the submission but not included in the formal clinical claim were that MRSC risperidone will "reduce the overall treatment burden, promote patient preference, and may facilitate more person-centred, community-based care" and "improve treatment adherence by addressing patient preferences impacting medication use related to convenience, comfort and control" due to its subcutaneous route of administration. No clinical evidence, specific to MRSC risperidone, to support these claims was provided.

6.52 The PSCR stated that oral antipsychotics, while first-line, are associated with poor adherence, and that IM LAIs may be avoided due to pain and gluteal exposure, as noted in Attachment 2 and Attachment 14 of the submission. It stated that SC administration is generally more acceptable, and that MRSC risperidone monthly dosing, no oral overlap, and the prefilled syringe dose form reduce treatment burden. The PSCR provided additional evidence, stating that RISE and SHINE, showed improvements in quality-of-life and patient-centred outcomes. It also stated that MRSC risperidone enables direct switching from oral risperidone and that both patient and clinician preferences in SHINE favoured SC administration due to smaller needles,

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[4] McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D–5L: South Australian population norms. *Health Qual Life Outcomes* 2016; 14:133.

[5] Cheng LJ, Chen LA, Cheng JY, Herdman M, Luo N. Systematic review reveals that EQ-5D minimally important differences vary with treatment type and may decrease with increasing baseline score. J Clin Epidemiol 2024; https://doi.org/10.1016/j.jclinepi.2024.111487

[6] Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psych Scand* 2001; 101:323-329.

easier technique, and the avoidance of gluteal exposure. The PSCR reiterated that clinical feedback supported reduced pain, lower anxiety, more dignity, and the potential for improved long-term outcomes.

ITC efficacy

6.53 The submission presented an ITC against PP1M and A1M using placebo as the common comparator for the outcomes of impending relapse and changes in PANSS scores.

6.54 The submission proposed non-inferiority margins of 20% for the risk of relapse and 7 points on the PANSS score, consistent with the approach used by the PBAC when considering R4WIM (Paragraph 6.30, Risperidone PSD, March 2024 PBAC Meeting). The submission stated that the 20% margin for the risk of relapse was "cited" by the PBAC in its July 2014 consideration of aripiprazole, however the PBAC used the 20% margin for direct comparisons and considered that an 11.5% margin would be more appropriate for indirect comparisons (Paragraph 6.14, 6.16, Aripiprazole PSD, July 2014 PBAC Meeting).

6.55 The results of the ITC for risk of relapse are shown in Table 5**Error! Reference source not found.**.

Table 5: ITC for risk of relapse.

	RISE	Rise	Hough, 2010	Hough, 2010	ASPIRE	ASPIRE
	MSCR risperidone q1m N = 183	**Placebo N = 181**	**PP1M N = 205**	**Placebo N = 203**	**A1M N = 269**	**Placebo N = 134**
Patients with relapse, n (%)	13 (7%)	53 (29%)	36 (18%)	97 (48%)	27 (10%)	53 (40%)
Risk Difference vs placebo (95% CI)	**-22.2 (-29.8, -14.6)**	-	**-30.2 (-38.8, -21.6)**	-	**-29.5 (-38.5, -20.5)**	-
Risk Ratio (95% CI)	**0.24 (0.14, 0.43)**	-	**0.37 (0.26, 0.51)**	-	**0.25 (0.17, 0.38)**	-
Odds Ratio (95% CI)	**0.18 (0.10, 0.35)**	-	**0.23 (0.15, 0.37)**	-	**0.17 (0.10, 0.29)**	-
Hazard Ratio for relapse vs placebo (95% CI)	**0.20 (0.11, 0.37)**	-	**0.28 (0.19, 0.41)**	-	**0.20 (0.12, 0.32)**	
MSCR risperidone q1m vs PP1M						
Risk Difference (95% CI)	8.0 (-3.5, 19.5)					
Risk Ratio (95% CI)	0.66 (0.34, 1.28)					
Odds Ratio (95% CI)	0.79 (0.36, 1.75)					
Hazard Ratio (95% CI)	0.72 (0.35, 1.48)					
MSCR risperidone q1m vs A1M						
Risk Difference (95% CI)	7.3 (-4.5, 19.1)					
Risk Ratio (95% CI)	0.96 (0.47, 2.50)					
Odds Ratio (95% CI)	1.08 (0.47, 2.50)					
Hazard Ratio (95% CI)	1.00 (0.47, 2.16)					

Source: Table 2-41, 2-42, pp152-3, p154 of the submission. **Bold** = statistically significant; A1M = aripiprazole; CI = confidence interval; PP1M = paliperidone.

6.56 All active treatments were superior to placebo, and no differences among them were apparent.

6.57 The placebo response rate in RISE was much lower than in other trials, suggesting population differences that may affect transitivity assumptions.

6.58 The results of the ITC for PANSS score are shown in Table 6. The evaluation noted that change from baseline in PANSS score was an exploratory outcome only (RISE CSR). The pre-specified key secondary outcomes measuring response in non-relapsing patients were stability and remission at study completion (Table 4).

6.59 The data used for the PANSS score ITC were from the last assessment during the double-blind phase, i.e., patients whose last assessment satisfied the relapse criterion appear to have been included. PANSS scores at end-of-treatment (EoT), which did not include patients who had relapsed, were much lower in the placebo group than the data used in the ITC, and differences between MRSC risperidone treated patients and placebo treated patients were less than the minimum clinically important difference (RISE CSR).

