5.35 RISPERIDONE

Powder for I.M. injection 75 mg (modified release) with 0.383 mL diluent in pre-filled syringe, Powder for I.M. injection 100 mg (modified release) with 0.49 mL diluent in pre-filled syringe, Okedi®, SERVIER LABORATORIES (AUST.) PTY. LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required listing for risperidone in-situ microparticles (ISM) long-acting injection (LAI) for the treatment of schizophrenia in adults whom tolerability and effectiveness have been established with oral risperidone.

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus risperidone 2-weekly LAI (RC) and paliperidone 1-monthly LAI (PP1M).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Schizophrenia in adults in whom tolerability and effectiveness has been established with oral risperidone
Intervention	Prefilled syringe containing 75 mg or 100 mg of risperidone ISM and prefilled syringe containing DMSO, to be administered every 4 weeks
Comparator	Risperidone 2-weekly LAI (Risperdal Consta®, RC) Paliperidone 1-monthly LAI (Invega Sustenna®, PP1M)
Outcomes	Efficacy: PANSS, CGI-S Safety: Incidence of SAE, incidence of TEAE
Clinical claim	In adults with schizophrenia, compared to the primary and secondary comparator, risperidone ISM is non-inferior in terms of efficacy and non-inferior in term of safety.

Source: Table 1-1, p15 of the submission.
CGI-S = Clinical Global Impression-Severity, DMSO = dimethyl sulfoxide, ISM = in-situ microparticles, LAI = long-acting injection, PANSS = Positive and Negative Syndrome Scale, PP1M = paliperidone 1-monthly long-acting injectable, RC = risperidone 2-weekly long-acting injectable, SAE = serious adverse event, TEAE = treatment emergent adverse event.

2 Background

Registration status

2.1 Risperidone ISM was submitted under the TGA/PBAC parallel process and registered by the TGA on 19 December 2023. The approved indication is for "the treatment of schizophrenia in adults for whom tolerability and effectiveness has been established with oral risperidone".

Previous PBAC consideration

2.2 Risperdal Consta (RC), a different LAI formulation to risperidone ISM, was considered and recommended by the PBAC for the treatment of schizophrenia in July 2004.

2.3 Other LAI antipsychotics that have been considered for the treatment of schizophrenia include paliperidone 1-monthly (PP1M), 3-monthly (PP3M) and 6-monthly (PP6M), olanzapine with a dosing frequency of 2-4 weeks and aripiprazole with a 4-weekly dosing frequency. The PBS restrictions for the LAIs with a dosing frequency of 3 months or more (e.g., PP3M and PP6M) include additional clinical criteria restricting use to patients who have previously received and been established on subsidised paliperidone.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	**Dispensed Price for Max. Qty**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
RISPERIDONE					
Risperidone 75mg powder and solvent for prolonged-release suspension for injection	$335.80	1	1	5	Okedi
Risperidone 100mg powder and solvent for prolonged-release suspension for injection	$407.03	1	1	5	Okedi
Category / Program: General Schedule					
Prescriber type: ☐Dental ☒Medical practitioners ☐Nurse practitioners ☐Optometrists ☐					
Restriction type: ☒Authority Required (STREAMLINED)					
Administrative Advice: Patient dosage is to be determined as per the dose transition table in the Product Information based on the current dose of oral risperidone. No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised.					
Condition: Schizophrenia					
Indication: Schizophrenia					
Treatment Phase: Initial and continuing					
Prescribing Instructions: Shared care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.					

3.1 Both proposed comparators (RC and PP1M) list Nurse Practitioners in addition to Medical Practitioners under Prescriber type. The proposed prescribing instructions

suggest that Nurse Practitioners may be intended to be included under Prescriber type given the proposed Shared care model.

3.2 The approved TGA indication and proposed population for PBS listing is for 'the treatment of schizophrenia in adults for whom tolerability and effectiveness has been established with oral risperidone'. The proposed PBS restriction does not require prior use of oral risperidone. However, the PBAC has previously considered that prescribers would be unlikely to initiate patients on a modified release injection formulation and therefore a listing simply for "schizophrenia" is appropriate and consistent with other PBS-listed modified release antipsychotic injections' (paragraph 7.2, aripiprazole, Public Summary Document (PSD), PBAC meeting July 2014).

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

4 Population and disease

4.1 Schizophrenia is a chronic severe psychiatric condition characterised by disturbances in thought, perceptions, behaviour, cognition and emotions. It has profound impacts on quality of life and is associated with reduced life expectancy. There is a high cost in health care use and in productivity impacts due to reduced participation in employment and carer burden. The onset is usually in early adulthood.

4.2 Antipsychotics are the mainstay of treatment of the symptoms of schizophrenia, with the main goal of relapse prevention. Adherence issues in patients with schizophrenia are common and can lead to poorer outcomes such as exacerbation of symptoms, hospitalisation and social harms. LAI antipsychotics, which are administered by a clinician, can improve adherence. LAIs are associated with lower rates of relapse and hospitalisation.

4.3 The proposed place of risperidone ISM in therapy is as an alternative to existing LAI antipsychotics in patients who have had tolerability and effectiveness established with oral risperidone.

4.4 Risperidone ISM is a LAI formulation of risperidone, a second-generation antipsychotic (class N05AX – other antipsychotics). It is based on technology that delivers risperidone via in-situ microparticles in a manner that results in similar therapeutic plasma levels on day 1 of treatment compared to oral risperidone, with these levels being sustained for up to 28 days. As such, it requires dosing 4-weekly and does not require initial oral risperidone supplementation nor loading doses.

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

5 Comparator

5.1 The submission nominated two comparators, risperidone 2-weekly LAI (RC) and paliperidone 1-monthly LAI (PP1M).

5.2 Risperidone ISM and RC are different formulations of risperidone, with different dosing schedules. RC is an extended-release microspheres formulation and is administered 2-weekly. It requires supplementation with oral risperidone for the first 3 weeks of treatment (compared to 4-weekly administration without need for oral supplementation with risperidone ISM). For both, it is recommended to establish tolerability on oral risperidone prior to initiating the LAI.

5.3 Paliperidone is the primary active metabolite of risperidone and PP1M is administered monthly. It requires loading doses at days 1 and 8 (if the patient is risperidone or paliperidone naïve). Risperidone ISM is likely to substitute for PP1M in some patients given that it is administered over a similar period (4-weekly for risperidone ISM compared to monthly for PP1M).

5.4 Given the availability of RC and PP1M, and the limited number of dose strengths available for risperidone ISM compared to PP1M, the ESC considered that the clinical need for risperidone ISM was unclear.

5.5 In the context of the CMA taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.6 For the requested population, the evaluation and the ESC considered the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: RC, PP1M, and aripiprazole 4-weekly.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on six randomised, placebo-controlled trials, and one phase 2b trial. The randomised trials comprised one trial that compared risperidone ISM to placebo (PRISMA-3), one that compared RC to placebo (Kane 2003) and four trials that compared PP1M to placebo (Gopal 2010, Nasrallah 2010, Bossie 2011, Takahashi 2013). The phase 2b trial for PP1M was Kramer 2010. No head-to-head randomised trials comparing risperidone ISM to either comparator was available.

6.4 For the comparison of risperidone ISM versus RC, the evidence for efficacy was informed by an ITC via the common placebo arm and the evidence for safety was informed by a comparison of single arms, both analyses using the risperidone ISM (PRISMA-3) and RC (Kane 2003) trials.

6.5 For the comparison of risperidone ISM versus PP1M, the evidence for efficacy was informed by an ITC via the common placebo arm using the risperidone ISM trial (PRISMA-3) and a meta-analysis using four PP1M trials (Gopal 2010, Nasrallah 2010, Bossie 2011, Takahashi 2013). A comparison of single arms for safety was based on the risperidone ISM trial (PRISMA-3) and a meta-analysis using three PP1M trials (Kramer 2010, Bossie 2011 and Takahashi 2013).

6.6 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Risperidone ISM trials		
PRISMA-3 NCT03160521	Multicenter, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intramuscular Injections of Risperidone ISM® in Patients with Acute Exacerbation of Schizophrenia (PRISMA-3). Study to Evaluate the Efficacy and Safety of Risperidone in Situ Microparticle (ISM)® in Patients With Acute Schizophrenia (PRISMA-3). Correll CU, Litman RE, Filts Y et al. Efficacy and safety of once-monthly Risperidone ISM® in schizophrenic patients with an acute exacerbation. Litman RE, Filts Y, Pata M et al. P.0839 Risperidone ISM® effect size evaluation: post-hoc findings from the prisma-3 phase III study.	02 June 2020 Clinicaltrials.gov, results first posted 04 February 2022 NPJ Schizophr 2020; 6(1):37-46. Eur Neuropsychopharmacol 2021; 53: S613-S614.
RC trials		
Kane 2003	Kane JM, Eerdekens M, Lindenmayer JP et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Lauriello J, McEvoy JP, Rodriguez S et al. Long-acting risperidone vs. placebo in the treatment of hospital inpatients with schizophrenia.	Am J Psychiatry 2003; 160(6):1125-32. Schizophr Res. 2005; 72(2-3):249-58.
PP1M trials		
Gopal 2010 NCT00147173	Gopal S, Hough DW, Xu H et al. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study.	Int Clin Psychopharmacol 2010; 25(5):247-56.
Nasrallah 2010 NCT00101634	Nasrallah HA, Gopal S, Gassmann-Mayer C et al. A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia.	Neuropsychopharmacology 2010; 35(10):2072-82.
Kramer 2010 NCT00074477	Kramer M, Litman R, Hough D et al. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study.	Int J Neuropsychopharmacol. 2010; 13(5):635-47.
Bossie 2011 NCT00590577	Bossie CA, Sliwa JK, Ma YW et al. Onset of efficacy and tolerability following the initiation dosing of long-acting paliperidone palmitate: post-hoc analyses of a randomized, double-blind clinical trial. Pandina GJ, Lindenmayer JP, Lull J et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. Sliwa JK, Bossie CA, Ma YW et al. Effects of acute paliperidone palmitate treatment in subjects with schizophrenia recently treated with oral risperidone.	BMC Psychiatry 2011; 11:79. J Clin Psychopharmacol 2010; 30(3):235-44. Schizophr Res 2011; 132(1):28-34.
Takahashi 2013 NCT01299389	Takahashi N, Takahashi M, Saito T et al. Randomized, placebo-controlled, double-blind study assessing the efficacy and safety of paliperidone palmitate in Asian patients with schizophrenia. An Efficacy and Safety Study of Paliperidone Palmitate in Participants With Schizophrenia	Neuropsychiatr Dis Treat 2013; 9:1889-98. Clinicaltrials.gov, results first posted 17 June 2013

Source: Table 2.5, p43 of the submission.
ISM = in-situ microparticles, PP1M = paliperidone 1-monthly long-acting injectable, RC = risperidone 2-weekly long-acting injectable.

