Dulaglutide: the long-awaited new agent to treat type 2 diabetes

Brought to you by He Ako Hiringa
Supported by PHARMAC TE PĀTAKA WHAIORANGA

Dr Ryan Paul

He Ako Hiringa
Learning Always

RELEVANT DISCLOSURES

- I am receiving an honorarium for this presentation
- I am a member of the Lilly Advisory Board for dulaglutide
- I recently convened the NZSSD national guidance on the management of type 2 diabetes
- I have had no experience with using dulaglutide
  - All my experience comes from using liraglutide + exenatide

TYPE 2 DIABETES (T2D)

- Prevalence of T2D continues to increase → > 250,000 in Aotearoa New Zealand
- 2/3^{rds} will die from cardiovascular disease (CVD)
- Creates some of the greatest disparities for Māori and Pacific peoples
  - Māori more likely to get T2D
  - Māori 1.5 x more likely to die from CVD + 4 x more likely to require dialysis
  - Disparities are even worse for Pacific peoples + have not changed over the past 20 years
- Until recently only funded glucose lowering therapies with independent CV + renal benefits were:
  - Metformin
  - Pioglitazone

2021 – THE YEAR OF CHANGE

- PREDICT CV risk calculator → disparities in CVD + T2D are not due to ethnicity *per se*
- Commitment from PHARMAC + He Ako Hiringa to reduce disparities in diabetes
  - Funding of empagliflozin + dulaglutide under SA criteria with ethnicity clause
  - Targeted advertising to Māori + Pacific peoples
- Empagliflozin (Jardiance/Jardiamet) available from February 2021
- Dulaglutide (Trulicity) available from 1st September 2021

CASE – MRS W

- 59 year old Māori woman with T2D + a history of:
  - Hypertension
  - Dyslipidaemia
  - Peripheral vascular disease
  - Central obesity (BMI 30.1 kg/m^2)
  - UACR 3.8 mg/mmol with eGFR > 90 mL/min

- HbA1c 63 mmol/mol on current medication regimen:
  - Metformin 1000mg/Vildagliptin 50 mg twice daily
  - Lantus insulin 30 units nocte
  - Atorvastatin 40 mg nocte
  - Perindopril 4 mg daily

- She makes an appointment after seeing the ad on Māori TV about whether she should be on the new diabetes medications. She is very motivated as her whānau all died in their 60's from MIs.

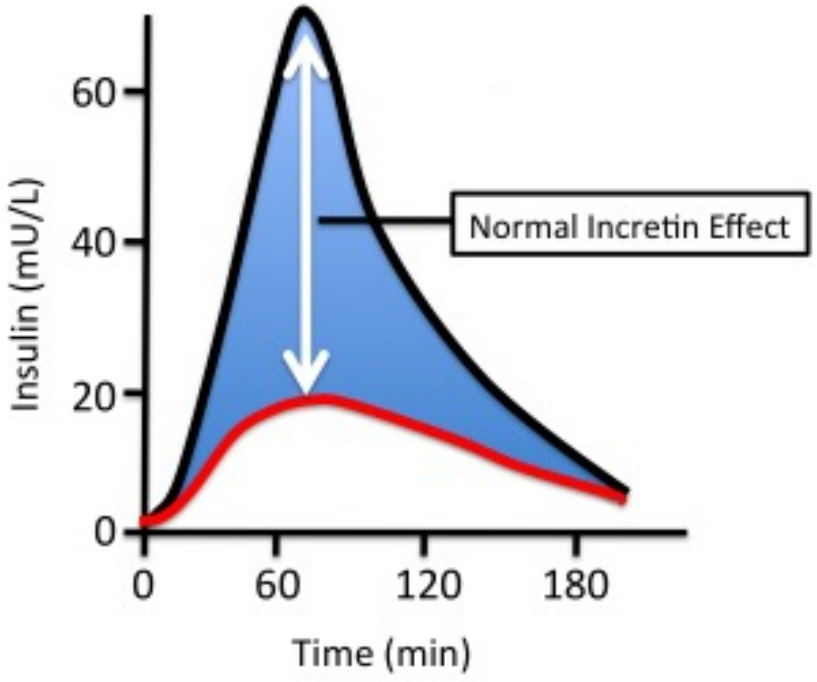
- Should she be on dulaglutide or empagliflozin? Which one is better for her?