Table 6: ITC for PANSS score

	RISE	RISE	Hough, 2010	Hough, 2010	ASPIRE	ASPIRE
	MRSC risperidone q1m N = 183	**Placebo N = 181**	**PP1M N = 205**	**Placebo N = 203**	**A1M N = 269**	**Placebo N = 134**
PANSS total score at baseline, Mean (SD)	61.5 (9.6)	61.0 (10.4)	53.1 (11.9)	52.1 (11.8)	54.5 (NR)	54.4 (NR)
PANSS total score at last assessment, Mean (SD)	59.9 (13.5)	67.9 (16.5)	NR	NR	NR	NR
LS mean difference vs placebo (95% CI)	**-8.2 (-10.9, -5.6)**	-	**-8.6 (-11.4, -5.8)**	-	**-10.1 (-12.7, -7.5)**	-
PANSS total score at end of treatment, Mean (SD)	56.5 (11.9)	56.3 (11.4)	NA	NA	NA	NA
LS mean difference vs placebo (95% CI)	**-4.6 (-6.7, -2.4)**	-	NA	NA	NA	NA
MRSC risperidone q1m vs PP1M						
Mean difference (95% CI)	-0.38 (-3.51, 4.27)					
MRSC risperidone q1m vs A1M						
Mean difference (95% CI)	1.89 (-1.82, 5.60)					

Source: Table 2-43, 2-42, p155 of the submission; Table 15.12.1.1, RISE CSR.
Bold = statistically significant; A1M = aripiprazole; CI = confidence interval; LS = least squares; NA = not applicable; NR = not reported; PANSS = positive and negative syndrome score; PP1M = paliperidone; SD = standard deviation.

Comparative harms

6.60 Table 7 shows selected adverse events in the double-blind phases of the submitted trials. Only data for patients in RISE randomised to monthly MRSC risperidone were included. Some important adverse events, such as weight gain, were excluded from the table because the published reports presented them inconsistently.

Table 7: Adverse events during the double-blind phases of the submitted trials.

	RISE		Hough, 2010		ASPIRE	
	MSCR risperidone q 1m N = 183	Placebo N = 179	PP1M N = 205	Placebo N = 203	A1M N = 269	Placebo N = 134
Any TEAE, n (%)	111 (61%)	92 (51%)	91 (44%)	91 (45%)	170 (63%)	83 (62%)
TEAE Grade ≥3, n (%)	6 (3%)	12 (7%)	NR	NR	NR	NR
SAE, n (%)	8 (4%)	14 (8%)	11 (5%)	26 (13%)	11 (4%)	9 (7%)
AE leading to withdrawal, n (%)	21 (12%)	10 (6%)	3 (2%)	1 (0.5%)	19 (7%)	18 (13%)
Death, n (%)	0	1 (0.5%)	0	0	1 (0.4%)	0
Patients with any injection site reaction, n (%)	31 (17%)	21 (12%)	NR	NR	NR	NR
Extra-pyramidal disorder, n (%)	9 (5%)	0	12 (6%)	4 (2%)	40 (15%)	13 (10%)
Dizziness, n (%)	7 (4%)	1 (0.5%)	NR	NR	NR	NR
Somnolence, n (%)	6 (3%)	1 (0.5%)	NR	NR	NR	NR

Source: Table 2-40, p145 of the submission. AE = adverse event; A1M = aripiprazole; PP1M = paliperidone; SAE = serious adverse event; TEAE = treatment emergent adverse event.

6.61 Although there were no deaths among patients randomised to monthly MRSC risperidone, there were four deaths among patients randomised to 2nd monthly treatment.

6.62 Weight gain and hyperglycaemia are important adverse effects of antipsychotic medication because of the high rate of serious cardiovascular disease in patients with schizophrenia.

6.63 In RISE, increased weight was reported as an adverse event in 10/183 (6%) of MRSC risperidone treated patients and 6/179 (3%) of placebo treated patients (Table 47, p185, RISE CSR).

- Increases in BMI of ≥5% but <10% were reported in 26 (17%) of MRSC risperidone-treated and 16 (10%) of placebo treated patients.
- Increases in BMI of ≥10% in 16 (10%) of MRSC risperidone treated and 6 (4%) of placebo treated patients.

6.64 In Hough (2010), weight gain ≥7% of double-blind baseline was reported in 6% of PP1M-treated patients and 3% of placebo-treated patients. However, weight gain ≥7% of enrolment baseline occurred in 23% of PP1M-treated patients and 12% of placebo-treated patients, indicating the extent to which the prolonged pre-randomisation treatment phases of the trials may have influenced adverse events. Increased weight was reported during the double-blind phase as an adverse event in 7% of PP1M-treated patients and in 1% of placebo-treated patients. Hyperglycaemia was reported as an adverse event in 3% of PP1M-treated patients and in 1% of placebo-treated patients.

6.65 In ASPIRE, weight gain ≥7% of baseline was observed in 6.4% and 5.2% of A1M and placebo-treated patients, respectively. Among patients whose fasting metabolic

parameters were normal at baseline, fasting hyperglycaemia developed in 7/157 (4.5%) A1M-treated patients and 2/80 (2.5%) of placebo-treated patients.