6.7 The key features of the included randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Risperidone ISM vs placebo					
PRISMA-3	Placebo (N = 147) Risperidone ISM 75 mg (N = 145) Risperidone ISM 100 mg (N = 146)	R, Phase 3, MC, PC, DB 12 weeks	High	Acute schizophrenia	Primary: PANSS total score Secondary: CGI-S total score
RC vs placebo					
Kane 2003	Placebo (N = 98) RC 25 mg (N = 99) RC 50 mg (N = 103) RC 75 mg (N = 100)	R, Phase 3, MC, PC, DB 12 weeks	Medium	Maintenance schizophrenia	Primary: PANSS total score Secondary: CGI-S total score
PP1M vs placebo					
Gopal 2010	Placebo (N = 136) PP1M 50 mg (N = 94) PP1M 100 mg (N = 97) PP1M 150 mg (N = 30)	R, Phase 3, MC, PC, DB 13 weeks	Medium	Acute schizophrenia	Primary: PANSS total score Secondary: CGI-S total score
Nasrallah 2010	Placebo (N = 127) PP1M 25 mg (N = 131) PP1M 50 mg (N = 129) PP1M 100 mg (N = 131)	R, Phase 3, MC, PC, DB 13 weeks	Medium	Schizophrenia, not stated whether acute	Primary: PANSS total score Secondary: CGI-S total score
Kramer 2010	Placebo (N = 84) PP1M 50 mg (N = 79) PP1M 100 mg (N = 84)	R, Phase 2b, MC, PC, DB 9 weeks	Medium	Schizophrenia, not stated whether acute, maintenance or both	Primary: PANSS total score Secondary: CGI-S total score
Bossie 2011	Placebo (N = 164) PP1M 50 mg (N = 160) PP1M 100 mg (N = 165) PP1M 150 mg (N = 163)	R, Phase 3, MC, PC, DB 12 weeks	Medium	Acute schizophrenia	Primary: PANSS total score Secondary: CGI-S total score
Takahashi 2013	Placebo (N = 164) PP1M 75 mg (N = 160)	R, Phase 3, MC, PC, DB 12 weeks	Low	Schizophrenia, not stated whether acute, maintenance or both	Primary: PANSS total score Secondary: CGI-S total score
PP1M 100 mg meta-analysis (efficacy: total PANSS score)	554	Included Gopal 2010, Nasrallah 2010, Bossie 2011 and Takahashi 2013; assessed PANSS total score			
PP1M 100 mg meta-analysis (safety: SAE)	324	Included Bossie 2011 and Takahashi 2013; assessed incidence of SAE			
PP1M 75 mg meta-analysis (safety: TEAE)	243	Included Kramer 2010 and Takahashi 2013; assessed incidence of TEAE			

Source: Table 2.17, pp70-72 of the submission, and Section 2.4 of the submission.

BMI = body-mass index, CGI-S = Clinical Global Impression-Severity, DB = double blind, ISM = in-situ microparticles, MC = multi-centre, PANSS = Positive and Negative Syndrome Scale, PC = placebo-controlled, PP1M = paliperidone 1-monthly long-acting injectable, R = randomised, RC = risperidone 2-weekly long-acting injectable, SAE = serious adverse event, TEAE = treatment emergent adverse event.

6.8 For the risperidone ISM (PRISMA-3) trial, there was a medium risk of performance and attrition bias associated with possible unblinding of 43 patients enrolled who were excluded from the modified intent-to-treat (mITT) population for the efficacy analysis (PRISMA-3 CSR). The evaluation and the ESC noted there was a high risk of selection

bias as patients who had an improvement of 20% or more in total PANSS score between the initial screening visit and first injection were excluded from randomisation.

6.9 The RC and PP1M trials also had some risks of bias associated with attrition (Kane 2003, Kramer 2010, Gopal 2010), selection (Kramer 2010), failure to report randomisation detail (Nasrallah 2010, Takahashi 2013) and failure to report outcome assessment blinding (PP1M trials).

6.10 While the submission proposed listing of risperidone ISM for the maintenance treatment of schizophrenia in adults for whom tolerability and effectiveness has been established with oral risperidone, patients with acute schizophrenia formed the study populations in the PRISMA-3, Gopal 2010 and Bossie 2011 trials.

6.11 Another key difference between trials was disease severity. The mean baseline total PANSS score for each treatment group in the PRISMA 3 trial (mean score range: 96.1-96.4) was higher than mean baseline scores in the RC trials (mean score range: 80.1-82.3) and the PP1M trials (mean score range: 85.2-92) due to differences in trial eligibility. The evaluation and the ESC noted this is likely to favour risperidone ISM since a subgroup analysis of patients with baseline total PANSS score ≥ 95 from the PRISMA-3 trial demonstrated a slightly greater magnitude of improvement with risperidone ISM treatments.

6.12 The treatment regimens in the risperidone ISM (PRISMA-3) and RC (Kane 2003) trials were consistent with the regimens recommended in their respective PI documents except for the PP1M trials. The initial doses used in the PP1M trials were generally lower than the recommended dosing schedule in the PI, which could compromise early treatment response and potentially favour risperidone ISM when compared with PP1M. There were also minor differences to the treatment schedule of maintenance dosing (i.e., 4-weekly in PP1M trials as opposed to monthly in the PI).

6.13 The primary outcome for the indirect treatment comparisons of risperidone ISM with both comparators was the mean change from baseline in total PANSS score. The submission proposed a minimum clinically important difference (MCID) of 7-points in the mean change from baseline in total PANSS score. This was consistent with the previously accepted non-inferiority margin accepted by the PBAC for schizophrenia of a 7-point difference in the total PANSS score (paragraph 8.4, paliperidone, PSD, November 2007 meeting; paragraph 9.2, lurasidone hydrochloride, PSD, March 2014 meeting; paragraph 6.10, brexpiprazole, PSD, March 2017 meeting; paragraph 6.9, cariprazine, PSD, November 2020 meeting).

6.14 The secondary outcome of mean change from baseline in total CGI-S score was considered for the ITC of risperidone ISM versus RC only. The submission stated that the CGI-S data was limited across the five PP1M trials and an ITC of risperidone ISM versus PP1M could not be successfully conducted for this clinical endpoint. The submission did not propose a MCID for mean change from baseline in total CGI-S score since only the primary outcome has been previously considered by the PBAC. The

Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review Clinical Review Report for brexpiprazole, an atypical antipsychotic drug indicated for the treatment of schizophrenia in adults, recognises a MCID for total CGI-S score of a 1-point difference[1]. The ESC noted that results for the secondary outcome of mean change from baseline in total CGI-S score were included in the submission but considered that the primary outcome of mean change from baseline in the total PANSS score was the pivotal outcome in relation to efficacy.

6.15 Given the chronicity of the condition and the need for long term treatment, the evaluation noted the lack of longer-term data, with the clinical claim being based on data from the PRISMA-3 trial, with a duration of 12-weeks.

Comparative effectiveness

6.16 For both risperidone ISM 75 mg and 100 mg, the submission estimated the therapeutic equivalent dose for each of the RC and PP1M comparators using the PI for each product, published guidelines and pharmacological evidence provided by the sponsor to establish a series of pairwise steady-state dose relationships. The therapeutic equivalent doses for risperidone ISM were stated to be:

- Risperidone ISM 75 mg 4-weekly is equivalent to RC 37.5 mg 2-weekly.
- Risperidone ISM 100 mg 4-weekly is equivalent to RC 50 mg 2-weekly.
- Risperidone ISM 75 mg 4-weekly is equivalent to PP1M 75 mg monthly.
- Risperidone ISM 100 mg 4-weekly is equivalent to PP1M 100 mg monthly.

6.17 From these therapeutic equivalences, the submission proposed that this would enable an ITC for efficacy of risperidone ISM 75 mg 4-weekly to both RC 37.5 mg 2-weekly and PP1M 75 mg monthly, and an ITC for efficacy of risperidone ISM 100 mg 4-weekly to both RC 50 mg 2-weekly and PP1M 100 mg monthly.

6.18 For the comparison with RC, the submission performed an ITC for efficacy of risperidone ISM 100 mg versus RC 50 mg but omitted the comparison of risperidone ISM 75 mg versus RC 37.5 mg justifying this by stating that there was no placebo-controlled efficacy data for RC 37.5 mg available.

6.19 The submission assumed that if risperidone ISM 100 mg showed similar drug levels at steady state to RC 50 mg, it could be expected that the risperidone ISM 75 mg would also show similar exposures at steady state to RC 37.5 mg. The submission justified their claim using information presented from a 2019 internal report of a pharmacokinetic study to stimulate and evaluate different possible risperidone ISM switching strategies from RC (ROVI, 2019). The report concluded that switching from RC 37.5 mg and 50 mg to risperidone ISM 75 mg and 100 mg, respectively was

[1] CADTH, (2017), 'CADTH Common Drug Review Clinical Review Report Brexpiprazole (Rexulti)', https://www.ncbi.nlm.nih.gov/books/NBK535498/

predicted to result in similar exposures, with steady state reached from the second injection onwards (ROVI 2019 sponsor's report). The sponsor presented these findings to the TGA. In the TGA Clinical Evaluation Report, the TGA acknowledged that the results of the pharmacokinetic analysis of RC and risperidone ISM supported switching between the two medicines at their therapeutic equivalent doses (Okedi Evaluation Report, TGA).

6.20 For the comparison with PP1M, the submission performed an ITC for efficacy of risperidone ISM 75 mg versus PP1M 75 mg, as well as for risperidone ISM 100 mg versus PP1M 100 mg. For the comparison of risperidone ISM 75 mg to PP1M 75 mg, the PP1M trial was directly informed by Takahashi 2013, whereas the meta-analysed results of the PP1M 100 mg (Gopal 2010, Nasrallah 2010, Bossie 2011 and Takahashi 2013) trials were used for the comparison of risperidone ISM 100 mg to PP1M 100 mg.

