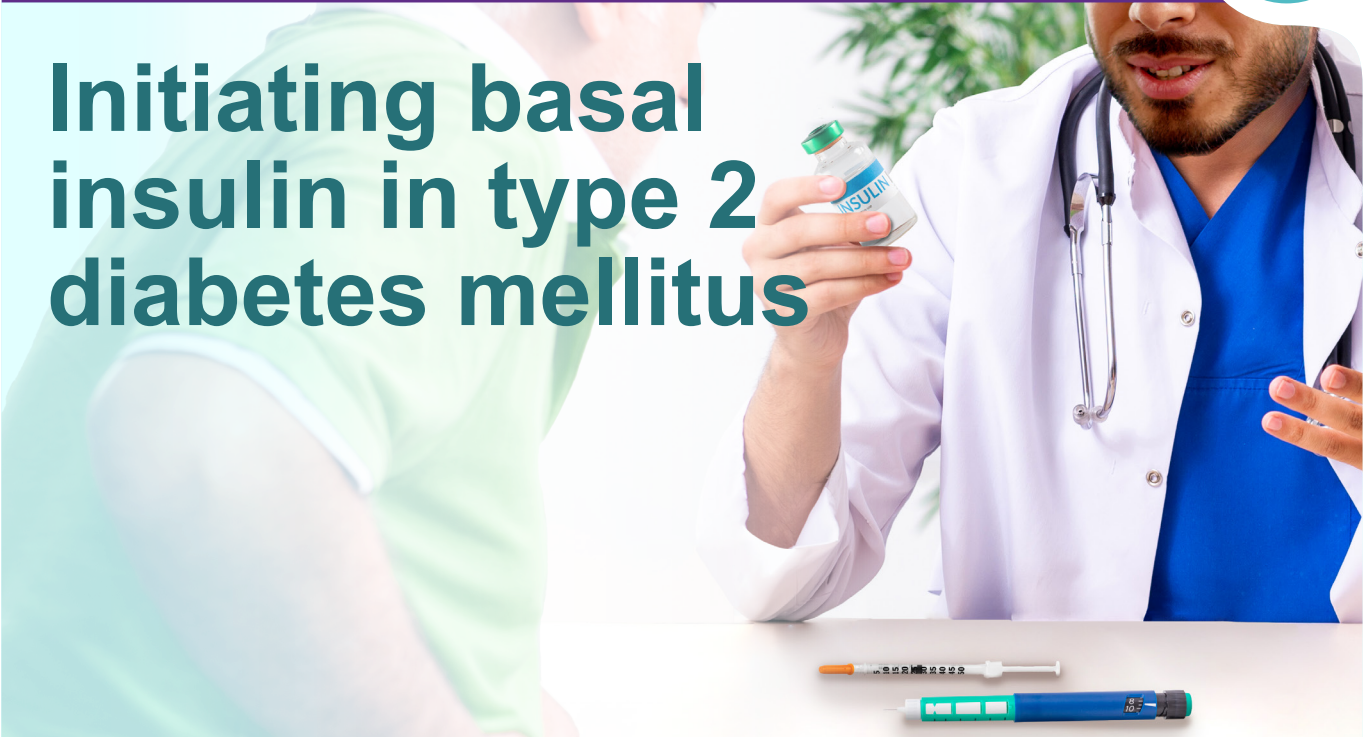




Initiating basal insulin in type 2 diabetes mellitus



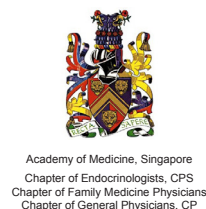
Objective	Scope	Target audience
To provide guidance on timely, safe and appropriate introduction of basal insulin in the management of type 2 diabetes	Commencement of basal insulin for patients with type 2 diabetes mellitus who are suboptimally controlled on other non-insulin diabetes medications	This clinical guidance is relevant to all healthcare professionals caring for patients with type 2 diabetes mellitus, such as those in primary care