6.66 Prolactin levels are increased by antipsychotic medications, and the elevation of prolactin may cause galactorrhoea, sexual dysfunction, and in females amenorrhoea and bone loss. There appears to be an association between antipsychotic medications, especially risperidone, and pituitary adenomas.[7]

6.67 In RISE, prolactin levels ≥2 times the upper limit of normal (ULN) were reported in 17/179 (10%) of placebo-treated and 62/183 (35%) of MRSC risperidone treated patients; increases to ≥5 times ULN were reported in 3 (2%) of placebo-treated and 14 (8%) of MRSC risperidone treated patients (RISE CSR).

6.68 Three patients treated with MRSC risperidone had galactorrhoea (one treated with monthly injections and two with 2nd monthly injections) and two had gynecomastia (one treated with monthly injections and one with 2nd monthly injections) (RISE CSR).

6.69 Hough (2010) reported prolactin-related adverse events in 5/203 (2%) PP1M-treated patients and 3/205 (2%) of placebo-treated patients. However, 28 patients had prolactin-related adverse events during the open-label transition and maintenance phases. The evaluation therefore considered the rate of prolactin-related adverse events in the double-blind phase may under-estimate the actual risk.

6.70 In ASPIRE, prolactin above the upper limit of normal was less frequent with A1M than with placebo: 1.9% vs 7.1%.

6.71 Overall, the evaluation considered the adverse events reported in the submitted trials were consistent with the known adverse event profiles of the medications.[8] In particular, risperidone and paliperidone are known to cause more prolactin elevation than other antipsychotics, especially A1M. The extrapyramidal symptoms corelated to the dose of risperidone, and the rate reported in RISE was lower than in studies where higher doses were used.

6.72 The PSCR stated that differences in the trial run-in periods may have influenced comparative outcomes, noting that RISE used a 12-week oral-only stabilisation phase, while the paliperidone and aripiprazole trials employed much longer 33–36-week stabilisation periods that would have filtered out more AE-prone or less stable patients before randomisation, potentially biasing indirect comparisons in favour of the comparators.

6.73 The PSCR stated that despite this, MRSC risperidone's AE profile remained consistent with recognised class effects, including dose-dependent extrapyramidal symptoms and higher prolactin elevations typical of risperidone and paliperidone. It also stated that the PBAC has previously considered LAI antipsychotics interchangeable,

[7] Szarfman A, Tonning JM, Levine JG, Doraiswamy PM. Atypical antipsychotics and pituitary tumors: a pharmacovigilance study. *Pharmacotherapy* 2006; 26:748-758.

[8] Jibson MD. Second-generation and other antipsychotic medications: Pharmacology, administration, and side effects. In: UpToDate, Connor RF, ed, Wolters Kluwer, accessed 21 November 2025.

referencing the aripiprazole LAI July 2014 decision, where PBAC accepted non-inferior safety and efficacy versus paliperidone despite differences in AE profiles.

ITC safety

6.74 The results of the ITC for safety are shown in Table 8.

6.75 Compared to aripiprazole, MRSC risperidone was associated with a higher risk of adverse events leading to treatment withdrawal, and large increases in the risks of prolactin-related adverse events and extra-pyramidal symptoms which were close to statistical significance and have been reported in other studies.

6.76 The evaluation did not expect major differences in adverse events between MRSC risperidone and PP1M except in relation to injection site reactions which were excluded from the ITC because this adverse event was not systematically reported in Hough (2010) or ASPIRE.

Table 8: ITC for safety.

		MSCR risperidone q1m vs PP1M	MSCR risperidone q1m vs A1M
Any TEAE	Risk Difference (95% CI), P-value	9.7% (4.3%, 23.7%) 0.18	8.0% (-6.3%, 22.3%) 0.273
Any TEAE	Relative Risk (95% CI), P-value	1.2 (0.9, 1.6) 0.23	1.2 (0.9, 1.5) 0.24
Any TEAE	Odds Ratio (95% CI), P-value	1.5 (0.8, 2.6) 0.18	1.4 (0.8, 2.5) 0.29
TEAE leading to withdrawal	Risk Difference (95% CI), P-value	4.9% (-1.1%, 10.9%) 0.11	**12.3% (3.6%, 20.9%) 0.006**
TEAE leading to withdrawal	Relative Risk (95% CI), P-value	0.7 (0.1, 7.4) 0.76	**3.91 (1.5, 10.1) 0.005**
TEAE leading to withdrawal	Odds Ratio (95% CI), P-value	0.7 (0.1, 8.1) 0.80	**4.5 (1.6, 12.6) 0.005**
SAE	Risk Difference (95% CI), P-value	4.0% (–3.4%, 11.4%) 0.291	–0.8% (–7.7%, 6.1%) 0.816
SAE	Relative Risk (95% CI), P-value	1.33 (0.45, 3.94) 0.602	0.92 (0.28, 3.05) 0.889
SAE	Odds Ratio (95% CI), P-value	1.40 (0.44, 4.44) 0.572	0.91 (0.25, 3.25) 0.884
Weight increase	Risk Difference (95% CI), P-value	–4.2% (–9.9%, 1.5%) 0.146	2.1% (–5.3%, 9.6%) 0.571
Weight increase	Relative Risk (95% CI), P-value	0.22 (0.04, 1.28) 0.093	1.64 (0.50, 5.30) 0.412
Weight increase	Odds Ratio (95% CI), P-value	0.21 (0.03, 1.29) 0.092	1.67 (0.48, 5.83) 0.419
Extrapyramidal symptoms	Risk Difference (95% CI), P-value	0.5% (–4.5%, 5.6%) 0.838	–0.3% (–7.6%, 7.1%) 0.943
Extrapyramidal symptoms	Relative Risk (95% CI), P-value	5.78 (0.28, 121.16) 0.259	12.13 (0.67, 219.75) 0.091
Extrapyramidal symptoms	Odds Ratio (95% CI), P-value	5.80 (0.27, 125.02) 0.262	12.02 (0.64, 224.61) 0.096
Prolactin-related AE	Risk Difference (95% CI), P-value	–0.4% (–3.5%, 2.7%) 0.816	**6.4% (1.2%, 11.5%) 0.015**
Prolactin-related AE	Relative Risk (95% CI), P-value	1.98 (0.06, 61.57) 0.698	18.66 (0.75, 463.95) 0.074
Prolactin-related AE	Odds Ratio (95% CI), P-value	1.97 (0.06, 62.78) 0.702	19.93 (0.78, 509.48) 0.070