DULAGLUTIDE

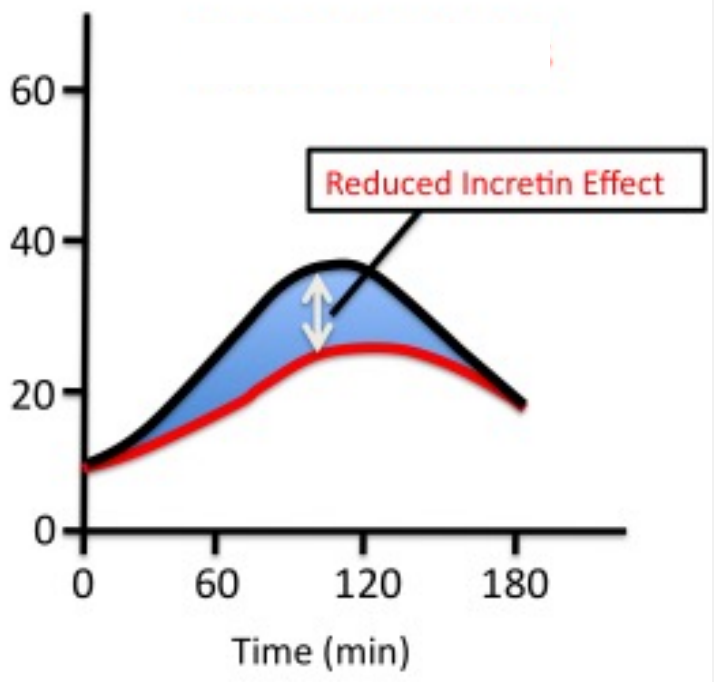
- Glucagon-like peptide-1 (GLP-1) receptor agonist (GLP1RA) that has been available worldwide since 2005
- GLP-1 is the main incretin produced by L cells in the gut in response to nutrients
- GLP-1 acts directly on pancreatic islet cells to:
  - Increase glucose-dependent insulin secretion
  - Decrease glucagon production
  - Possibly preserve ß-cell mass
- **NB: GLP1RA very rarely cause hypoglycaemia alone as insulin release is glucose-dependent**
  - **All episodes of severe hypoglycaemia have occurred in patients on insulin and/or sulfonylureas**

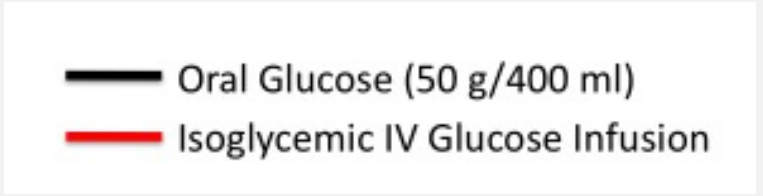
DIABETES + THE 'INCRETIN EFFECT'