6.21 Table 4, Table 5 and Table 6 present the results of the primary outcome (total PANSS score) from the risperidone ISM (PRISMA-3), RC (Kane 2003) and PP1M (Gopal 2010, Nasrallah 2010, Kramer 2010, Bossie 2011 and Takahashi 2013) trials, respectively, for treatment regimens that were then used in the ITCs. Negative values indicate improvement.

Table 4: Results of change from baseline in total PANSS score in the risperidone ISM trial (PRISMA-3 mITT and ITT populations)

Efficacy measure	Placebo N = 132 (mITT) N = 145 (ITT)	Risperidone ISM 75 mg N = 129 (mITT) N = 143 (ITT)	Risperidone ISM 100 mg N = 129 (mITT) N = 145 (ITT)
mITT			
Baseline, mean (SD)	96.4 (7.21)	96.3 (8.47)	96.1 (8.42)
Change from baseline to endpoint (Day 85), LS means (SE)	-11.0 (1.56)	-24.6 (1.51),	-24.7 (1.54)
Treatment difference (95% CI), p-value[a]	-	**-13.6 (-17.8, -9.3), <0.0001**	**-13.6 (-17.9, -9.3), <0.0001**
ITT			
Baseline, mean (SD)	96.1 (7.25)	96.2 (8.40)	95.9 (8.50)
Change from baseline to endpoint (Day 85), LS means (SE)	-11.8 (1.48)	-23.9 (1.44)	-24.5 (1.46)
Treatment difference (95% CI), p-value[a]	-	**-12.0 (-16.1, -8.0), <0.0001**	**-12.7 (-16.8, -8.6), <0.0001**

Source: Table 2.30, p98 of the submission, Table 2.31, p99 of the submission, Table 2.32, p100 of the submission, Table 2.33, p100 of the submission, Table 14.2.1.1.1.1, p472 of the PRISMA -3 CSR, Table 14.2.1.1.2.1, p480 of the PRISMA-3 CSR, Table 14.2.2.1.1.1.1, p598 of the PRISMA-3 CSR, and Table 14.2.2.1.1.2.1, p609 of the PRISMA -3 CSR.

CI = confidence interval, ISM = in-situ microparticles, ITT= intent-to-treat, LS = least-squares, mITT = modified intent-to-treat, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation, SE = standard error.

[a] Treatment difference compared with placebo.

Bold indicates statistically significant results.

Table 5: Results of change from baseline in total PANSS score in the RC trial (Kane 2003)

Efficacy measure	Placebo N = 92	RC 25 mg N = 93	RC 50 mg N = 98	RC 75 mg N = 87
Baseline, mean (SD)	82.0 (14.4)	81.7 (12.5)	82.3 (13.9)	80.1 (14.0)
Change from baseline to endpoint (Day 84), LS mean (SD)	2.6 (16.9)	-6.2 (16.9)	-8.5 (16.9)	-7.4 (16.9)
Treatment difference (95% CI), p-value[a]	-	**-8.8 (-13.7, -3.9), 0.002**	**-11.1 (-15.9, -6.3), <0.001**	**-10.0 (-15.0, -5.0), <0.001**

Source: Table 2.40, p107 of the submission, Table 2.41, p109 of the submission and sponsor's attachment "20221027 ITC- Okedi".
CI = confidence interval, CGI-S = Clinical Global Impression-Severity, LS = least-squares, NR = not reported, PANSS = Positive and Negative Syndrome Scale, RC = risperidone 2-weekly long-acting injectable, SD = standard deviation.
[a] Treatment difference compared with placebo.
Bold indicates statistically significant results.

Table 6: Results of change from baseline in total PANSS score in the PP1M trials (Gopal 2010, Nasrallah 2010, Kramer 2010, Bossie 2011 and Takahashi 2013)

Gopal 2010	**Placebo (N = 132)**	**PP1M 100 mg (N = 94)**
Baseline, mean (SD)	92 (12.6)	90 (11.7)
Change from baseline to Day 92, LS means (SE)	-4.1 (1.83)	NR
Treatment difference (95% CI), p-value[a]	-	**-6.9 (NR), 0.019**
Nasrallah 2010	**Placebo (N = 125)**	**PP1M 100 mg (N = 131)**
Baseline, mean (SD)	90.7 (12.22)	90.8 (11.7)
Change from baseline to Day 92, LS means (SE)	-7.0 (20.07)	-16.1 (20.36)
Treatment difference (95% CI), p-value[a]	-	**-9.1 (-14.0, -4.1), <0.001**
Kramer 2010	**Placebo (N = 66)**	**PP1M 100 mg (N = 68)**
Baseline, mean (SD)	87.8 (13.9)	85.2 (11.09)
Change from baseline to Day 64, LS means (SE)	6.2 (18.25)	-7.8 (19.40)
Treatment difference (95% CI), p-value[a]	-	**-14.0 (-20.4, -7.6), <0.0001**
Bossie 2011	**Placebo (N = 160)**	**PP1M 100 mg (N = 161)**
Baseline, mean (SD)	86.8 (10.31)	86.2 (10.77)
Change from baseline to Day 92, LS means (SE)	2.9 (NR)	-11.6 (NR)
Treatment difference (95% CI), p-value[a]	-	**-8.7 (NR), <0.001**
Takahashi 2013	**Placebo (N = 164)**	**PP1M 75 mg (N = 159)**
Baseline, mean (SD)	83.5 (15.18)	85.7 (14.57)
Change from baseline to Day 92, LS means (SE)	6.9 (19.13)	-3.1 (20.32)
Treatment difference (95% CI), p-value[a]	-	**-9.7 (-14.0, -5.4), <0.0001**

Source: Section 2.5.3 of the submission and relevant trial publications.
CI = confidence interval, CGI-S = Clinical Global Impression-Severity, PANSS = Positive and Negative Syndrome Scale, PP1M = paliperidone 1-monthly long-acting injectable, NR = not reported, SD = standard deviation.
[a] Treatment difference compared with placebo.
Bold indicates statistically significant results.

6.22 Significant improvements to patients' total PANSS score were observed when either risperidone ISM (75 mg or 100 mg), RC (50 mg) and PP1M (75 mg or 100 mg) were compared to placebo. There were no meaningful differences between risperidone ISM 75 mg and 100 mg with respect to mean change from baseline in total PANSS score.

6.23 The submission performed several meta-analyses of different strengths for PP1M. The results of the meta-analysis of PP1M 100 mg were subsequently used as the primary

analysis in the ITC of risperidone ISM versus PP1M. The submission selected four studies (Gopal 2010, Nasrallah 2010, Bossie 2011 and Takahashi 2013) for the meta-analysis of PP1M 100 mg. The submission considered a sensitivity analysis for the meta-analysis of PP1M 100 mg by including trial results from Kramer 2010 (see Table 7). The Kramer 2010 study was initially excluded from the base-case analysis because the trial duration was considerably shorter than in the other studies (9 weeks of treatment in Kramer 2010 versus 12 weeks of treatment in the other studies). It was unclear why the Takahashi 2013 trial was included since the treatment regimen from Takahashi 2013 investigated the use of PP1M 75 mg and not PP1M 100 mg. There was a larger treatment difference in the mean change from baseline to endpoint of total PANSS score for the PP1M 75 mg trial arm of Takahashi 2013 than in the PP1M 100 mg trial arms of Gopal 2010, Nasrallah 2010 and Bossie 2011, and therefore the inclusion of Takahashi 2013 could have led to the analysis showing a greater improvement in total PANSS score for PP1M 100 mg compared to placebo. Consequently, when the results of the meta-analysis of PP1M 100 mg were used for the ITC with risperidone ISM 100 mg, this could have potentially favoured PP1M 100 mg. The Pre-Sub-Committee Response (PSCR) agreed that there was a potential mismatch in study selection of the meta-analysis of PP1M 100 mg and stated that this was unlikely to have negatively affected the clinical claim, given that the bias was potentially against risperidone ISM.

6.24 Table 7 summarises the least squares (LS) mean difference from placebo for total PANSS score change from baseline for the meta-analysis of PP1M 100 mg.

Table 7: Summary of pooled values (base case and sensitivity analysis) for LS mean difference from placebo for total PANSS score change from baseline

PP1M dose	LS mean difference from placebo (SE)[a]	95% CI
Base case		
PP1M 100 mg[b]	-8.72 (1.1)	-11.0, -6.5
Sensitivity analysis		
PP1M 100 mg[c]	-9.29 (1.1)	-11.4, -7.2

Source: Table 2.72, p133 of the submission.
CI = confidence interval, LS = least squares, NA = not applicable, PP1M = paliperidone 1-monthly long-acting injectable, SE = standard error.
[a] Change in baseline of total PANSS score.
[b] Base case pooled value obtained by excluding Kramer 2010.
[c] Sensitivity analysis carried out by including Kramer 2010.

6.25 Results of the meta-analysis for PP1M 100 mg demonstrated a significant improvement in the total PANSS score for PP1M compared to placebo of -2.32 (95% CI: -3.6, -1.0).

6.26 The submission claimed that transitivity assumption assessment in both the indirect treatment comparisons of risperidone ISM versus RC and risperidone ISM versus PP1M reported no major differences for comparable parameters between the baseline characteristics of the trials included in the respective networks. Apart from baseline differences in gender, ethnicity, BMI across the trials, the baseline total PANSS score for the PRISMA-3 trial was generally higher than other trials across treatment groups due to the inclusion criteria differing between the two populations.

Hence, the mean baseline total PANSS scores from each treatment group of the PRISMA 3 trial (mean score range: 96.1-96.4) were higher than those from the RC (mean score range: 80.1-82.3) and PP1M (mean score range: 85.2-92) trials. Therefore, efficacy estimates from the ITC analyses may be biased towards risperidone ISM.

6.27 The submission noted that there is 16-year gap between the risperidone ISM (PRISMA-3) and RC (Kane 2003) trials, which could be a source of difference in baseline characteristics, and generally a source of difference in quality of trial results observed.