Source: Table 2-44, p157 of the submission.
Bold = statistically significant AE = adverse event; A1M = aripiprazole CI = confidence interval; PP1M = paliperidone; SAE = serious adverse event; TEAE = treatment emergent adverse event.

Benefits/harms

6.77 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.78 The submission described MRSC risperidone as non-inferior in terms of effectiveness compared to PP1M, A1M, R2WIM, and R4WIM. The evaluation considered that the claim regarding paliperidone and aripiprazole was not convincingly supported because of concerns about the transitivity assumptions underlying the ITC but was probably

reasonable given the duration and extent of clinical experience with these medications. The evaluation further noted that no evidence to support the claim regarding non-inferiority to R2WIM and R4WIM was presented, but considered the claim is probably reasonable. The ESC noted the concerns regarding the transitivity assumptions underlying the ITC and agreed with the evaluation that the claim of non-inferior effectiveness was reasonable.

6.79 The submission described MRSC risperidone as non-inferior in terms of safety compared to PP1M and A1M. The evaluation considered this claim was not adequately supported regarding aripiprazole. Adverse events leading to treatment withdrawal, adverse events related to prolactin elevation, and adverse events related to extrapyramidal symptoms were more frequent with MRSC risperidone. The PSCR argued the results from the network meta-analysis supported comparable effectiveness and safety across long-acting antipsychotics, reinforcing the plausibility of the non-inferiority conclusion, and that MRSC risperidone demonstrated advantages in some safety measures, including a lower likelihood of ≥7% weight gain compared with PP1M, supporting the comparative safety profile[9]. The ESC noted the concerns raised by the evaluation and noted the PSCR. While the ESC agreed with the safety concerns raised by the evaluation and that it may impact the validity of the non-inferior safety claim, the ESC considered the safety concerns to be manageable and low risk. The ESC therefore considered the claim of non-inferior safety likely reasonable.

6.80 The PBAC considered that the claim of non-inferior comparative effectiveness and non-inferior comparative safety was reasonable.

Economic analysis

6.81 The submission presented a cost minimisation approach to the lowest cost alternative. The submission considered that all PBS-listed antipsychotic LAIs for the treatment of schizophrenia, except olanzapine, could replace MRSC risperidone in practice and therefore would be alternative therapies .

6.82 The submission has not claimed that MRSC risperidone provides a significant improvement in efficacy nor reduction in toxicity over the alternative therapies.

6.83 The key components and assumptions used in the approach are shown in Table 9.

[9] Franzenburg KR, Corpuz R, Heinloth AN, et al. Efficacy and Safety of TV-46000 and Second-Generation Long-Acting Injectable Antipsychotics in Schizophrenia: A Network Meta-Analysis. Advances in Therapy. 2025;42(7):2847-2867

Table 9: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be non-inferior.
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be non-inferior.
Evidence base	MRSC risperidone vs paliperidone - indirect comparison using 1 RCT for each MRSC risperidone vs aripiprazole - indirect comparison using 1 RCT for each
Equi-effective doses	Used PI based dosing adjusted for frequency of injection to calculate weighted average drug cost per month
Direct medicine costs, AEMP weighted average cost per month	R2WIM - PBS items 8780D, 8781E, 8782F- $232.21 PP1M - PBS items 5100K, 5102M, 5107T, 5109X - $227.66 A1M - PBS items 10219W, 10224D - $295.92
Other costs or cost offsets	Health Care Provider costs for injections, MBS item 23

Source: Compiled from Attachment 12, Section 3 of the submission.
PI = TGA Product Information; RCT = randomised controlled trial; R2WIM = risperidone 2 weekly intramuscular injection; PP1M = paliperidone once-monthly intramuscular injection, A1M = aripiprazole once-monthly intramuscular injection.

6.84 The equi-effective doses were derived from the doses recommended in the PIs, adjusted for frequency of injection and weighted according to the proportion of PBS services for the specified PBS items based on 2024 Services Australia data. The PBS items for R2WIM include use in bipolar disorder whereas the other item numbers are specific for schizophrenia. The submission presented a dose comparison which is shown in Table 10.

