

Second-generation antipsychotic injections

for treating schizophrenia

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended listing paliperidone or aripiprazole injections on the Medication Assistance Fund (MAF) for treating schizophrenia, due to unacceptable cost-effectiveness compared with first-generation antipsychotic injections at the prices proposed by the manufacturers.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

- 1.1 The MOH Drug Advisory Committee (“the Committee”) considered the evidence presented for the technology evaluation of injectable second-generation antipsychotics (SGAs)—paliperidone and aripiprazole injections—for treating schizophrenia. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for paliperidone and aripiprazole injections was considered in line with the registered indications for each product.
- 1.2 By request of the manufacturer, risperidone injection was not included in the evaluation.
- 1.3 The evidence was used to inform the Committee’s deliberations around four core decision-making criteria:
 - Clinical need of patients and nature of the condition
 - Clinical effectiveness and safety of the technology
 - Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives
 - Estimated annual technology cost and the number of patients likely to benefit from the technology
- 1.4 Additional factors, including social and value judgments, may also inform the Committee’s subsidy considerations.

Clinical need

- 2.1 The Committee understood the majority of patients with schizophrenia in Singapore are treated at the Institute for Mental Health (IMH) and about half are currently receiving first-generation long-acting injectable antipsychotics (FGAs).
- 2.2 The Committee noted that long-acting injectable antipsychotics are increasingly being used earlier in the clinical course of schizophrenia, when oral treatment adherence has been poor, or patients have had an inadequate response to oral agents.
- 2.3 In local clinical practice, SGAs (paliperidone, risperidone, and aripiprazole injections) are typically used after failure of at least one oral antipsychotic agent. This is in line with international clinical guidelines. However, while using injectable SGAs enables continuity of care for patients who started treatment with oral SGAs, their high cost can be prohibitive. Therefore,

injectable FGAs are most commonly prescribed given they are significantly more affordable, and are subsidised on SDL.

Clinical effectiveness and safety

- 3.1 The Committee agreed that the main comparator for injectable SGAs in this evaluation was injectable FGAs. Injectable SGAs were also compared with one another.
- 3.2 The Committee considered available clinical evidence and acknowledged that randomised controlled trials demonstrated aripiprazole injection was superior to placebo and non-inferior to oral aripiprazole for treating schizophrenia. Paliperidone injection was shown to be superior to placebo and non-inferior to risperidone injection.
- 3.3 Limited data comparing injectable SGAs with injectable FGAs was available, but extensive studies for their oral formulations showed SGAs led to fewer extrapyramidal symptom-related events than FGAs. However, SGAs were associated with more metabolic-related adverse events than FGAs.
- 3.4 The Committee understood one open-label clinical trial directly comparing aripiprazole and paliperidone injections was identified. Results favoured aripiprazole for the primary endpoint of change in Heinrichs-Carpenter Quality-of-Life Scale, however, this difference was not considered clinically significant when compared with paliperidone (minimal clinically important difference not met). Adverse events were generally similar between treatment groups, although more weight gain was observed with paliperidone injection in the continuation phase of the trial.
- 3.5 The Committee noted that one clinical trial comparing paliperidone and long-acting haloperidol injections was available. The trial demonstrated comparable efficacy between both agents. With regards to safety outcomes, paliperidone was associated with more raised serum prolactin and weight gain, while haloperidol was linked to more akathisia events.

Cost effectiveness

- 4.1 In the absence of local cost-effectiveness studies, the Committee considered published economic evaluations from overseas. It noted an analysis conducted in the US reported an incremental cost-effectiveness ratio (ICER) of USD\$508K per QALY gained for paliperidone injection versus long-acting haloperidol injection.
- 4.2 Manufacturers were invited to provide value-based pricing (VBP) proposals for their products to inform the evaluation. The Committee observed that discounts offered were insufficient, but based on equi-effective doses, the

weighted cost price of aripiprazole injection was lower than for paliperidone injection. The Committee concluded that paliperidone and aripiprazole injections were not cost-effective at the proposed prices, noting they were at least 10 times more costly than injectable FGAs, which was not justified by the clinical benefits they offered over FGAs.

Estimated annual technology cost

- 5.1 The Committee estimated up to 4,450 people with schizophrenia in Singapore would benefit from government assistance for paliperidone or aripiprazole injections. Because of high treatment costs and large numbers of patients eligible for treatment, the annual cost impact was high and estimated to be between \$3 million to <\$5 million in the first year of listing either product on the MAF.
- 5.2 The Committee noted that the high degree of uncertainty surrounding the cost impact calculations, and considered they were likely to be an underestimate once patients switching from oral antipsychotics to injectable SGAs were taken into account.

Recommendation

- 6.1 Based on available evidence the Committee recommended not listing paliperidone or aripiprazole injections on the MAF because of unacceptable cost-effectiveness and high uncertainty surrounding the estimated annual cost impact of subsidising each treatment at the prices proposed by the manufacturers.

About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health. It conducts evaluations to inform the subsidy of treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore. When using the guidance, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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