6.28 The efficacy outcomes for the risperidone ISM (PRISMA-3) trial in the ITC were reported at endpoint (defined by the trial as Day 85 or last post baseline double-blind assessment). Conversely, the efficacy outcomes for the RC (Kane 2003) trial were reported for patients with observations at Day 84 as opposed to endpoint (defined by the trial as Day 84 or last observation carried forward values). This discrepancy between whether the PRISMA-3 and Kane 2003 trial included the patients' last observation/assessment for the evidence network is likely to limit the transitivity assumption. The evaluation revised the analysis to use trial results at endpoint from PRISMA-3 and Kane 2003.

6.29 Table 8 presents the efficacy results for the ITC of risperidone ISM versus RC.

Table 8: Indirect treatment comparison of risperidone ISM versus RC (mean change from baseline in total PANSS score)

Analysis	Trial	Comparison	Mean difference (95% CI)
Base case: Analysed using Least-squares mean difference			
Risperidone ISM 100 mg vs RC 50 mg	PRISMA-3	Risperidone ISM 100 mg vs placebo	-13.6 (-17.9, -9.3)
	Kane 2003[b]	RC 50 mg vs placebo	-11.1 (-15.9, -6.3)
	Indirect comparison	Risperidone ISM 100 mg vs RC 50 mg	-2.5 (-9.0, 4.0)
Sensitivity analysis: Analysed using Lawrence and Hung mean difference from the PRISMA-3 trial			
Risperidone ISM 100 mg vs RC 50 mg	PRISMA-3	Risperidone ISM 100 mg vs placebo	-13.3 (-17.6, -8.9)
	Kane 2003[b]	RC 50 mg vs placebo	-11.1 (-15.9, -6.3)
	Indirect comparison	Risperidone ISM 100 mg vs RC 50 mg	-2.2 (-8.7, 4.3)

Source: Table 2.62, p128 of the submission, and Table 2.63, pp128-129 of the submission.
CI = confidence interval, ISM = in-situ microparticles, PANSS = Positive and Negative Syndrome Scale, RC = risperidone 2-weekly long-acting injectable.

6.30 For the primary outcome of mean change from baseline in total PANSS score, the estimated mean difference between risperidone ISM 100 mg versus RC 50 mg was - 2.5 (95% CI: -9.0, 4.0). The evaluation and the ESC considered that as the point estimate is within the MCID of 7-point difference, and the upper bound estimate of the 95% CI did not cross 7, non-inferiority was demonstrated. Non-inferiority was also supported by the sensitivity analysis and supplementary analysis in the submission.

6.31 Table 9 presents the efficacy results for the ITC of risperidone ISM versus PP1M.

Table 9: Indirect treatment comparison of risperidone ISM versus PP1M (change from baseline in total PANSS score)

Analysis	Trial	Comparison	Mean difference (95% CI)
Base-case: Analysed using Least-squares mean difference			
Risperidone ISM 100 mg vs PP1M 100 mg	PRISMA-3	Risperidone ISM 100 mg vs placebo	-13.6 (-17.9, -9.3)
	PP1M meta-analysis	Pooled PP1M 100 mg vs placebo	-8.7 (-11.0, -6.5)
	Indirect comparison	Risperidone ISM 100 mg vs pooled PP1M 100 mg	-4.9 (-9.7, 0.0)
Risperidone ISM 75 mg vs PP1M 75 mg	PRISMA-3	Risperidone ISM 75 mg vs placebo	-13.6 (-17.8, -9.3)
	Takahashi 2013	PP1M 75 mg vs placebo	-9.7 (-14.0, -5.4)
	Indirect comparison	Risperidone ISM 75 mg vs PP1M 75 mg	-3.9 (-9.9, 2.2)
Sensitivity analysis 1: Analysed using Lawrence and Hung mean difference data from PRISMA-3			
Risperidone ISM 100 mg vs PP1M 100 mg	PRISMA-3	Risperidone ISM 100 mg vs placebo	-13.3 (-17.6, -8.9)
	PP1M meta-analysis	Pooled PP1M 100 mg vs placebo	-8.7 (-11.0, -6.5)
	Indirect comparison	Risperidone ISM 100 mg vs pooled PP1M 100 mg	-4.6 (-9.4, 0.3)
Risperidone ISM 75 mg vs PP1M 75 mg	PRISMA-3	Risperidone ISM 75 mg vs placebo	-13.3 (-17.6, -8.9)
	Takahashi 2013	PP1M 75 mg vs placebo	-9.7 (-14.0, -5.4)
	Indirect comparison	Risperidone ISM 75 mg vs PP1M 75 mg	-3.3 (-9.4, 2.7)
Sensitivity analysis 2: Base case analysis plus inclusion of Kramer 2010 to PP1M meta-analysis			
Risperidone ISM 100 mg vs PP1M 100 mg	PRISMA-3	Risperidone ISM 100 mg vs placebo	-13.6 (-17.9, -9.3)
	PP1M meta-analysis	Pooled PP1M 100 mg vs placebo	-9.3 (-11.4, -7.2)
	Indirect comparison	Risperidone ISM 100 mg vs pooled PP1M 100 mg	-4.3 (-9.1, 0.5)
Sensitivity analysis 3: Analysed using Lawrence and Hung mean difference data from PRISM-3 plus inclusion of Kramer 2010 to PP1M meta-analysis			
Risperidone ISM 100 mg vs PP1M 100 mg	PRISMA-3	Risperidone ISM 100 mg vs placebo	-13.3 (-17.6, -8.9)
	Takahashi 2013	Pooled PP1M 100 mg vs placebo	-9.3 (-11.4, -7.2)
	Indirect comparison	Risperidone ISM 100 mg vs pooled PP1M 100 mg	-4.0 (-8.8, 0.8)

Source: Table 2.79, p140 of the submission, Table 2.80, p140-141 of the submission, Table 2.81, p141 of the submission, and Table 2.82, p142 of the submission.

CI = confidence interval, CGI-S = Clinical Global Impression-Severity, ISM = in-situ microparticles, LS = least squares, PANSS = Positive and Negative Syndrome Scale, PP1M = paliperidone 1-monthly long-acting injectable.

6.32 For the primary outcome of total PANSS score, the estimated mean difference between risperidone ISM 100 mg versus PP1M 100 mg was -4.9 (95% CI: -9.7, 0.0) and between risperidone ISM 75 mg versus PP1M 75 mg the estimated mean difference was -3.9 (95% CI: -9.9, 2.2). The point estimate was within the MCID of 7-points, and the upper bound estimate of the 95% CI did not cross 7. The evaluation and the ESC considered that non-inferiority was supported.

Comparative harms

6.33 Tables 10, 11 and 12 summarise the safety outcomes from the risperidone ISM (PRISMA-3), RC (Kane 2003) and three PP1M (Kramer 2010, Bossie 2011 and Takahashi 2013) trials, respectively for the treatment regimens that were used in the comparison of single arms.

Table 10: Summary of key adverse events in the randomised risperidone ISM trial (PRISMA-3)

Safety measure	Placebo N= 147	Risperidone ISM 75 mg N = 144	Risperidone ISM 100 mg N = 149
TEAE (n (%))	65 (44.2)	80 (55.6)	94 (64.4)
SAE (n (%))	5 (3.4)	2 (1.4)	5 (3.4)
Any AE resulting in death (n (%))	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to study discontinuation (n (%))	10 (6.8)	6 (4.2)	9 (6.2)

Source: Table 2.68, p131 of the submission, Table 2.69, p311 of the submission Table 84, p238 of the PRISMA -3 CSR.
AE = adverse event, ISM = in-situ microparticles, SAE = serious adverse event, TEAE = treatment emergent adverse event.

Table 11: Summary of key adverse events in the randomised RC trial (Kane 2003)

Safety measure	Placebo N = 98	RC 50 mg N = 103
TEAE (n (%))	81 (82.7)	85 (82.5)
SAE (n (%))	23 (23.5)	14 (13.6)
Any AE resulting in death (n (%))	1 (1.0)	0 (0.0)
AE leading to study discontinuation (n (%))	12 (12.2)	12 (11.6)

Source: Table 2.68, p131 of the submission, and Table 2.69, p131 of the submission.
AE = adverse event, NR = not reported, RC = risperidone 2-weekly long-acting injectable, SAE = serious adverse event, TEAE= treatment emergent adverse event.

Table 12: Summary of key adverse events in the randomised PP1M trials

Kramer 2010	**Placebo (N = 84)**	**PP1M 100 mg (N = 84)**
TEAE (n (%))	54 (64)	50 (60)
SAE (n (%))	6 (7)	13 (8)[a]
Any AE resulting in death (n (%))	NR	NR
AE leading to study discontinuation (n (%))	8 (10)	2 (2)
Bossie 2011	**Placebo (N = 164)**	**PP1M 100 mg (N = 165)**
TEAE (n (%))	107 (65.2)	NR (60.0-63.2)[a]
SAE (n (%))	23 (14.0)	22 (13.3)
Any AE resulting in death (n (%))	0 (0.0)	0 (0.0)
AE leading to study discontinuation (n (%))	11 (6.7)	NR (6.1-8.0)[a]
Takahashi 2013	**Placebo (N = 164)**	**PP1M 75 mg (N = 159)**
TEAE (n (%))	134 (81.7)	136 (85.5)
SAE (n (%))	25 (15.2)	10 (6.3)
Any AE resulting in death (n (%))	1 (0.6)	0 (0.0)
AE leading to study discontinuation (n (%))	49 (29.9)	27 (17.0)

Source: Section 2.5.4 of the submission and relevant trial publications.
AE = adverse event, NR = not reported, PP1M = paliperidone 1-monthly long-acting injectable, SAE = serious adverse event, TEAE = treatment emergent adverse event.
[a] Among total PP1M groups.

6.34 The incidence of TEAE for the risperidone ISM trial (PRISMA-3) was higher in the risperidone ISM 100 mg (64.4%) and 75 mg (55.6%) groups than in the placebo group (44.2%). There were 5 (3.4%) SAEs from risperidone ISM 100 mg treatment, 2 (1.4%) SAEs from risperidone ISM 75 mg treatment and 2 (3.4%) SAEs from the placebo arm. Of the risperidone ISM interventions, worsening of schizophrenia was the most common SAE occurring in three patients, with other SAEs including appendicitis, skin infection, fall and humeral fracture, agitation. No deaths were reported.

6.35 The incidence of TEAE for the RC trial (Kane 2003) was similar for placebo and different doses of RC, but the incidence of SAE was lower in the RC 50 mg (13.6%) than in the placebo group (23.5%). One death from the placebo group was reported.