Table 10: Dose equivalence of oral risperidone, MRSC risperidone, R2WIM, PP1M, and R4WIM

Oral risperidone (1-daily)	MRSC risperidone (1-monthly)	R2WIM (2-weekly)	PP1M (1-monthly)	R4WIM (4-weekly)
1 mg			25 mg [d]	
2 mg	50 mg [a]	25 mg [b, c]	50 mg [b, d]	
3 mg	75 mg [a]	37.5 mg [b, c]	75 mg [b, d]	75 mg [e]
4 mg	100 mg [a]	50 mg [b, c]	100 mg [b, d]	100 mg [e]
5 mg	125 mg [a]			
6 mg			150 mg [d]	

Source: Table 1-6 of the submission
q1m = every month; q2m = every 2 months; q2w =every 2 weeks; q4w = every 4 weeks.
a. dose equivalence of risperidone oral and Uzedy from Uzedy AU PI (Attachment 1).
b. dose equivalence of Risperdal Consta and Invega Sustenna from Invega Sustenna PI (Janssen 2023b)
c. dose equivalence of risperidone oral and Risperdal Consta from (Therapeutic Guidelines 2021b)
d. dose equivalence of risperidone oral and Invega Sustenna from (Russu et al. 2018).
e. dose equivalence of risperidone oral, Risperdal Consta and Risvan from Risvan PI (Servier Laboratories 2023)

6.85 The submission used the same weighting approach to derive the effective price and proposed a flat pricing structure so that all strengths would have the same effective AEMP.

6.86 The calculations used to determine the lowest cost alternative are shown in Table 11.

Table 11: Lowest Cost comparator derivation (June 2025 PBS prices)

Product	AEMP (Oct 2025)	Cost of drug per calendar month	PBS Services (2024 Rx)		Weighted Avg Drug cost per month	No. of HCP injections/annum	Cost of HCP/annum	Cost of HCP/month	Total cost per month of treatment
R4WIM				Total					
75 mg, 28 days	$183.21	$199.02	-	-	Not calculated due to insufficient duration of listing				
100 mg, 28 days	$225.16	$244.59	-						
R2WIM				Total					
25 mg, 14 days	$78.88	$171.38	8,962	33,960	$232.21[1]	26.07	$1,144.54[1]	$95.38[1]	$327.59[1]
37.5 mg, 14 days	$102.71	$223.15	9,935						
50 mg, 14 days	$126.29	$274.38	15,063						
PP1M				Total					
25 mg 1 month	$76.51	$76.51	3,589	163,306	$227.76[1]	12.00	$526.80[1]	$43.90[1]	$271.66[1]
50 mg, 1 month	$153.01	$153.01	11,929						
75 mg, 1 month	$199.05	$199.05	23,198						
100 mg, 1 month	$244.62	$244.62	57,347						
150 mg, 1 month	$244.62	$244.62	67,243						
A1M				Total					
300 mg, 1 month	$252.36	$252.36	46,730	150,913	$295.92[1]	12.00	$526.80[1]	$43.90[1]	$339.82[1]
400 mg, 1 month	$315.46	$315.46	104,183						

Source: Table 3.3, p 181 of the submission.
AEMP = approved ex-manufacturer price; HCP = Healthcare provider consult MBS item 23 ($43.90); R2WIM = risperidone 2-weekly intramuscular injection; PP1M = paliperidone once-monthly intramuscular injection, A1M = aripiprazole once-monthly intramuscular injection.

6.87 The submission identified PP1M as the least costly comparator, from which the MRSC risperidone AEMP of $[redacted] was derived, as shown in Table 12.

Table 12: Results of CMA, RMS risperidone vs PP1M

	PP1M	MRSC risperidone	R2WIM	A1M
Drug cost per annum	$2733.12	$[redacted]	$2786.52	$3551.05
Number of HCP injections	12.00	12.00	26.07	12.00
Cost per injection	$43.90	$43.90	$43.90	$43.90
Total cost of HCP injections	$526.80	$526.80	$1144.54	$526.80
Total cost per annum	$3259.92	$[redacted]	$3931.06	$4077.85
Weighted average drug cost per calendar month	$227.76	$[redacted]	$232.21	$295.92

Source: Table 3.4, p 183 of the submission.
AEMP = approved ex-manufacturer price; HCP = Healthcare provider MBS item 23 ($43.90); R2WIM = risperidone 2 weekly intramuscular injection; PP1M = paliperidone once-monthly intramuscular injection, A1M = aripiprazole once-monthly intramuscular injection.

6.88 The submission used a weighted average estimate of the different doses to derive the effective price for the cost-minimisation. The evaluation considered the weighted

approach was not appropriate because it resulted in a higher price relative to the lowest-cost alternative. The PSCR stated that the pricing approach used for MRSC risperidone is consistent with the methodology applied in the R4WIM submission (risperidone PSD, March 2024), and that paliperidone was identified as the lowest-cost LAI comparator, forming the basis for calculating R4WIM's weighted AEMP. The ESC noted that this methodology was not accepted by the PBAC as the PBAC considered that there was no basis for a weighted comparator, and that R4WIM should be listed on a cost-minimisation basis the lowest cost alternative therapy on a cost per patient basis (Paragraph 6.63 PBAC PSD March 2024). The ESC noted that the cost-minimisation approach must establish that the cost per patient for treatment with MRSC risperidone would be no more than the cost per patient of the non-inferior comparators. The Secretariat advised that where the cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe. The ESC therefore advised that MRSC risperidone should be cost-minimised to the lowest-cost alternative on a cost/patient/year basis.

