Nintedanib and pirfenidone

for treating idiopathic pulmonary fibrosis

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended listing nintedanib or pirfenidone on the Medication Assistance Fund (MAF) for treating idiopathic pulmonary fibrosis, because of limited clinical benefits and unacceptable cost-effectiveness compared with best supportive care 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 nintedanib and pirfenidone for treating idiopathic pulmonary fibrosis (IPF). The Agency for Care Effectiveness conducted the evaluation in consultation with the MOH IPF Expert Working Group comprising senior healthcare professionals from the public healthcare institutions.

1.2 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; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3 Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1 International clinical practice guidelines recommend nintedanib or pirfenidone as monotherapy to slow disease progression in patients with mild to moderate IPF. In local clinical practice, few patients are currently receiving either treatment because of their high cost.

2.2 The Committee heard that IPF is a heterogeneous disease characterised by progressive and irreversible decline in lung function. Symptoms are variable with some patients (~20%) remaining asymptomatic or only presenting with mild symptoms for a long duration, while others experience severe symptoms following rapid decline in lung function and exacerbations (~20%). In local clinical practice, about 60% of patients are diagnosed with moderate IPF.

2.3 The Committee acknowledged there are no other treatment alternatives for IPF. Therefore, there is a high clinical need for subsidising an anti-fibrotic treatment to address this therapeutic gap.

Clinical effectiveness and safety

3.1 The Committee agreed that best supportive care was the appropriate comparator for both treatments. Nintedanib and pirfenidone were also compared with one other.

3.2 **Nintedanib versus placebo**

The Committee considered available clinical evidence and acknowledged that randomised controlled trials demonstrated that nintedanib was statistically superior to placebo in improving disease-related outcomes (such as lung function decline, measured by forced vital capacity [FVC]). However, there was no statistical difference compared with placebo in patient-related outcomes (mortality), although the point estimates favoured nintedanib. For health-related quality of life outcomes (measured by St George's respiratory questionnaire), nintedanib showed statistically significant improvement over placebo, but results were not clinically significant. Nintedanib was associated with an increase in gastrointestinal adverse events (mainly diarrhoea, nausea, and vomiting).

3.3 **Pirfenidone versus placebo**

The Committee noted randomised controlled trials demonstrated that pirfenidone was statistically superior to placebo in improving disease-related outcomes (reduced decline in FVC). However, statistically significant improvement in patient-related outcomes (improved mortality and progression-free survival) was only shown when the estimates from key studies were pooled. Results for improvement in physical function (6-minute walk test [6MWT]) and dyspnoea symptoms were not consistent across the studies. Pirfenidone was associated with more skin-related adverse events (rash and photosensitivity).

3.4 **Nintedanib versus pirfenidone**

The Committee noted that indirect evidence showed no significant differences between nintedanib and pirfenidone in reducing FVC decline and mortality (all-cause and respiratory-related mortality). Nintedanib and pirfenidone were considered to have comparable efficacy but different safety profiles.

3.5 The Committee acknowledged that the available evidence for nintedanib and pirfenidone was relatively immature and the clinical benefits afforded by both treatments were limited. Evidence was also lacking for severe IPF. On balance, the Committee considered that asymptomatic patients, or even those with mild to moderate IPF, were unlikely to want antifibrotic treatment for an extended duration given that it does not typically alleviate symptoms and is associated with high pill burden and side effects.

Cost effectiveness

4.1 The Committee noted that while the manufacturers of nintedanib and pirfenidone offered confidential price discounts in their value-based pricing (VBP) proposals, both treatment costs remained high. The Committee acknowledged ACE's cost effectiveness analysis that showed the base-case incremental cost-effectiveness ratios (ICERs) for nintedanib and pirfenidone compared with best supportive care were both well above SG$105,000 per QALY gained, and agreed they were not a cost-effective use of healthcare resources at the prices proposed by the manufacturers.

Estimated annual technology cost

5.1 The Committee estimated around 59 people with IPF in Singapore would benefit from government assistance for nintedanib or pirfenidone if they were listed on the MAF. The annual cost impact was estimated to be between SG$500,000 to <SG$1 million in the first year of listing either agent on the MAF.

Recommendation

6.1 Based on available evidence, the Committee recommended not listing nintedanib or pirfenidone on the MAF because of limited clinical benefits and unacceptable cost-effectiveness compared to best supportive care at the prices proposed by the manufacturers.