Approximately 1 in 4 Singaporeans with diabetes mellitus have poor glycaemic control, hence are at increased risk of diabetes-related complications and poor clinical outcomes.¹⁻⁴ For patients with type 2 diabetes mellitus (T2DM), non-insulin T2DM medications can help patients to achieve initial glycaemic control but may not be able to do so in the long term. Patients with T2DM who are unable to reach their glycaemic targets despite optimal treatment with non-insulin T2DM medications alone should be started on insulin therapy.⁵

Patient education and shared decision making is integral to the successful initiation of insulin for patients with T2DM. Health care professionals play an important role in empowering patients and their caregivers by engaging them in discussions relating to insulin use, from addressing insulin-related concerns, to appropriate and safe use, and preventing and managing hypoglycaemia.

Statement of Intent

This ACE Clinical Guidance (ACG) provides concise, evidence-based recommendations and serves as a common starting point nationally for clinical decision-making. It is underpinned by a wide array of considerations contextualised to Singapore, based on best available evidence at the time of development. The ACG is not exhaustive of the subject matter and does not replace clinical judgement. The recommendations in the ACG are not mandatory, and the responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.



Recommendation 1

Start basal insulin if glycaemic targets are not met despite optimal treatment with non-insulin T2DM medications.

When progression of type 2 diabetes requires the introduction of insulin therapy, the use of basal insulin alone is one of the simplest and most convenient ways to do so. Basal insulin is used to control fasting blood glucose and can be categorised into intermediate- or long-acting insulin according to the time-action profile (see Table 1 below).

Intermediate-acting insulin isophane, or neutral protamine Hagedorn (NPH), has traditionally been used. It is usually injected once daily at bedtime. Long-acting insulin analogues (LAIAs) are as effective as NPH in lowering fasting blood glucose. LAIAs are associated with fewer hypoglycaemic events, especially nocturnal hypoglycaemia, but are more expensive than insulin NPH.⁶

The various LAIAs registered in Singapore (insulin detemir, insulin glargine, insulin degludec) are comparable in efficacy and safety. To achieve similar glycaemic control, insulin degludec and insulin glargine are usually injected once daily, whereas insulin detemir may need to be injected twice daily.^{7,8} Insulin degludec has the longest duration of action, which results in less nocturnal hypoglycaemia than insulin detemir and insulin glargine.⁸⁻¹¹ Include cost considerations in choosing a basal insulin.



Other indications for insulin therapy in T2DM

This ACG focuses on the initiation of insulin therapy for patients with T2DM who are suboptimally controlled on other non-insulin diabetes medications. Insulin therapy should also be considered for patients with T2DM who are experiencing symptoms of hyperglycaemia or showing signs of ongoing catabolism (e.g. unexpected weight loss), regardless of their current non-insulin diabetes medications or stage of T2DM.⁵ Further assessment or referral may be warranted for such patients.

Table 1. Types and profiles of basal insulin

Registered insulin compound (brand name)	Dosage form	Onset	Peak	Duration	Dosing
Intermediate-acting					
Isophane/NPH (Insulatard)	U-100 vial (see note 1 below)	1–4 h	8–12 h	12–20 h	Once to twice daily
Long-acting (analogues)					
Detemir (Levemir) (see note 2 below)	U-100 prefilled pen U-100 cartridge	1–4 h	No peak	18–24 h	Once to twice daily
Glargine (Lantus)	U-100 vial U-100 prefilled pen	1–4 h	No peak	24 h	Once daily*
Glargine biosimilar (Semglee)	U-100 prefilled pen	1–4 h	No peak	24 h	Once daily*
Glargine (Toujeo)†	U-300 prefilled pen	6 h	No peak	24–36 h	Once daily
Degludec (Tresiba)	U-100 prefilled pen U-200 prefilled pen	1–4 h	No peak	42 h	Once daily

NPH, neutral protamine Hagedorn

Insulin listed in order of increasing duration of action. Dosage forms in bold denote availability on government subsidy list.

* Patients requiring high doses may need twice-daily dosing.

† U-300 glargine has a longer duration of action than U-100 glargine due to the lower injection volume needed for the same insulin dose (as U-300 is more concentrated than U-100), and the smaller precipitate surface area leads to more sustained release.