Drug cost/patient/year

6.89 The submission calculated the effective DPMQ to be $[redacted]. Based on this price the cost per patient for 12 months of treatment would be $[redacted]. The effective DPMQ was derived from its proposed AEMP and using the latest wholesaler and pharmacy mark-ups and fees.

Estimated PBS usage & financial implications

6.90 This submission was not considered by the DUSC.

6.91 The submission used a market share approach to estimate the likely use and financial impact of listing MRSC risperidone.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
PBS market antipsychotics for schizophrenia	PBS Statistics for: R2WIM: 25 mg, 37.5 mg, 50 mg R4WIM: 75 mg, 100 mg PP1M: 25 mg, 50 mg, 75 mg, 100 mg A1M: 300 mg, 400 mg	Consistent with CMA
Market growth	PBS Service data over 5 years: 3.7%	Reasonable
Uptake rate	Up to [redacted]% of total market for long-acting antipsychotics for schizophrenia. Assumes different rates for different products. Year / R2WIM / R4WIM / PP1M / A1M 2026: [redacted]% / [redacted]% / [redacted]% / [redacted]% 2027: [redacted]% / [redacted]% / [redacted]% / [redacted]% 2028: [redacted]% / [redacted]% / [redacted]% / [redacted]% 2029: [redacted]% / [redacted]% / [redacted]% / [redacted]% 2030: [redacted]% / [redacted]% / [redacted]% / [redacted]% 2031: [redacted]% / [redacted]% / [redacted]% / [redacted]%	Sponsor assumption; unable to be independently verified
Drug prices	PBS Listing of AEMP and DPMQ for current products; calculated effective price for MRSC risperidone	Appropriate
copayments	Based on current distribution for products listed above: PBS $31.60 and $7.70 RPBS $7.70 and 0. Average copayment $11.24 and $6.80	Appropriate
Market expansion rate	Assume to be zero given established market	Reasonable
Script equivalence	For R2WIM and R4WIM 0.92; for PP1M and A1M: 1.0	Reasonable
Grandfathered patients	None	Appropriate
MBS item	MBS Item 23, HCP visits for fortnightly injections and 'other monthly administered medications for a portion of patients.' Based on patients switching from fortnightly injections to monthly and switching from 13.04 injections/yr to 12. Full fee $43.90, 80% used in analysis.	Should not be included

Source: Tables 4.1, 4.2, 4.3, 4.5 pp189-198, of the submission.

6.92 The estimated use and financial impact of listing MRSC risperidone is shown in Table 14.

Table 14: Estimated use and financial implications, effective price

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use by preparation, scripts dispensed						
50 mg	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
75 mg	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
100 mg	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]
125 mg	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]
Total	[redacted][3]	[redacted][5]	[redacted][6]	[redacted][5]	[redacted][5]	[redacted][6]
Estimated financial implications of MRSC risperidone						
Cost to PBS/RPBS less copayments	$[redacted][7]	$[redacted][7]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]
Estimated financial implications for R2WIM and R4WIM, PP1M and A1M						
Cost to PBS/RPBS less copayments	-$[redacted][7]	-$[redacted][7]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]	-$[redacted][9]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net cost to MBS	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net cost to PBS/RPBS/MBS	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net cost to PBS/RPBS/MBS with MBS items removed	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Sensitivity analyses, net cost to PBS						
Dose distribution increased	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Increase market uptake	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]

Source: Tables 4.4, 4.7,4.10, 4.11, 4.12, 4.13, 4.16 pp196-206 of the submission.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*
[2] *5,000 to < 10,000*
[3] *10,000 to < 20,000*
[4] *20,000 to < 30,000*
[5] *30,000 to < 40,000*
[6] *40,000 to < 50,000*
[5] *50,000 to < 60,000*
[6] *70,000 to < 80,000*
[7] *$0 to < $10 million*
[8] *$10 million to < $20 million*
[9] *$20 million to < $30 million*

6.93 The total cost to the PBS/RPBS of listing MRSC risperidone was estimated to be $10 million to < $20 million in Year 6 with a net cost of -$0 to < $10 million. Over 6 years, the total cost of listing MRSC risperidone total was estimated as $70 million to < $80 million offset by the reduction in cost of the replaced antipsychotics with a resulting net saving over 6 years of $0 to < $10 million.

6.94 The submission presented sensitivity analyses for the estimates of total use and cost, varying the dose of MRSC risperidone and the market uptake. Varying the dose used had no impact on the estimates because a flat effective price was applied. The assumption used in the market share analyses, that more expensive products would be replaced, resulted in larger savings. The evaluation considered this may not be reasonable.

6.95 The evaluation considered the costs of health care provider (HCP) visits should not have been included in the analyses and provided revised estimates as shown in Table 15. The evaluation noted a significant proportion of the projected savings was

removed when this cost was removed. The PSCR stated that the inclusion of HCP services costs has previously been applied and reflects the price derivation of R2WIM and R4WIM (risperidone PSD, March 2024). It argued that regardless of the inclusion of HCP cost-offsets, cost-minimisation calculations using the lowest comparator price result in an identical weighted AEMP of $[redacted]. The ESC disagreed with the inclusion of the HCP services cost and considered the corrected estimates (see Table 15) provided by the evaluation to be appropriate.