Healthy patients



Patients with T2D





Adapted from Nauck et al. Diabetologia 1986; 29:46

EXTRA-PANCREATIC EFFECTS OF DULAGLUTIDE

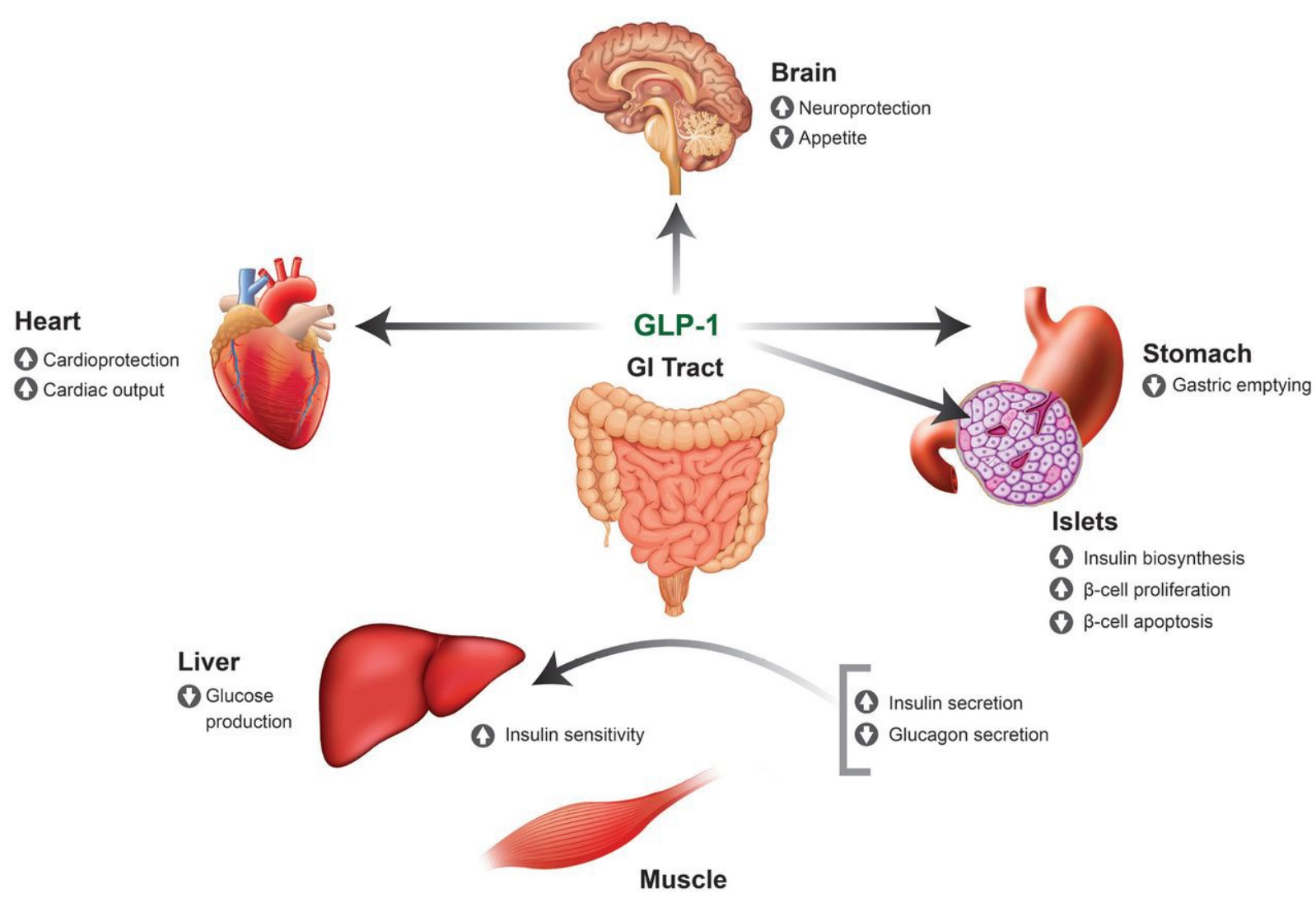
- Stomach → decreased gastric emptying
- Brain → decreased appetite
- Heart → increased cardiac output + cardioprotective
- Blood vessels → decreased atherosclerosis
- Kidney → increased naturesis + renoprotective
- Bone → may increase bone formation

Weight loss

Reduced CVD

Slowed progression of renal disease

MECHANISM OF ACTION OF DULAGLUTIDE



Hinnen et al. Diab. Spect. 2017; 30:202

DULAGLUTIDE + VILDAGLIPTIN

- Endogenous GLP-1 is rapidly deactivated by the enzyme dipeptidyl peptidase IV (DPPIV)
- DPPIV inhibitors (e.g. vildagliptin) are useful in T2D due to decreased GLP1 + increased DPPIV activity
- GLP1RA are resistant to degradation by DPPIV
- **Therefore, vildagliptin should be stopped when dulaglutide started as redundant**