Note:

1. The supply of insulin isophane/NPH (Insulatard) U-100 penfill cartridges was discontinued in Singapore in August 2024, based on information from the manufacturer. Please check with your distributor or institution pharmacist for information on remaining stock availability.
2. Insulin detemir (Levemir) will be discontinued in Singapore from August 2025, based on information from the manufacturer. Please check with your distributor or institution pharmacist for information on actual stock availability and consider continuity of supply before prescribing.



Notes on insulin prescribing

Different insulin compounds (Table 1), even within the same time-action category, are not identical and the decision to switch between products should be evaluated by the clinician. Include brand names when prescribing to distinguish between products and minimise errors.

Biosimilars are biological products with physicochemical characteristics, biological activity, safety, and efficacy similar to their originator reference products¹² and they may offer some cost savings.

Insulin glargine biosimilars are non-inferior to reference insulin glargine in efficacy and safety.¹³



Addressing concerns about starting insulin

Many patients have concerns about starting insulin, with reported barriers including stigma and perceived failure, fear of injection and pain, concerns about weight gain, and fear of hypoglycaemia.¹⁴ These barriers contribute to a delay in the timely initiation of insulin, which is associated with suboptimal glycaemic control,¹⁵ and for some patients, the development of diabetes-related complications.¹⁶

Early conversations about the potential need for insulin and regular patient education can help address these barriers.¹⁷



Explaining the need for insulin therapy

- ✓ Explain to patients the progressive nature of T2DM, with the body increasingly not being able to respond to insulin properly (insulin resistance) and not making enough insulin (insulin deficiency due to loss of β -cell function).
- ✓ Emphasise the role and benefits of insulin in maintaining glycaemic control when T2DM cannot be managed adequately with other non-insulin T2DM medications.
- ✓ Assure patients that the need for insulin is no one's fault and is not a punishment.

Recommendation 2

Review concomitant T2DM medications when starting basal insulin and continue them at the current or lower dose where appropriate.

When starting basal insulin for a patient with T2DM, review the use of concomitant T2DM medications regularly, taking into account their benefits and risks, and considering the patient's need for them as well as overall treatment burden.

Figure 1. Considerations for concomitant T2DM medications when initiating basal insulin

Possible reasons for continuing non-insulin T2DM medications at the current or lower dose



- To improve glycaemic control through synergistic effects while potentially reducing insulin requirements¹⁸⁻²⁰
- To retain positive effects of concomitant medication beyond glycaemic control
 - E.g. continuing SGLT2 inhibitor or GLP-1 RA for their cardiovascular or renal benefits, particularly for patients with relevant comorbidities²¹⁻²³
- To offset potential weight gain associated with insulin therapy^{24,25}
 - E.g. continuing metformin or SGLT2 inhibitor