6.96 During evaluation, the Secretariat identified the following issues in the financial estimates which were addressed in the model the evaluation used to revise the estimates shown in Table 15:

- The patient co-payment amount of $31.60 was not current as of 1 January 2026 and updated to $25.00.
- The service volumes for expected substitutable medicines in the current PBS market were not current. These were updated with the PBS service volume data from the 2025 calendar year (January – December).
- The estimated annual growth rates were not accurate. The source and justification were provided for the estimated annual growth, and the 5-year average calculation was updated to incorporate growth rates from 2021-2025.
- The estimated growth in some cells provided a value of 10000% in 2025. This error was assumed to be typographical and was corrected.

6.97 In the updated estimates, the total cost to the PBS/RPBS of listing MRSC risperidone was estimated to be $20 million to < $30 million in Year 6 with a net cost of -$0 to < $10 million. Over 6 years, the total cost of listing MRSC risperidone total was estimated as $$80 million to < $90 million offset by the reduction in cost of the replaced antipsychotics with a resulting net saving over 6 years of $0 to < $10 million.

Table 15: Estimated use and financial implications, effective price (Secretariat Updates)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use by preparation, scripts dispensed						
50 mg	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
75 mg	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
100 mg	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
125 mg	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]
Total	[redacted][4]	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][9]
Estimated financial implications of MRSC risperidone						
Cost to PBS/RPBS less copayments	$[redacted][10]	$[redacted][10]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][12]
Estimated financial implications for R2WIM and R4WIM, PP1M and A1M						
Cost to PBS/RPBS less copayments	-$[redacted][10]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][12]	-$[redacted][12]
Net financial implications						
Net cost to PBS/RPBS/MBS	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Sensitivity analyses, net cost to PBS						
Dose distribution increased	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Increase market uptake	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*
[2] *5,000 to < 10,000*
[3] *10,000 to < 20,000*
[4] *20,000 to < 30,000*
[5] *30,000 to < 40,000*
[6] *50,000 to < 60,000*
[7] *60,000 to < 70,000*
[8] *70,000 to < 80,000*
[9] *80,000 to < 90,000*
[10] *$0 to < $10 million*
[11] *$10 million to < $20 million*
[12] *$20 million to < $30 million*

Quality Use of Medicines

6.98 The submission provided a list of activities in relation to quality use of medicines for MRSC risperidone.

For more detail on PBAC's view, see section 7 PBAC outcome

7 PBAC outcome

7.1 The PBAC recommended the listing of MRSC risperidone for the treatment of adult patients with schizophrenia on a cost-minimisation basis to the lowest cost long-acting injection antipsychotic (of risperidone, paliperidone or aripiprazole).

7.2 The PBAC considered that the primary comparators, PP1M and A1M, were appropriate. The PBAC considered the submission's claim of non-inferior comparative effectiveness and safety of MRSC risperidone to the comparators to be reasonable, despite the identified transitivity limitations within the comparative evidence base. The PBAC agreed with the PSCR that MRSC risperidone would be non-inferior to the IM risperidone LAIs and therefore advised, consistent with its March 2024 advice, that LAIs of risperidone, paliperidone and aripiprazole, but not olanzapine, be considered

alternative therapies, noting that olanzapine is associated with post-injection syndrome requiring at least two to three hours of post-administration monitoring (Paragraphs 7.3 and 7.14, Risperidone PSD, March 2024 PBAC Meeting).

7.3 The PBAC noted the weighted average dose approach used in the submission and agreed with the ESC advice that the appropriate economic framework should be cost-minimisation to the lowest-cost LAI alternative on a cost per patient per year basis.

7.4 The PBAC noted the submission's equi-effective dose comparison was informed by the TGA Product Information. In the absence of direct switching data, the PBAC considered a pragmatic approach PI–based switching was considered acceptable in the absence of prior PBAC recommendations. As such, the PBAC considered the equi-effective doses as shown in Table 16.

Table 16: PBAC recommended equi-effective dosing

Oral risperidone (1-daily)[a]	MRSC risperidone (1-monthly)[a]	R4WIM (4-weekly)[a,b]	R2WIM (2-weekly)[b]	PP1M (1-monthly)[b,c]	A1M (1-monthly)[c]
1 mg	25 mg	25 mg	12.5 mg	25 mg	118 mg
2 mg	50 mg	50 mg	25 mg	50 mg	235 mg
3 mg	75 mg	75 mg	37.5 mg	75 mg	352 mg
4 mg	100 mg	100 mg	50 mg	100 mg	470 mg
5 mg	125 mg	125 mg	62.5 mg	125 mg	587 mg
6 mg	150 mg	150 mg	75 mg	150 mg	705 mg

A1M = Aripiprazole once-monthly intramuscular injection; MRSC = modified release subcutaneous injection; PP1M = paliperidone once-monthly intramuscular injection; R2WIM = risperidone 2-weekly intramuscular injection; R4WIM = risperidone 4-weekly intramuscular injection

[a] TGA Product Information

[b] risperidone PSD, March 2024

[c] aripiprazole PSD, July 2014

7.5 The PBAC advised that MRSC risperidone is non-inferior in comparative effectiveness to PP1M and A1M for relapse prevention in adults with schizophrenia. The PBAC noted that MRSC risperidone, PP1M and A1M were each superior to placebo in maintenance trials, and by indirect comparative analyses against placebo, which the PBAC considered appropriate for assessing non-inferiority in the absence of direct head-to-head evidence. Limitations affecting transitivity across the trials which included differences in stabilisation and run-in procedures, baseline symptom severity, relapse definitions, and notably lower placebo relapse rates in the RISE study, were acknowledged by the PBAC. However, these limitations were deemed insufficient to undermine the overall interpretation of comparative effectiveness. In particular, the PBAC accepted that the direction and magnitude of treatment effects versus placebo were broadly consistent across trials and considered that the application of a 20% non-inferiority margin for direct comparisons, and a more conservative margin of 11.5% for indirect comparisons, was appropriate.