6.36 Patients treated with PP1M 100 mg had a lower incidence of TEAE than placebo, but a higher incidence of SAE. Conversely, patients treated with PP1M 75 mg had a higher incidence of TEAE than placebo, but a lower incidence of SAE. Some of the common SAEs are psychiatric symptoms/disorders and worsening of schizophrenia.

6.37 The submission selected Bossie 2011 and Takahashi 2013 trial data for the meta-analysis of PP1M 100 mg for SAE. The Kramer 2010 and Takahashi 2013 trial data was used for the meta-analysis of PP1M 100 mg TEAE. These meta-analyses were used to inform the comparison of single arms with risperidone ISM. It was unclear why Takahashi 2013 trial was included since the treatment regimen from Takahashi 2013 investigated the use of PP1M 75 mg and not PP1M 100 mg. In considering the individual point estimates of incidence of SAE and TEAE from the Kramer 2010, Bossie 2011 and Takahashi 2013 trials, the inclusion of Takahashi 2013 was likely to have resulted in an increase in the incidence of TEAE and a decrease in the incidence of SAE calculated. Additionally, differences in treatment duration for the Kramer 2010 and Takahashi 2013 trial data may limit the comparability of treatments.

6.38 Table 13 summarises the pooled value for the safety outcomes of PP1M 100 mg.

Table 13: Summary of pooled values for safety outcomes of PP1M 100 mg

Safety measure	PP1M 100 mg n/N (%)	Placebo n/N (%)
Base-case		
TEAE	186/243 (76.5)	188/248 (75.8)
SAE[a]	32/324 (9.9)	48/328 (14.6)
Sensitivity analysis		
SAE[b]	45/408 (11.0)	54/412 (13.1)

Source: Table 2.75, p136 of the submission, Table 2.77, p138 of the submission, Table 2.84, p143 of the submission, and sponsor's attachment "20221027 ITC- Okedi".

PP1M = paliperidone 1-monthly long-acting injectable, SAE = serious adverse event, TEAE = treatment emergent adverse event.

[a] Base case pooled value obtained by excluding Kramer 2010.

[b] Sensitivity analysis carried out by including Kramer 2010.

6.39 The submission used the meta-analysis of PP1M 100 mg for comparison of single arms of risperidone ISM 100 mg versus PP1M 100 mg. Results of the meta-analysis demonstrate that TEAEs occurred in 186 (76.5%) patients receiving PP1M 100 mg and in 188 (75.8%) patients receiving placebo. The incidence of SAEs was higher in the placebo (14.6%) than the PP1M 100 mg (9.9%) intervention arm. No formal statistical comparison with placebo was considered.

6.40 The submission conducted a comparison of single arms of risperidone ISM versus RC and a comparison of single arms of risperidone ISM versus PP1M, using safety data from relevant trials. The submission claimed that for either analysis, an ITC could not be performed because the incidence of SAE and TEAE in the placebo arm varied significantly in the respective trials, and therefore transitivity could not be assumed. However, this conflicted with the submission's ITC for efficacy where transitivity was

assumed because the submission claimed that the baseline characteristics were comparable across trials. The PSCR presented an ITC of the incidence of SAEs across the trials, noting that the 95% CI of the odds ratio for the comparisons were very wide, and while no statistically significant difference was observed, that this result should be interpreted with great caution.

6.41 Table 14 summarises the comparison of single arms of risperidone ISM versus RC and PP1M of safety endpoints categorised by their therapeutic equivalence.

Table 14: Comparison of single arms of risperidone ISM versus RC and PP1M (incidence of SAE and TEAE)

Safety measure	Trial	Comparison[a]	Intervention n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	Relative risk (95% CI)	Risk difference (95% CI)
Comparison of risperidone ISM 100 mg, RC 50 mg, and PP1M 100 mg							
SAE	PRISMA-3	Risperidone ISM 100 mg	5/146 (3.4)	5/147 (3.4)	1.01 (0.29, 3.56)	1.01 (0.30, 3.40)	0.0% (-4.1%, 4.2%)
	Kane 2003	RC 50 mg	14/103 (13.6)	23/98 (23.5)	0.51 (0.25, 1.07)	0.58 (0.32, 1.06)	-9.9% (-20.6%, 0.8%)
	PP1M meta-analysis	PP1M 100 mg	32/324 (9.9%)	48/328 (14.6%)	0.64 (0.40, 1.03)	0.67 (0.44, 1.03)	-4.8% (-9.8%, 0.3%)
TEAE	PRISMA-3	Risperidone ISM 100 mg[b]	94/146 (64.4)	65/147 (44.2)	2.28 (1.43, 3.65)	1.46 (1.17, 1.81)	20.2% (9.0%, 31.3%)
	Kane 2003	RC 50 mg[c]	85/103 (82.5)	81/98 (82.7)	0.99 (0.48, 2.06)	1.00 (0.88, 1.13)	-0.1% (-10.6%, 10.4%)
	PP1M meta-analysis	PP1M 100 mg	186/243 (76.5)	188/248 (75.8)	1.04 (0.69, 1.58)	1.01 (0.91, 1.11)	0.7% (-6.8%, 8.3%)
Comparison of risperidone ISM 75 mg and PP1M 75 mg							
SAE	PRISMA-3	Risperidone ISM 75 mg	2/144 (1.4)	5/147 (3.4)	0.40 (0.08, 2.10)	0.41 (0.08, 2.07)	-2.0% (-5.5%, 1.5%)
	Takahashi 2013	PP1M 75 mg	10/159 (6.3)	25/164 (15.2)	0.37 (0.17, 0.81)	0.41 (0.20, 0.83)	-9.0% (-15.6%, -2.3%)
TEAE	PRISMA-3	Risperidone ISM 75 mg[b]	80/144 (55.6)	65/147 (44.2)	1.58 (0.99, 2.50)	1.26 (1.00, 1.59)	11.3% (-0.1%, 22.8%)
	Takahashi 2013	PP1M 75 mg	136/159 (85.5)	134/164 (81.7)	1.32 (0.73, 2.40)	1.05 (0.95, 1.15)	3.8% (-4.2%, 11.9%)

Source: Table 2.67, p130 of the submission, Table 2.69, p131 of the submission, Table 2.84, p143 of the submission, Table 286, p144 of the submission, and the sponsor's attachment "20221027 ITC- Okedi".

CI = confidence interval, ISM = in-situ microparticle, PP1M = paliperidone 1-monthly long-acting injectable, RC = risperidone 2-weekly long-acting injectable, SAE = serious adverse event, TEAE = treatment emergent adverse event.

[a] Treatment compared to placebo.

[b] Incidence of TEAE reported in the PRISMA-3 trial accounted for TEAEs occurring in 2% or more subjects.

[c] Incidence of TEAE reported in the Kane 2003 trial accounted for TEAEs occurring in 5% or more subjects.

6.42 The comparison of single arms revealed a lower incidence of SAE in the risperidone ISM 100 mg arm of the PRISMA-3 trial when compared to the RC 50 mg arm of the RC trial. Similarly, the incidence of SAE was lower in the risperidone ISM 100 mg and 75 mg arm of the PRISMA-3 trial when compared to PP1M 100 mg (pooled values) and 75 mg (Takahashi 2013), respectively.

6.43 The comparison of TEAE incidence showed that there were fewer TEAEs in risperidone ISM 100 mg (PRISMA-3) when compared separately to both RC 50 mg (Kane 2003) and

PP1M 100 mg (pooled values). There was also a lower incidence of TEAE observed for risperidone ISM 75 mg when compared to PP1M 75 mg (Takahashi 2013).

Benefits/harms

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

Clinical claim

6.45 The submission described risperidone ISM as non-inferior in terms of efficacy and safety compared to RC and PP1M in adults with schizophrenia. The evaluation considered that this claim may be adequately supported based on the evidence presented in the submission, noting however, the following uncertainties should be considered:

- There was a lack of long-term data available for risperidone ISM and the RC and PP1M comparators, with the trial treatment durations being limited to 9 to 13 weeks. The PSCR stated that the results of the Open Label Extension part of the PRISMA 3 study indicated a continued therapeutic effect of risperidone ISM over a period of more than 1 year.
- Differences in race/ethnicity, BMI, and disease severity between trials considered in the submission. In general, the baseline total PANSS score for the risperidone ISM trial (PRISMA-3) was generally higher than the baseline score of participants in other trials.
- Overall high risk of bias due to medium risk of performance and attrition bias associated with possible unblinding of study participants and high risk of selection bias from excluding patients with improvement in total PANSS score 20% or greater between the initial screening visit and first injection in the risperidone ISM trial (PRISMA-3).
- The assumption that if the risperidone ISM 100 mg showed similar exposures at steady state to RC 50 mg, that risperidone ISM 75 mg would also show similar exposures at steady state to RC 37.5 mg, based on dose linearity from a report provided by the sponsor. Although the assumption is reasonable, it is still a source of uncertainty. The PSCR stated that "the TGA acknowledged that the results of the pharmacokinetic analysis of RC and risperidone ISM supported switching between the two medicines at their therapeutic equivalent doses" (Okedi Evaluation Report, TGA).
- For the meta-analyses of efficacy, incidence of SAE and incidence of TEAE in PP1M 100 mg, it was unclear why the Takahashi 2013 trial was included since the treatment regimen from Takahashi 2013 was PP1M 75 mg and not PP1M 100 mg. Additionally, for the meta-analysis of incidence of TEAE in PP1M 100 mg, the treatment of the trials considered (Takahashi 2013 and Kramer 2010) may not be directly comparable given the differences in treatment duration.

6.46 The PBAC considered that on balance, the clinical claim of non-inferior efficacy and safety was likely met for risperidone ISM 100 mg versus RC 50 mg, risperidone ISM 100 mg versus PP1M 100 mg and risperidone ISM 75 mg versus PP1M 75 mg.

6.47 The Committee considered it was unclear whether the submission's claim that risperidone ISM 75 mg is non-inferior in efficacy and safety to RC 37.5 mg was reasonably supported, given no available trial data permitted a comparison of risperidone ISM 75 mg with RC 37.5 mg, that the sponsor justified the non-inferiority claim through pharmacokinetic data (with supportive TGA acknowledgement).

Economic analysis

6.48 The submission presented a CMA of risperidone ISM to a weighted comparator of RC and PP1M. A CMA was appropriate given the claim of non-inferior efficacy and safety.