Possible reasons for discontinuing non-insulin T2DM medications

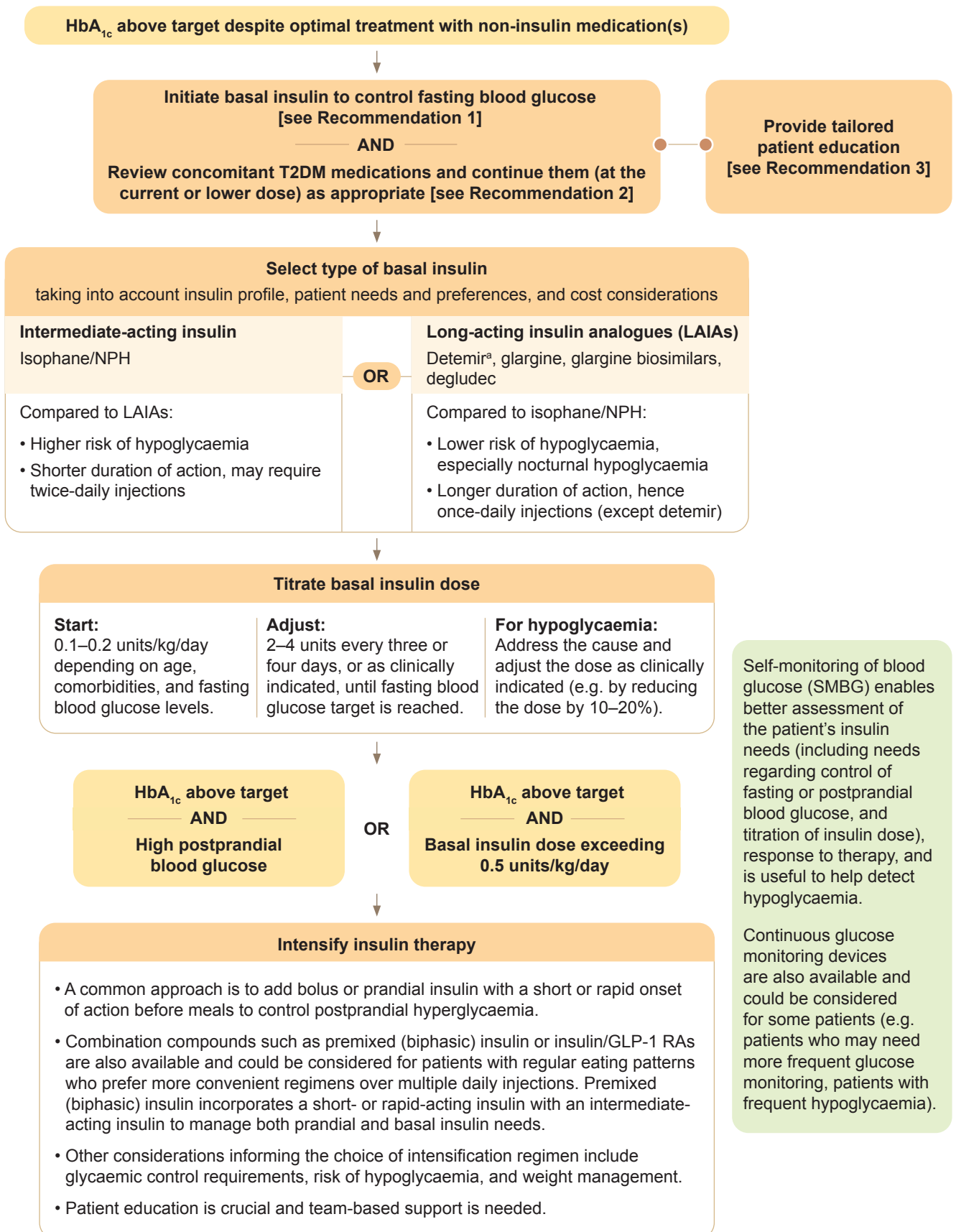


- To prevent adverse effects from concomitant use
 - E.g. discontinuing thiazolidinediones due to increased risk of oedema and heart failure¹⁸
 - E.g. discontinuing sulfonylurea or meglitinide due to increased risk of hypoglycaemia and weight gain²⁶

SGLT2 inhibitor, sodium-glucose co-transporter 2; GLP-1 RA, glucagon-like peptide-1 receptor agonist

Figure 2 summarises the steps involved in commencing insulin therapy for patients with T2DM with poor glycaemic control despite optimal treatment with non-insulin medication(s).

Figure 2. Starting and titrating basal insulin for patients with type 2 diabetes mellitus (T2DM)



GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HbA_{1c}, glycated haemoglobin; NPH, neutral protamine Hagedorn

^a Insulin detemir (Levemir) will be discontinued in Singapore from August 2025, based on information from the manufacturer. Please check with your distributor or institution pharmacist for information on actual stock availability and consider continuity of supply before prescribing.

Recommendation 3**Educate patients and their caregivers on how to use insulin safely and effectively, including how to prevent and manage hypoglycaemia.**

When starting insulin therapy, it is critical to ensure that the patient and their caregiver are engaged in the process, and are equipped to manage their insulin use so that insulin therapy is not only safe, but also effective. Where feasible, enlist the support of other healthcare professionals in educating the patient and their caregiver.

