Technology Guidance

Cabotegravir with rilpivirine

for treating Human Immunodeficiency Virus type 1 (HIV-1) infection

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended cabotegravir with rilpivirine for inclusion on the MOH List of Subsidised Drugs for treating Human Immunodeficiency Virus type 1 (HIV-1) infection. The decision was based on the unfavourable cost-effectiveness of cabotegravir with rilpivirine at the price proposed by the company compared with subsidised oral antiretroviral therapies.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the July 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of cabotegravir (tablet and injection) and rilpivirine injection for treating Human Immunodeficiency Virus type 1 (HIV-1) infection. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions and individuals living with human immunodeficiency virus (HIV) from local voluntary organisations. Published clinical and economic evidence for cabotegravir with rilpivirine was considered in line with their registered indications.

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 funding considerations.

Clinical need

2.1 The Committee noted that there are approximately 7,000 individuals living with HIV in Singapore, with the majority receiving oral antiretroviral therapy (ART) and achieving durable virologic suppression.

2.2 The Committee heard that prolonged-release injections of cabotegravir and of rilpivirine are a long-acting ART combination regimen for treating HIV infection in Singapore. The injections are given intramuscularly. The Committee noted that the injections (dosed every 2 months) are given to a small number of individuals who are virologically suppressed but require regimen simplification from daily oral ARTs to address adherence issues and improve quality of life (QoL). Combination treatment of cabotegravir tablets and rilpivirine tablets may be considered before initiating the long-acting injection formulations to assess medication tolerability, or as bridging therapy for individuals who miss their planned injections.

2.3 The Committee noted that other subsidised treatment options for individuals who require treatment simplification include oral ART co-formulations such as dolutegravir/abacavir/lamivudine, dolutegravir/lamivudine, and abacavir/lamivudine in combination with rilpivirine.

2.4 The Committee considered testimonials from 17 individuals living with HIV about their lived experiences with HIV-1 infection and the treatments they have received. They heard that the respondents' greatest concerns were HIV-related stigma and discrimination which adversely affected their mental and emotional well-being. The Committee heard that this could lead to social isolation, reluctance to seek help and treatment, and impede career advancement. They noted that all respondents were taking daily oral ART tablets and considered the treatment effective and well-tolerated with manageable side effects. The Committee acknowledged that although most respondents found taking their oral tablets easy, some felt it was inconvenient to travel overseas with their medication due to HIV-related restrictions imposed by some countries. Although most respondents had no difficulties adhering to the daily oral regimen, some found treatment adherence challenging, especially shift workers. Furthermore, some respondents saw the tablets as a constant reminder of their HIV status.

2.5 The Committee noted that although none of the respondents had been treated with cabotegravir or rilpivirine injections, eight were aware of these treatments. They acknowledged that most respondents preferred ART injections given every one to two months over daily oral tablets, and expected ART injections to offer benefits, including less mental stress from the daily regimen, less disruption to daily activities, improved convenience for travelling and treatment adherence, and better QoL. However, respondents were concerned about the high cost and potential side effects of ART injections, as well as the need for more clinic visits to receive the injections. Overall, the respondents identified affordability and the ability to suppress viral load as the most important factors when considering a new treatment for HIV-1 infection.

Clinical effectiveness and safety

4-weekly cabotegravir with rilpivirine versus oral ARTs

3.1 The Committee reviewed published clinical evidence from pooled results of two open-label phase III randomised controlled trials (RCTs; ATLAS and FLAIR) comparing cabotegravir with rilpivirine to oral ARTs in virologically suppressed individuals. At week 48, cabotegravir with rilpivirine given every 4 weeks, was non-inferior to oral ARTs in terms of virologic response and non-response.

3.2 The Committee heard that between the treatment arms, improvements in HIV Treatment Satisfaction Questionnaire scores and 12-item short-form survey (SF-12) scores were small and inconsistent across studies. They also noted there were no established minimal clinically important differences for these outcomes. The Committee noted that the lack of blinding in the trials may have introduced bias regarding patient-reported outcomes. Overall, the Committee agreed that the evidence did not support a definitive conclusion that treatment with cabotegravir with rilpivirine was associated with improvements in QoL over oral ARTs.

3.3 The Committee noted that a higher incidence of adverse events (AEs) was observed with 4-weekly cabotegravir with rilpivirine compared to oral ARTs during the maintenance phase in the pooled analysis. However, the Committee noted that the majority of the AEs were transient injection-site reactions. The Committee also noted that individuals receiving oral ARTs may have experienced fewer AEs as they were already receiving oral ARTs and may have developed tolerance. The Committee agreed that on balance, it is reasonable to consider 4-weekly cabotegravir with rilpivirine non-inferior in safety compared with oral ARTs.

<u>8-weekly cabotegravir with rilpivirine versus 4-weekly cabotegravir with rilpivirine</u>

3.4 Based on the results of a phase III open-label RCT (ATLAS-2M), the Committee agreed that 4-weekly cabotegravir with rilpivirine was non-inferior compared to 8-weekly cabotegravir with rilpivirine at week 48 in terms of virologic non-response and response.

3.5 The Committee considered that 4-weekly and 8-weekly cabotegravir with rilpivirine were non-inferior in terms of safety, as the incidence of AEs was comparable across treatment arms.

<u>8-weekly cabotegravir with rilpivirine versus oral ARTs</u>

3.6 Given the evaluation did not include head-to-head RCTs comparing 8-weekly cabotegravir with rilpivirine to oral ARTs, the Committee acknowledged the results of indirect treatment comparisons considered by PBAC (Australia) and agreed that, on balance, it is reasonable to consider 8-weekly cabotegravir with rilpivirine non-inferior to oral ARTs in terms of efficacy and safety.

Cost effectiveness

4.1. In view of comparable efficacy and safety, the Committee agreed that a cost-minimisation approach versus oral ARTs was appropriate to evaluate the cost-effectiveness of cabotegravir with rilpivirine. A 2-year time horizon was selected, in line with the cost-minimisation analysis (CMA) previously accepted by PBAC.

The Committee reviewed the results of the CMA, which showed that the 2-year treatment cost of cabotegravir with rilpivirine was substantially higher than all oral ARTs included in the evaluation. Overall, the Committee concluded that cabotegravir with rilpivirine did not represent an acceptable use of healthcare resources in the local context based on the company's proposal, which was also not adequate to ensure budget certainty.

Estimated annual technology cost

5.1 The Committee noted that the additional cost impact to the public healthcare system was estimated to be less than SG$1 million per year, in the first five years of listing cabotegravir with rilpivirine on the MOH List of Subsidised Drugs.

Recommendations

6.1 Based on available evidence, the Committee recommended not listing cabotegravir with rilpivirine on the MOH List of Subsidised Drugs for treating HIV-1 infection. This decision was based on the unfavourable cost-effectiveness of cabotegravir with rilpivirine at the price proposed by the company compared with subsidised oral ARTs.