6.49 Table 15 describes key components and assumptions of the CMA.

Table 15: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in the submission, effectiveness is assumed to be non-inferior.
Therapeutic claim: safety	Based on evidence presented in the submission, safety is assumed to be non-inferior.
Evidence base	Risperidone ISM versus RC: An ITC based on a single, placebo-controlled trial for risperidone ISM (PRISMA-3) and a single, placebo-controlled trial for RC. Risperidone ISM versus PP1M: An ITC based on a single, placebo-controlled trial for risperidone ISM (PRISMA-3), and five placebo-controlled trials for PP1M.
Equi-effective doses	Risperidone ISM versus RC: Risperidone ISM 75 mg per 4-weekly = RC 37.5 mg per 2-weekly Risperidone ISM 100 mg per 4-weekly = RC 50 mg per 2-weekly Risperidone ISM versus PP1M: Risperidone ISM 75 mg per 4-weekly = PP1M 75 mg per month Risperidone ISM 100 mg per 4-weekly = PP1M 100 mg per month
Direct medicine costs	The submission derived the cost-minimised price of a 4-weekly treatment cycle for risperidone ISM versus RC and risperidone ISM versus PP1M, separately. These prices included cost offsets. The ESC noted that the evaluation had not adjusted for the difference in the dosing frequency (i.e., 4-weekly versus monthly). The submission used a weighted price calculation to propose the AEMP of risperidone ISM for the 75 mg and 100 mg doses. These weights were estimated by the proportion of equivalent patients from corresponding doses of the RC and PP1M PBS services derived from Medicare Statistics data in the 2021/2022 financial year. The conversion of PBS services in 2021/2022 financial year to equivalent patients assumes 1 year of treatment at 100% compliance for patients with schizophrenia. The submission referenced the PBS item numbers 8781E and 8782F as part of the calculations of RC equivalent patients. The proposed AEMP for risperidone ISM is dependent on the estimates of the likely market uptake of each comparator. However, these PBS item numbers are not specific to schizophrenia alone (i.e., bipolar I disorder). Corrections were made during the evaluation to reflect the proportion of PBS services from schizophrenia patients.
Other costs or cost offsets	Cost offsets relating to supplementary oral risperidone and PP1M loading doses were excluded during the evaluation as a conservative approach. The PSCR stated that in reality it is most likely that a proportion of patients commencing treatment with PP1M or RC would require a loading dose. The ESC considered that this was reasonable.

Source: Table 3.1, p150 of the submission, Section 3.1, p149 of the submission, and Section 3,4, pp154-155 of the submission.
AEMP = approved ex-manufacturer price, ISM = in-situ microparticles, ITC = indirect treatment comparison, PBS = Pharmaceutical Benefits Scheme, PP1M = paliperidone 1-monthly long-acting injectable, RC = risperidone 2-weekly long-acting injectable, PSCR = Pre-Sub-Committee Response.

6.50 The submission stated that the equi-effective doses for risperidone ISM with RC and PP1M were determined using the dose equivalence for switching between medications from the (draft and approved) PI for each product. The submission acknowledged that given that patients treated with LAIs were expected to be administered these treatments as ongoing medications, steady state dose comparisons were generally most relevant to establish equi-effective doses. However, establishing steady state dose was not feasible given that the trials included in the submission randomised patients to specific doses of each medication.

6.51 The equi-effective doses between risperidone ISM, RC and PP1M proposed by the submission were as described in Table 16.

Table 16: Proposed equi-effective doses for risperidone ISM and comparators, RC and PP1M

Risperidone ISM	RC	PP1M
75 mg 4-weekly	37.5 mg 2-weekly	75 mg monthly
100 mg 4-weekly	50 mg 2-weekly	100 mg monthly

Source: Table 3-2, p151 of the submission.
ISM = in-situ microparticles, PP1M = paliperidone 1-monthly long-acting injectable, RC = risperidone 2-weekly long-acting injectable.

6.52 Further, it was noted that there are currently only two strengths of risperidone ISM, while there are three (25 mg, 37.5 mg and 50 mg) for RC and five (25 mg, 50 mg, 75 mg, 100 mg and 150 mg) for PP1M listed on the PBS. This may have further implications on the CMA, given that PP1M pricing for the cost-minimisation presented in the evaluation was based on a weighted use of different strengths in practice.

6.53 The submission incorporated several cost offsets. For the comparison of risperidone ISM versus RC, the submission included the cost of 3 weeks' oral risperidone supplementation for RC and reduced frequency of medical visits as cost-offsets. The 4-weekly schedule of risperidone ISM was associated with one less medical visit in a 4-week period than the 2-weekly schedule of RC. For the comparison of risperidone ISM versus PP1M, the submission included the cost of the initial loading 150 mg dose of PP1M as a cost-offset. The inclusion of the cost offset for oral risperidone supplementation in RC and initial loading doses in PP1M may be inappropriate. Patients are expected to switch from another LAI to risperidone ISM after being previously stabilised, and therefore patients will not need concomitant or supplemental medications to use risperidone ISM.

6.54 Table 17 and Table 18 summarise the cost-minimisation of risperidone ISM 75 mg and 100 mg with RC 37.5 mg and 50 mg, respectively. Table 19 and Table 20 summarise the cost-minimisation of risperidone ISM 75 mg and 100 mg with PP1M 75 mg and 100 mg, respectively. The cost-offset of oral risperidone supplementation and initial PP1M loading doses were removed from these calculations given they introduced uncertainty and possibly resulted in the price of risperidone ISM being overestimated, but are presented in a sensitivity analysis. The ESC noted that the cost-minimisation calculations do not account for the one monthly dosing regimen of PP1M, and therefore, the price of risperidone ISM is overestimated in these calculations as a one-month cost for PP1M is stated to be the 4-week cost of risperidone ISM.

Table 17: Cost-minimisation of risperidone ISM 75 mg versus RC 37.5 mg

	Cost-minimisation based on RC 37.5 mg
Base-case	
AEMP of RC	$153.00
AEMP of RC per mg	$4.08
Risperidone ISM equivalent treatment dose per 4 weeks	75 mg
Cost of risperidone ISM medicine per 4 weeks	$306.00
Cost of medical visit per 4 weeks	$39.75
Total cost-minimised price of risperidone ISM 75 mg	$345.75
Sensitivity analysis[a]	
Total cost-minimised price of risperidone ISM 75 mg from base-case analysis	$345.75
Cost of oral risperidone supplementation per 4 weeks	$0.37
Total cost-minimised price of risperidone ISM 75 mg	$346.12

Source: Table 3.4, p153 of the submission.
AEMP = approved ex-manufacturer price, ISM = in-situ microparticles, RC = risperidone 2-weekly long-acting injectable.
[a] Sensitivity analysis included cost of oral risperidone supplementation using DPMQ as presented by the submission as a cost offset. This was apportioned over an average treatment duration of 2.69 years.

Table 18: Cost-minimisation of risperidone ISM 100 mg versus RC 50 mg

	Cost-minimisation based on RC 50 mg
Base-case	
AEMP of RC	$188.13
AEMP of RC per mg	$3.76
Risperidone ISM equivalent treatment dose per 4 weeks	100 mg
Cost of risperidone ISM medicine per 4 weeks	$376.26
Cost of medical visit per 4 weeks	$39.75
Total cost-minimised price of risperidone ISM 100 mg	$416.01
Sensitivity analysis[a]	
Total cost-minimised price of risperidone ISM 100 mg from base case analysis	$416.01
Cost of oral risperidone supplementation per 4 weeks	$0.37
Total cost-minimised price of risperidone ISM 100 mg	$416.38

Source: Table 3.4, p153 of the submission.
AEMP = approved ex-manufacturer price, ISM = in-situ microparticles, RC = risperidone 2-weekly long-acting injectable.
[a] Sensitivity analysis included cost of oral risperidone supplementation using DPMQ as presented by the submission as a cost offset. This was apportioned over an average treatment duration of 2.69 years.

Table 19: Cost-minimisation of risperidone ISM 75 mg versus PP1M 75 mg

	Cost-minimisation based on PP1M 75 mg
Base-case	
AEMP of PP1M	$269.35
AEMP of PP1M per mg	$3.59
Risperidone ISM equivalent treatment dose per 4 weeks	75 mg
Cost of risperidone ISM medicine per 4 weeks	$269.35
Total cost-minimised price of risperidone ISM 75 mg	$269.35
Sensitivity analysis[a]	
Total cost-minimised price of risperidone ISM 75 mg from base case analysis	$269.35
Cost of Day 0 initial loading dose per 4 weeks	$9.47
Total cost-minimised price of risperidone ISM 75 mg	$278.82

Source: Table 3.6, p154 of the submission.
AEMP = approved ex-manufacturer price, ISM = in-situ microparticles, PP1M = paliperidone 1-monthly long-acting injectable.
[a] Sensitivity analysis included cost of initial PP1M loading dose as a cost offset. This was apportioned over an average treatment duration of 2.69 years.

Table 20: Cost-minimisation of risperidone ISM 75 mg versus PP1M 75 mg

	Cost-minimisation based on PP1M 100 mg
Base-case	
AEMP of PP1M	$331.02
AEMP of PP1M per mg	$3.31
Risperidone ISM equivalent treatment dose per 4 weeks	100 mg
Cost of risperidone ISM medicine per 4 weeks	$331.02
Total cost-minimised price of risperidone ISM	$331.02
Sensitivity analysis[a]	
Total cost-minimised price of risperidone ISM from base case analysis	$331.02
Cost of Day 0 initial loading dose per 4 weeks	$9.47
Total cost-minimised price of risperidone ISM	$340.49

Source: Table 3.6, p154 of the submission.
AEMP = approved ex-manufacturer price, ISM = in-situ microparticles, PP1M = paliperidone 1-monthly long-acting injectable.
[a] Sensitivity analysis included cost of initial PP1M loading dose as a cost offset. This was apportioned over an average treatment duration of 2.69 years.

6.55 The total cost-minimised price of risperidone ISM 75 mg to RC 37.5 mg was $345.75 and the total cost-minimised price of risperidone ISM 100 mg to RC 50 mg was $416.01. There was a marginal increase of $0.37 to the total cost-minimised price of risperidone ISM 75 mg and 100 mg when oral risperidone supplementary doses were included in sensitivity analysis.

