Technology Guidance

GLP-1 receptor agonist injections

for treating type 2 diabetes mellitus

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

✓ Dulaglutide 0.75 mg and 1.5 mg solution for injection in pre-filled pen for treating type 2 diabetes mellitus:
- as a triple therapy in combination with two oral anti-diabetic drug (OAD) therapies for patients with inadequate glycaemic control despite treatment with optimal doses of dual OAD therapy, or as a dual therapy in combination with one OAD therapy if a dual OAD therapy is contraindicated or not tolerated; and
- in combination with insulin and metformin, unless metformin is contraindicated or not tolerated.

Funding status

Dulaglutide 0.75 mg and 1.5 mg solution for injection in pre-filled pen is recommended for inclusion on the MOH Medication Assistance Fund (MAF) for the abovementioned indications from 1 February 2023.

MAF assistance **does not** apply to any formulations or strengths of liraglutide or semaglutide for treating type 2 diabetes mellitus.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of glucagon-like peptide-1 receptor agonist (GLP-1 RA) injections (dulaglutide and semaglutide) for treating type 2 diabetes mellitus (T2DM). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical and patient experts from the public healthcare institutions and local patient and voluntary organisations. Published clinical and economic evidence for GLP-1 RAs was considered in line with their registered indications. By the request of the company, liraglutide injection was not included in the evaluation.

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 recognised that GLP-1 RAs have a different mechanism of action compared with other commonly used, subsidised treatment options for T2DM such as OAD therapies (metformin, sulfonylureas, sodium-glucose co-transporter [SGLT2] inhibitors, dipeptidyl peptidase 4 [DPP-4] inhibitors) and insulin.

2.2. In line with international clinical practice guidelines, the Committee noted that GLP-1 RA injections may be used at various points in the treatment pathway for T2DM, taking into consideration patients' comorbidities, glycaemic control, tolerability, body weight and preferences.

2.3. The Committee acknowledged that the clinical need for a GLP-1 RA injection was highest in the following settings:
- as triple therapy in combination with two OAD therapies for patients with inadequate glycaemic control despite treatment with optimal doses of dual OAD therapy; and,
- in combination with insulin and metformin.

2.4. The Committee considered testimonials from local patient experts about what it is like living with T2DM and their experience with different treatments. The Committee heard that most patients who provided inputs into the evaluation were receiving treatment with OAD therapies or insulin, and felt that their treatments were effective with minimal side effects. They noted however, that patients cited difficulties having to regularly monitor blood sugar levels, administer treatments and avoid foods high in sugar, which had a significant negative impact on their daily lives. Most patients were not familiar with GLP-1 RAs but considered that any new treatments for T2DM should be affordable, have less side effects than current treatments and be simple to administer.

Clinical effectiveness and safety

3.1. The Committee heard that GLP-1 RAs were compared in a head-to-head randomised controlled trial (RCT; SUSTAIN-7) which showed a statistically significant improvement in HbA1c reduction for semaglutide versus dulaglutide. However, given that the treatment difference (-0.41%, 95% CI -0.57 to -0.25) did not meet the minimal clinically important difference (MCID) of 0.5% for superiority which was previously accepted by the Committee *(ACE guidance: SGLT2 inhibitors for type 2 diabetes mellitus)*, this difference was not considered to be clinically significant. Overall, the Committee agreed that dulaglutide was non-inferior to semaglutide in terms of HbA1c control and safety profile.

3.2. The Committee noted that dulaglutide (AWARD-9) or semaglutide (SUSTAIN-5) added to basal insulin resulted in a clinically significant HbA1c reduction compared to basal insulin intensification alone (MCID of 0.5% for superiority was met). Another RCT (SUSTAIN-11) showed that semaglutide added to basal insulin was non-inferior to a basal-bolus insulin regimen in terms of mean change from baseline in HbA1c. Overall, the Committee agreed that both GLP-1 RA injections as add-on therapy to insulin were at least non-inferior to insulin intensification in terms of HbA1c control with a tolerable safety profile.

3.3. The Committee reviewed the available clinical evidence from three RCTs which compared dulaglutide (AWARD-2, Wang et. al.) or semaglutide (SUSTAIN-4) with insulin glargine as add-on to OAD therapies. The Committee noted that while both GLP-1 RAs were statistically superior to insulin glargine in terms of mean change in HbA1c from baseline, treatment differences did not consistently meet the MCID of 0.5% for superiority.

3.4. In terms of safety, GLP-1 RAs had a lower incidence of hypoglycaemia compared to insulin glargine. While gastrointestinal side effects were more commonly reported with GLP-1 RAs, treatment was generally well-tolerated, and rates of discontinuation were low. Overall, the Committee agreed that both GLP-1 RA injections were at least non-inferior to insulin glargine when used as add-on to OAD therapies in terms of HbA1c control, with a tolerable safety profile.

3.5. In addition to HbA1c outcomes, the Committee noted that a statistically significant reduction in weight was reported for semaglutide versus dulaglutide in SUSTAIN-7, as well as for GLP-1 RAs versus basal insulin or insulin intensification in other studies. The Committee agreed that the sustainability of this weight reduction with use of GLP-1 RAs and its translation into long-term clinical outcomes was unclear. The Committee noted results of the REWIND and SUSTAIN-6 trials which demonstrated the cardiovascular safety of dulaglutide and semaglutide compared with placebo. Dulaglutide also demonstrated superiority in terms of reduction in cardiovascular events compared with placebo.

Cost effectiveness

4.1. The companies of dulaglutide and semaglutide were invited to submit value-based pricing (VBP) proposals for their products for funding consideration. The Committee agreed that a cost-minimisation approach was appropriate to assess the cost-effectiveness of the GLP-1 RA injections. The Committee noted that dulaglutide, which had the lower cost, was the more cost-effective option and the proposal was adequate to manage the uncertainty of the overall budget impact.

4.2. The Committee noted that the proposed prices were comparable to overseas reference jurisdictions. Based on the proposals, the Committee agreed that dulaglutide was likely to be considered an acceptable use of healthcare resources when used as add-on to OAD therapies or in combination with insulin, in line with recommendations by overseas reference HTA agencies.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be between SG$1 million to less than SG$3 million in the first year of listing dulaglutide on the MAF.

Recommendations

6.1. Based on available evidence, the Committee recommended dulaglutide 0.75 mg and 1.5 mg solution for injection in pre-filled pen be listed on the MAF for treating T2DM given its clinical need and acceptable clinical and cost-effectiveness.

6.2. The Committee recommended not listing semaglutide on the MOH List of Subsidised Drugs due to unacceptable cost-effectiveness compared with dulaglutide based on the company's proposal.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 25 August 2022. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. 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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