7.6 The PBAC noted that the adverse event profile of MRSC risperidone was consistent with the known safety profile of PP1M. The PBAC noted higher rates of treatment-emergent adverse events leading to withdrawal and prolactin-related events in indirect comparisons with A1M but considered these findings consistent

with recognised class effects and influenced by differences in trial design and run-in phases. The PBAC noted that no unexpected safety signals were identified and considered that, overall, the evidence supported a conclusion of non-inferior comparative safety relative to PP1M and A1M.

7.7 Overall, the PBAC advised the clinical evidence presented by the submission reasonably demonstrated comparative non-inferior effectiveness and safety, and considered that it was broadly consistent with other LAI trials and sufficiently informative for decision making.

7.8 The PBAC noted that the submission had requested a Special Pricing Arrangement (SPA). The PBAC could not advise the Minister that MRSC risperidone generates substantial incremental benefits for its intended population (over standard treatment). The PBAC advised that the SC route of administration, which may facilitate improved ease of use and better injection experience, and the potential for future self-administration, could be considered unique characteristics of MRSC risperidone. However, the PBAC considered that these differences could not be considered substantial relative to IM LAIs for the same indication, as the submission did not present any evidence that demonstrated a benefit in patient outcomes.

7.9 The PBAC supported the methodology used to develop the submission's financial estimates model for listing MRSC risperidone but with the exclusion of health care provider (HCP) visit costs. The PBAC agreed with the ESC advice to exclude health care provider visit costs, acknowledging that this materially reduced the projected cost savings. The PBAC noted that revisions were made to the financial estimates model during the evaluation. The PBAC noted the revised estimates corrected patient co-payments, PBS service volumes, growth rate assumptions and data errors, which indicated a modest net saving to the PBS over six years. The PBAC advised that the revised estimates with the exclusion of the HCP visit costs were appropriate.

7.10 The PBAC noted the proposed restriction wording and agreed with the ESC advice which it noted was consistent with the listing of R4WIM. The PBAC therefore advised that the restriction should remain consistent with that of R4WIM, that is, it should include advice on switching between oral and MRSC risperidone and the DSM-5 definition of schizophrenia, and should not require specification of stabilisation on oral risperidone for a minimum period of 12 weeks.

7.11 The PBAC advised that MRSC risperidone is suitable for prescribing by nurse practitioners consistent with current PBS listings for oral and IM risperidone and paliperidone/aripiprazole (oral tablet and LAI) for the treatment of schizophrenia.

7.12 The PBAC considered this restriction to be simple.

7.13 The PBAC advised that the Early Supply Rule (Safety Net Penalty) should not apply consistent with the current PBS listings for oral and IM risperidone and paliperidone/aripiprazole (oral tablet and LAI) for the treatment of schizophrenia.

7.14 In the context of the cost-minimisation approach taken by the submission, the PBAC advised, under subsection 101(3B) of the *National Health Act 1953*, that MRSC

risperidone does not provided a significant and clinically relevant improvement in efficacy and/or reduction of toxicity over the alternative therapies. For the same reason the PBAC also advised that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met and because MRSC risperidone is not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, nor would it be in the public interest for a pricing application relating to the drugs or medicinal preparations to be in this category.

7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new listing as follows:

MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
RISPERIDONE						
Risperidone 50 mg/0.14 mL subcutaneous modified release injection prefilled syringe drug		NEW	1	1	5	Uzedy
Risperidone 75 mg/0.21 mL subcutaneous modified release injection prefilled syringe drug		NEW	1	1	5	Uzedy
Risperidone 100 mg/0.28 mL subcutaneous modified release injection prefilled syringe drug		NEW	1	1	5	Uzedy
Risperidone 125 mg/0.35 mL subcutaneous modified release injection prefilled syringe		NEW	1	1	5	Uzedy
Restriction Summary [new 1]/ Treatment of Concept: [new 2]						
Concept ID (for internal Dept. use)	**Category / Program:** General Schedule Section 85					
	Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners					
	Restriction type: ☒Authority Required (STREAMLINED)					
	Condition: Schizophrenia					
	Indication: Schizophrenia					
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
	Administrative Advice: No increase in the maximum number of repeats may be authorised					
	Administrative Advice: For a patient switching from oral risperidone, the prescriber must determine the patient dosage of this drug based on the current dose of oral risperidone according to the dose transition table in the Therapeutic Goods Administration (TGA) approved Product Information.					
	Administrative Advice: For the purpose of administering this restriction, Schizophrenia refers to schizophrenia spectrum disorders outlined in the DSM-5 criteria					

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Teva is committed to working with the Department through the PBS listing process, resolving any outstanding items, and to support timely access in Australia, ensuring those living with schizophrenia can access clinically appropriate antipsychotic treatment.