6.56 The total cost-minimised price of risperidone ISM 75 mg to PP1M 75 mg was $269.35 and the total cost-minimised price of risperidone ISM 100 mg to PP1M 100 mg was $331.02. There was an increase of $9.47 to the total cost-minimised price of risperidone ISM 75 mg and 100 mg when PP1M loading doses were included in sensitivity analysis.

6.57 Using the AEMP derived in the cost-minimisation compared to each of the individual comparators, a weighted price for risperidone ISM was derived from a weighting of the comparators. Weighting was based on the proportion of equivalent patients on each corresponding doses of each comparator, whereby equivalent patients were converted from PBS services in the 2021/2022 financial year. The submission estimated a weight of 16.5% for RC and 83.5% for PP1M.

6.58 The submission converted PBS services in the 2021/2022 financial year to equivalent patients, assuming 26 RC and 13 PP1M scripts over a 1-year period and at 100% compliance for patients with schizophrenia. This conversion is also dependent on the estimates of the likely market uptake of each comparator. Other issues regarding the estimation of these weights included:

- The total number of PBS services for item numbers for RC 37.5 mg (8781E) and 50 mg (8782F) was completely attributable to the schizophrenia patient population, but other indications for these medications include bipolar I disorder.
- 26 RC scripts over a 1-year period where this should be corrected to 13 RC scripts. RC has a maximum quantity of 2 packs, with 1 vial of RC available per pack. Since a script of RC will contain 2 vials of RC which is equivalent to a 4-week treatment

period per script, this will represent a total of 13 scripts in 1 year (as opposed to 26 scripts).

- 13 PP1M scripts over a 1-year period where this should be corrected to 12 PP1M scripts. PP1M is dosed monthly (as opposed to per four weeks), which would result in 12 scripts per year as opposed to 13 scripts in the submission.

6.59 During the evaluation, PBS service data for items 8781E and 8782F (i.e., schizophrenia, bipolar I disorder or missing streamlined authority code) on the number of scripts for schizophrenia during the 2021 calendar year (as opposed to the 2021/2022 financial year in the submission) were used together with 13 RC scripts per year and 12 PP1M scripts per year to calculate a new weight for the split between RC and PP1M equivalent patients. The new weight was calculated as 25.8% for RC equivalent patients and 74.2% for PP1M equivalent patients.

6.60 Table 21 presents the cost-minimised AEMP for risperidone ISM based on the weighted comparator approach.

Table 21: Cost-minimised AEMP for risperidone ISM based on weighted comparator

Component	Weighting	Cost-minimised price	Weighted AEMP
Risperidone ISM 75 mg			
RC 37.5 mg	25.8%	$345.75	$89.37
PP1M 75 mg	74.2%	$269.35	$199.73
Total weighted price of risperidone ISM 75 mg			$289.10
Risperidone ISM 100 mg			
RC 50 mg	25.8%	$416.01	$107.53
PP1M 100 mg	74.2%	$331.02	$245.46
Total weighted price of risperidone ISM 100 mg			$352.99

Source: Sponsor's attachment "20221027 Okedi S3".
AEMP = approved ex-manufacturer price, ISM = in-situ microparticles, PP1M = paliperidone 1-monthly long-acting injectable, RC = risperidone 2-weekly long-acting injectable.
Note: The cost-minimised price for risperidone ISM 75 mg and 100 mg versus PP1M 75 mg and 100 mg was not adjusted for the difference in dosing frequency, and therefore the weighted AEMP will be lower than stated

6.61 The submission estimated the AEMP of $291.12 for risperidone ISM 75 mg and $354.21 for risperidone ISM 100 mg. After revising the weights and cost-minimised prices, the evaluation calculated an AEMP of $289.10 for risperidone ISM 75 mg and $352.99 for risperidone ISM 100 mg.

6.62 For the requested population, other LAI antipsychotics listed on the PBS for the treatment of schizophrenia and that could be considered alternative therapies include PP3M, PP6M, and aripiprazole 4-weekly.

6.63 The PBAC considered that there was no basis for a weighted comparator, and that risperidone ISM should be listed on a cost-minimisation basis the lowest cost alternative therapy. Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with risperidone ISM would be no more than the cost per patient of the comparators, RC and PP1M. Where these 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. Costs associated with oral risperidone and PP1M loading doses are uncertain and their inclusion increase the cost of risperidone ISM. Not accounting for monthly, as opposed to 4-weekly, administration of PP1M increases the cost of risperidone ISM.

Drug cost/patient/year

6.64 Table 22 and Table 23 summarise the estimated drug cost per patient per year for risperidone ISM 75 mg and 100 mg, and their respective comparators.

Table 22: Drug cost (DPMQ) per patient for risperidone ISM 75mg, RC 37.5 mg and PP1M 75 mg

	Risperidone ISM 75 mg	RC 37.5 mg	PP1M 75 mg
Dose and frequency	75 mg every 4 weeks	37.5 mg every 2 weeks	75 mg every month
Number of doses per year	13	13	12
Drug cost per dose/ script	$335.80 ($333.52[a])	$352.62	$311.23
Total cost/ patient/ year	$4,365 ($4,336 [a])	$4,584	$3,735

Source: Compiled during the evaluation

[a] Estimated based on the revised cost-minimised price estimated during the evaluation. Note: The cost-minimised price for risperidone ISM 75 mg versus PP1M 75 mg was not adjusted for the difference in dosing frequency between risperidone ISM and PP1M in these calculations.

Table 23: Drug cost (DPMQ) per patient for risperidone ISM 100mg, RC 50 mg and PP1M 100 mg

	Risperidone ISM 100 mg	RC 50 mg	PP1M 100 mg
Dose and frequency	100 mg every 4 weeks	50 mg every 2 weeks	100 mg every month
Number of doses per year	13	13	12
Drug cost per dose/ script	$407.03 ($405.65[a])	$431.92	$380.85
Total cost/ patient/ year	$5,291 ($5,273 [a])	$5,615	$4,570

Source: Compiled during the evaluation

[a] Estimated based on the revised cost-minimised price estimated during the evaluation. Note: The cost-minimised price for risperidone ISM 100 mg versus PP1M 100 mg was not adjusted for the difference in dosing frequency between risperidone ISM and PP1M in these calculations.

6.65 At the proposed DPMQ prices (at the time of submission), the estimated cost per patient per year of risperidone ISM 75 mg was $4,365 and risperidone ISM 100 mg was $5,291.

Estimated PBS usage & financial implications

6.66 This submission was not considered by DUSC. The submission utilised a market share approach. Table 24 outlines the key inputs relied on in the financial estimates.

Table 24: Key inputs for financial estimates

Data	Source	Comment
Current units of dispensed comparator (100 mg PP1M, 75 mg PP1M, 37.5 mg RC, 75 mg RC)	Service volumes available from current PBS market.	The choice of substituted comparators was based on selected strengths of RC and PP1M expected to be replaced by risperidone ISM. There are other strengths listed on the PBS that were not considered. The submission did not consider that risperidone ISM would replace any other therapies.
Treatment utilisation		
Proportion of PP1M applicable to indication (substitution rate)	Using substitution rates from previous submissions of PP3M and PP6M.	The evaluation considered this uncertain. The calculation incorporated a 5-year constant average of PP3M to PP1M substitution rate in its calculation. The source of the data and the calculation of the 5-year average is unclear and could be verified. The assumption that the next 6 calendar years will have a constant substitution rate of PP1M by PP3M is also uncertain.
Proportion of RC 37.5 mg and 75 mg applicable to indication (substitution rate)	Assumption. 100% applicable to substitution	RC is also listed on the PBS for bipolar I disorder, therefore assuming 100% substitution will overestimate the number of scripts relevant to schizophrenia. Data relating to patient numbers and scripts by indications obtained during the evaluation showed that approximately 90% of RC scripts were for the schizophrenia indication.
Proportion of RC affected by risperidone ISM (uptake rate)	Assumption. Ranges from [redacted]% in Year 1 to [redacted]% in Year 6	The evaluation considered this to be uncertain. The submission assumed this uptake rate (increasing over time and did not provide justification).
Proportion of PP1M affected by risperidone ISM (uptake rate)	Assumption. Ranges from [redacted]% in Year 1 to [redacted]% in Year 6	The evaluation considered this to be uncertain. The submission assumed this uptake rate (increasing over time and did not provide justification).
Costs		
Proposed medicine (risperidone ISM 75 mg)	DPMQ – proposed price	The financial estimates were presented in the evaluation using AEMPs of $289.10, DPMQ $333.52. The ESC noted that these prices were overestimated, given the CMA had not adjusted for the difference in the dosing frequency between risperidone ISM and PP1M.
Proposed medicine (risperidone ISM 100 mg)	DPMQ – proposed price	The financial estimates were presented in the evaluation using AEMPs of $352.99, DPMQ $405.65. The ESC noted that these prices were overestimated, given the CMA had not adjusted for the difference in the dosing frequency between risperidone ISM and PP1M.
GP consultation	MBS Item Number 23	

Source: Table 4-3, p.160 of the submission; Table 4-4, p161 of the submission; Table 4-5 p.162 of the submission; Table 4-6, p. 162 of the submission; Table 4-7, p163-164 of the submission; Table 4-9, p.164-165 of the submission; Table 4-12, p167 of the submission,
Abbreviations: RC = Risperidone 2-weekly LAI, PP1M = 1-month Paliperidone Palmitate LAI, PBS = Pharmaceutical Benefits Scheme, MBS = Medicare Benefits Scheme, PP3M = 3-month Paliperidone LAI, PP6M = 6-month Paliperidone LAI

6.67 Table 25 presents the estimated use and financial implications of listing risperidone ISM to the PBS/RPBS and impact on comparators RC and PP1M.