Given the wide array of topics to cover, the discussion about insulin therapy needs to be tailored to each individual and the stage they are at. Some topics need to be addressed prior to starting (e.g. concerns with insulin use – see 'Addressing concerns about starting insulin' on page 3), others at the start of treatment (e.g. preventing and managing hypoglycaemia; insulin use and storage), and others as they become relevant across the patient's life journey (e.g. fasting during Ramadan, or travelling while on insulin).

Preventing and managing hypoglycaemia

Hypoglycaemia (blood glucose level below 4 mmol/L) is a potentially serious adverse effect of insulin therapy. Hypoglycaemia is, therefore, a major limiting factor in achieving good glycaemic control. Prevention and prompt management of hypoglycaemia are crucial.

Hypoglycaemia is associated with many symptoms (Table 2) but is sometimes not perceived or experienced by the patient, including lack of early warning symptoms. This is known as hypoglycaemia unawareness and can be detected through blood glucose monitoring.

Patients who are at increased risk of hypoglycaemia include those with:

- Advanced age
- Renal impairment
- Intensive or high-dose insulin regimens
- Poor oral intake or prolonged fasting with high activity levels
- Concurrent illness, such as infection or sepsis
- Cognitive dysfunction
- Polypharmacy or medication non-adherence

Individualise glycaemic targets for these patients as appropriate, and review insulin regimens (and concomitant T2DM medications) for patients with frequent hypoglycaemia or hypoglycaemia unawareness.

**Hypoglycaemia**

- ✓ Educate patients and their caregivers about hypoglycaemia and its management (Table 2).
- ✓ Advise patients who are at increased risk of hypoglycaemia to be more vigilant with their SMBG.
- ✓ Encourage patients to keep a record of each hypoglycaemic event (including possible causes), and review this at each clinic visit.

**Hypoglycaemia unawareness (HU)**

HU or impaired awareness of hypoglycaemia significantly increases the risk of severe hypoglycaemia, and HU has been reported in 9 to 18% of patients with insulin-treated T2DM.²⁷

Patients with HU do not experience or perceive typical early warning symptoms of hypoglycaemia (such as tremors, palpitations, sweating) when their blood glucose is low. This may occur in patients with repeated hypoglycaemic events or in those with concomitant autonomic neuropathy.

Advise patients with HU to raise their glycaemic targets for several weeks to months to avoid hypoglycaemia.²⁸⁻³⁰ Use of continuous glucose monitoring could be helpful.

Table 2. Hypoglycaemia and its management

	Typical symptoms and signs	Management
Mild to moderate hypoglycaemia (self-management is possible)	Tremors, palpitations, sweating, excessive hunger, headaches, mood changes, confusion, irritability, decreased attentiveness, paraesthesias, visual disturbances	<p>15-15 rule</p> <ul style="list-style-type: none"> • Glucose 15 g[§] is preferred (e.g. dextrose powder or 3 teaspoons of Glucolin), although any form of carbohydrate that contains glucose can be used (e.g. ½ cup juice, ½ can regular soft drink, 1 can low-sugar soft drink, 3 teaspoons sugar). • Advise patients and their caregivers to re-check blood glucose levels after 15 minutes. Repeat treatment (glucose 15 g[§]) and seek medical advice when the patient's symptoms or signs do not improve or when blood glucose level remains <4 mmol/L. • Once blood glucose level is ≥4 mmol/L, advise patients to consume a meal or snack to prevent the recurrence of hypoglycaemia.
Severe hypoglycaemia (requires assistance)	Unresponsiveness, unconsciousness, seizures, coma	<ul style="list-style-type: none"> • Call 995 for an ambulance and seek urgent medical assistance. • Do not administer anything orally to prevent choking.

§ 30 g glucose is needed if blood glucose level <2.8 mmol/L.