Table 25: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed [a]	[1]	[2]	[3]	[4]	[4]	[4]
Estimated financial implications of risperidone ISM						
Cost to PBS/RPBS less co-payments [b]	[5]	[6]	[7]	[7]	[7]	[7]
Estimated financial implications for comparator (RC and PP1M)						
Cost to PBS/RPBS less co-payments [c]	[8]	[8]	[8]	[8]	[8]	[8]
Net financial implications [5]						
Net financial cost to the PBS/RPBS	[5]	[5]	[5]	[5]	[5]	[5]
MBS cost offsets due to reduced consultations	[8]	[8]	[8]	[8]	[8]	[8]
Net cost to health budget	[8]	[8]	[8]	[8]	[8]	[8]
Net cost to health budget [d]	[8]	[8]	[8]	[8]	[8]	[8]

Source: Table 4-3, p.160 of the submission; Table 4-4, p161 of the submission; Table 4-5 p.162 of the submission; Table 4-6, p. 162 of the submission; Table 4-7, p163-164 of the submission; Table 4-9, p.164-165 of the submission

[a] Corrections to PP1M script equivalence (applied 0.92 instead of 1) and revised proportion of uptake RC applicable for substitution (90%) based on schizophrenia indication only

[b] Priced based on submission calculated DPMQ prices (risperidone ISM 75 mg = $335.80; risperidone ISM 100mg = $407.03)

[c] Excluding submission proposed oral risperidone supplemental and PP1M loading dose

[d] Priced based on evaluation calculated DPMQ prices (risperidone ISM 75 mg = $333.52; risperidone ISM 100mg = $405.65), which did not include the adjustment required to account for the difference in dosing frequency between risperidone ISM and PP1M

The redacted values correspond to the following ranges:

[1] 10,000 to < 20,000

[2] 30,000 to < 40,000

[3] 50,000 to < 60,000

[4] 60,000 to < 70,000

[5] $0 to < $10 million

[6] $10 million to < $20 million

[7] $20 million to < $30 million

[8] net cost saving

6.68 The submission assumed a one-to-one script equivalence between risperidone ISM and RC and PP1M. For the purposes of estimating script numbers, the submission assumed that risperidone ISM is administered monthly, matching the monthly PP1M 1-monthly administration. Given that risperidone ISM is recommended to be administered 4-weekly and PP1M is recommended to be administrated 1-monthly, the script equivalence for PP1M is 0.923. This would result in a decrease in the number of PP1M scripts being displaced by risperidone ISM. This was corrected during the evaluation. The PSCR considered that this was appropriate.

6.69 Data relating to RC patient numbers and scripts by indications obtained during the evaluation showed that approximately 90% of RC scripts were for the schizophrenia indication. The financial estimates were revised during the evaluation to reflect this.

6.70 The projected total risperidone ISM scripts were calculated to be 10,000 to < 20,000 in 2023, increasing up to 60,000 to < 70,000 by 2028, totalling 300,000 to < 400,000 scripts over the 6-year period. As the assumptions on uptake and substitution rates and the number of RC and PP1M scripts that would be displaced were not clearly

justified, the evaluation stated that this contributed to the uncertainty of the financial estimates presented by the submission.

6.71 The submission assumed no further market growth would be likely upon listing of the drug given an assumption of no market expansion was accepted by the PBAC in its March 2022 meeting for paliperidone palmitate 6 monthly LAI (paragraph 6.29, p10 PSD, PBAC meeting March 2022). Historical data from the PBS showed a decrease in RC scripts (average of 10% year on year decrease) for the schizophrenia indication.

6.72 The submission estimated that the proportion of PP1M scripts that might be substituted should risperidone ISM 75 mg and 100 mg be listed on the PBS, decreased through the years from % in 2023 to % in 2028 respectively. The submission derived these values based on the estimated replacement rate of PP1M by PP3M and PP6M. While the overall approach used appeared reasonable, there were uncertainties in the assumptions made with respect to the substitution rates, particularly those by PP3M which would have flow on effects to the financial estimates.

6.73 The net cost of listing risperidone ISM to the PBS/RPBS was estimated to be $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6. These estimates should be interpreted with caution given the following:

- The cost-minimised price for risperidone ISM should be lower than the price used in the financial estimates, given that the price was not derived adjusting for the difference in dosing frequency between risperidone ISM and PP1M.
- The source and justification for the assumptions on the proportion of RC and PP1M affected by risperidone ISM (uptake rate) which ranged from % to % for PP1M and from % to % for RC could not be verified.
- The likely substitution rate for PP1M was uncertain, with the direction of impact unclear.
- The observed increase in PP1M scripts and decrease in RC scripts based on historical PBS data were not considered. The direction of impact was considered unclear.
- The estimates did not consider what impact the availability of other strengths of RC and PP1M might have.
- Given that RC is also indicated for bipolar I disorder (approximated 9% of RC scripts based on PBS data), and given the popularity of the use of risperidone, especially in the elderly, the evaluation and the ESC considered that there may also be a potential for off-label use.

6.74 The total impact on health budget was estimated to be a net cost saving in 2023 increasing to a net cost saving in 2028. The evaluation considered these estimates uncertain for the reasons described in paragraph 6.73. Revised estimates considering adjustments to script equivalence, proportion of RC relevant to schizophrenia

indication, exclusion of supplementary or loading doses resulted in a 24% increase in the estimated cost savings.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority required (Streamlined) listing of risperidone in-situ microparticles (ISM) 4-weekly long-acting injection (LAI) for the treatment of schizophrenia in adults for whom tolerability and effectiveness has been established with oral risperidone, on a cost-minimisation basis versus the lowest cost alternative therapy.

7.2 The PBAC considered that, given the availability of other LAIs for the treatment of schizophrenia in a range of doses and the limited doses available for risperidone ISM (in particular, the lack of a lower dose option), the clinical need for risperidone ISM was low.

7.3 The PBAC considered that paliperidone 1-monthly LAI (PP1M) and risperidone 2-weekly LAI Risperdal Consta (RC) were appropriate comparators but noted that any of the following PBS listed antipsychotic long-acting injections are alternative therapies: RC, paliperidone LAIs, and aripiprazole 4-weekly. The PBAC considered that olanzapine 2 to 4-weekly should not be considered an alternative therapy due to it being associated with post injection syndrome that requires monitoring of patients for signs and symptoms for at least two to three hours after administration (olanzapine Product Information, and section 12, olanzapine, PSD, PBAC Meeting July 2009).

7.4 As no head-to-head randomised trials comparing risperidone ISM to either comparator were available, the PBAC noted the submission was based on the following Indirect Treatment Comparisons (ITCs) for efficacy and comparisons of single arms for safety:

- risperidone ISM 100 mg (PRISMA-3 trial) versus RC 50 mg (Kane 2003 trial),
- risperidone ISM 100 mg (PRISMA-3 trial) versus a meta-analysis of the Gopal 2010, Nasrallah 2010, Bossie 2011 and Takahashi 2013 trials for PP1M 100 mg, and
- risperidone ISM 75 mg (PRISMA-3 trial) versus PP1M 75 mg (Takahashi 2013 trial).

7.5 The PBAC noted there were transitivity issues with the clinical data forming the basis of the ITCs as discussed in paragraph 6.26. The Committee noted there were differences in the mean baseline total PANSS score for each treatment group in PRISMA-3 (mean score range: 96.1-96.4) compared to Kane 2003 (mean score range: 80.1-82.3) and the PP1M trials (mean score range: 85.2-92) due to differences in trial eligibility.

7.6 The PBAC noted that the base case ITCs showed that there were no significant differences in mean change from baseline in total PANSS score for risperidone ISM 100 mg versus RC 50 mg (mean difference: -2.5 (95% CI: -9.0, 4.0)), and no significant

differences for risperidone ISM 100 mg versus PP1M 100 mg and for risperidone 75 mg ISM versus PP1M 75 mg (mean difference: -4.9 (95% CI:-9.7, 0.0) for the 100 mg comparison and -3.9 (95% CI: -9.9, 2.2) for the 75 mg comparison).

7.7 The PBAC noted the submission's comparison of safety showed that there were no significant differences for the outcomes of serious adverse events or treatment emergent adverse events for risperidone ISM 100 mg compared to RC 50 mg or PP1M, and for risperidone ISM 75 mg versus PPM 75 mg. The Committee noted that while there was a lack of long-term data available for risperidone ISM that the Pre-Sub-Committee Response stated that the results of the Open Label Extension part of the PRISMA-3 trial indicated a continued therapeutic effect of risperidone ISM over a period of more than 1 year.

7.8 The PBAC considered that on balance, the clinical claim of non-inferior efficacy and safety was likely met for risperidone ISM 100 mg versus RC 50 mg, risperidone ISM 100 mg versus PP1M 100 mg and risperidone ISM 75 mg versus PP1M 75 mg.

7.9 The Committee considered it was unclear whether the submission's claim that risperidone ISM 75 mg is non-inferior in efficacy and safety to RC 37.5 mg was reasonably supported, given this was supported by pharmacokinetic data only. The PBAC acknowledged the TGA accepted these data.

7.10 The PBAC considered the equi-effective doses to be:

- Risperidone ISM 75 mg every 4 weeks = RC 37.5 mg every 2 weeks
- Risperidone ISM 75 mg every 4 weeks = PP1M 75 mg monthly
- Risperidone ISM 100 mg every 4 weeks = RC 50 mg every 2 weeks
- Risperidone ISM 100 mg every 4 weeks = PP1M 100 mg monthly.

7.11 The PBAC considered the financial estimates to be highly uncertain for the reasons outlined in paragraph 6.73. However, the PBAC noted if listed on a cost-minimisation basis with the least costly alternative, the listing would most likely be cost neutral or modestly cost saving to the PBS as it will only replace therapies that are either of equivalent cost or more expensive.

7.12 The PBAC advised that risperidone 4-weekly is suitable for prescribing by nurse practitioners under a shared care model, where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan.

7.13 The PBAC recommended that the Early Supply Rule should not apply, as it does not apply to other LAI forms of paliperidone and risperidone.

7.14 The PBAC recommended that risperidone ISM should be treated as interchangeable on an individual patient basis with RC, paliperidone LAIs and aripiprazole 4-weekly, according to Section 101(3BA) of the *National Health Act 1953*.

7.15 The PBAC noted that this submission is not eligible for an Independent Review as it

received a positive recommendation. The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because risperidone ISM is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over RC, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

Outcome:
Recommended

8 Recommended listing

Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
RISPERIDONE					
risperidone 75 mg modified release injection [1 syringe] (&) inert substance diluent [0.383 mL syringe], 1 pack	NEW	1	1	5	Okedi
risperidone 100 mg modified release injection [1 syringe] (&) inert substance diluent [0.49 mL syringe], 1 pack	NEW	1	1	5	Okedi

Restriction Summary [new 1] / Treatment of Concept: [new 2]	
Concept ID	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction type: ☒Authority Required – Streamlined [new code 2]
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Indication: Schizophrenia
	Prescribing Instructions: 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.
	Prescribing Instructions: Shared care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.

This restriction 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

The sponsor had no comment.