Insulin administration and storage

- ✓ Advise patients to inspect the insulin to ensure that it looks as it should. For example, NPH should look cloudy, while LAIAs should appear clear. Insulin should not be used if there is clumping, frosting, precipitation, change in colour, or if the patient is uncertain about the appearance.
- ✓ Ensure patients know how to inject insulin correctly.
 - If the insulin is retrieved from the fridge, inform patients to wait for a while for the insulin to be less cold as injecting cold insulin can be more painful.
 - Insulin should be injected subcutaneously into the abdomen, arms, thighs, or buttocks. Note that absorption rates of insulin vary between body areas. Keep to one body area and do not massage injection sites.
 - Patients should avoid areas with bruises, scar tissue, parts near joints, the groin, and the navel.
- Used syringes and needles should be discarded in a puncture-resistant container (hard plastic/metal/sharps container) with a secured lid. Do not reuse them.
- Remind patients to rotate injection sites regularly within their preferred body area to avoid the development of lipohypertrophy.
- ✓ Discuss how to store insulin properly.
 - For unopened insulin, store in the fridge between 2°C and 8°C. Do not freeze.
 - Open one insulin pen, vial or cartridge at a time. Once opened, keep it in a cool area below 30°C for up to 4, 6, or 8 weeks depending on the product. Advice regarding refrigeration of opened products varies between products. Please refer to individual product information leaflets for details.



Diet

- ✓ Advise patients regarding a healthy and balanced diet. Skipping or delaying meals, or changing the amount or type of food can affect their blood glucose levels.
- ✓ Advise patients who are on fixed insulin doses that they need consistent patterns of carbohydrate intake.
- ✓ Refer patients to a dietitian or other suitably trained healthcare professional for dietary advice, if available.



Fasting and physical activity

- ✓ Encourage patients to discuss any changes in diet (including religious fasting) and physical activities as their insulin requirements may change.
- ✓ Before patients start fasting (e.g. during Ramadan):
 - Assess their suitability to fast.
 - Discuss the need to adjust medication doses if they proceed with the fast.
 - Discuss risks associated with fasting and address any problems encountered during previous fasts.
- Reinforce SMBG and how to prevent and manage hypoglycaemia.
- Advise them to end their fast if hypoglycaemia or severe hyperglycaemia occurs.
- Advise them to maintain a healthy and balanced diet when they break their fast.
- ✓ Schedule a follow-up appointment after they complete their fast.



Sick days

- ✓ Advise patients to continue their insulin and monitor their blood glucose more regularly as blood glucose levels may rise when they are ill.
- ✓ Encourage patients not to skip meals but to consume smaller, more frequent meals or to drink liquid supplements suitable for patients with diabetes if their appetite decreases.



Travel

- ✓ Remind patients to:
 - Bring sufficient insulin and injection/testing equipment, and to keep them in carry-on baggage.
 - Store their insulin at the appropriate temperature while travelling.
 - Carry glucose tablets or glucose-containing sweets in case of hypoglycaemia.
- ✓ Ensure that patients have a doctor's letter certifying that they need their insulin and injection/testing equipment at all times.



Patient information and resources on insulin

Click or scan the QR codes to access examples of patient information and resources from HealthHub which can be used to complement patient education about insulin.



The National Diabetes Reference Materials contain comprehensive information on diabetes management (available in English, Chinese, Malay and Tamil). The 'Be Proactive' slides contain insulin-related information, including hypoglycaemia and its management, SMBG, and insulin injections.



This page provides an overview of insulin types and insulin administration, including videos on how to inject insulin (available in English, Chinese, Malay and Tamil).



This series of visual guides cover many aspects of diabetes management, including the role of insulin ('What is type 2 diabetes?') and insulin use ('How to draw insulin from a vial', 'How to inject insulin', 'Insulin storage' and 'How to safely dispose of syringes').

References

Click or scan the QR code for the reference list to this clinical guidance



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About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare by conducting health technology assessments (HTA), publishing healthcare guidance and providing education. ACE develops ACE Clinical Guidances (ACGs) to inform specific areas of clinical practice. ACGs are usually reviewed around five years after publication, or earlier, if new evidence emerges that requires substantive changes to the recommendations. To access this ACG online, along with other ACGs published to date, please visit www.ace-hta.gov.sg/acg

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