DULAGLUTIDE (TRULICITY)

- Only available in 1.5 mg weekly subcutaneous injections

- Can be injected at any time of day on any day of the week
  - Usual injection sites abdomen, thigh + upper arm (inbuilt 29 gauge needle)
  - Missed doses can be taken up to 3 days late

- Pens can be stored at room temperature for 2 weeks – otherwise refrigerate

- **No need for dose titration at present**

DULAGLUTIDE (TRULICITY) INJECTIONS

1

Uncap the pen

2

Place and unlock

3

Press and hold
for 10 seconds

The injection is complete when grey part is visible

IMPROVEMENTS IN GLYCAEMIC CONTROL WITH DULAGLUTIDE

- Mean reduction in HbA1c dependent on baseline HbA1c
  - - 6 mmol/mol if baseline HbA1c 56 mmol/mol (REWIND)
  - - 13 mmol/mol if baseline HbA1c < 69 mmol/mol (AWARD-CHN1+2)
  - - 25 mmol/mol if baseline HbA1c > 69 mmol/mol (AWARD-CHN1+2)

- Reductions in HbA1c greater with dulaglutide than basal insulin in insulin-naïve patients
  - -12 mmol/mol versus – 6 mmol/mol (AWARD-2 + DISPEL)
  - Multiple potential mechanisms for greater efficacy of dulaglutide:
    - Reduced oral intake + slowed absorption of glucose
    - Increased endogenous insulin + reduced glucagon production
    - Lower fear of hypoglycaemia

- **Patients may be able to stop insulin if on < 40 units per day + HbA1c to target**

OTHER BENEFITS OF DULAGLUTIDE

- Mean reduction in weight of 2 kg at 5 years (REWIND)
  - Associated with mean reductions in systolic BP of 2 mmHg + LDL cholesterol of 0.05 mmol/L

- Reduced risk of major adverse cardiovascular events - cardiovascular death, non-fatal MI or stroke (REWIND)
  - NNT = 18 for 5.4 years if established CVD
  - **NNT = 60 if subclinical vascular disease or ≥ 2 CVD risk factors i.e. primary prevention**
  - Decrease in events predominantly due to reduced non-fatal stroke

- Reduced development of macroalbuminuria (REWIND)
  - **No evidence to date of preventing need for dialysis or renal death**

- **NB: Benefits are additional to improved glycaemic control + standard treatment e.g. statins, ACEi etc.**

ADVERSE EFFECTS OF DULAGLUTIDE

- Transient nausea will occur in 8-30% of patients
  - Typically peaks in 1st 2-3 days + resolves within weeks (< 2% stop treatment)
  - Rarely associated with vomiting – case reports of acute renal injury in high risk patients
  - May also be associated with transient constipation or diarrhoea
- Transient injection site reactions (e.g. redness, nodules) may also occur
- Risks of pancreatitis + medullary thyroid carcinoma controversial
  - All GLP1RAs mildly increase pancreatic enzymes but risk of pancreatitis similar to placebo
  - Increased risk of medullary thyroid carcinoma only seen in rodents
- Hypoglycaemia if on insulin and/or sulfonylureas

TIPS TO REDUCE ADVERSE EFFECTS

- Eat smaller meals more slowly + avoid food 2 hours before bed
- Avoid fried/fatty foods + alcohol
- Ensure adequate hydration
- Reduce dose of insulin and/or sulfonylureas if HbA1c < 64 mmol/mol
  - Halve dose of sulfonylureas + 15-20% reduction in total daily dose of insulin good starting point
  - Also consider reducing doses if HbA1c < 75 mmol/mol + high risk of hypoglycaemia – glucose levels best guide
- Ensure adequate follow up
  - 3 month follow up likely appropriate for most but organise earlier follow up if high risk

PRECAUTIONS WITH USE OF DULAGLUTIDE

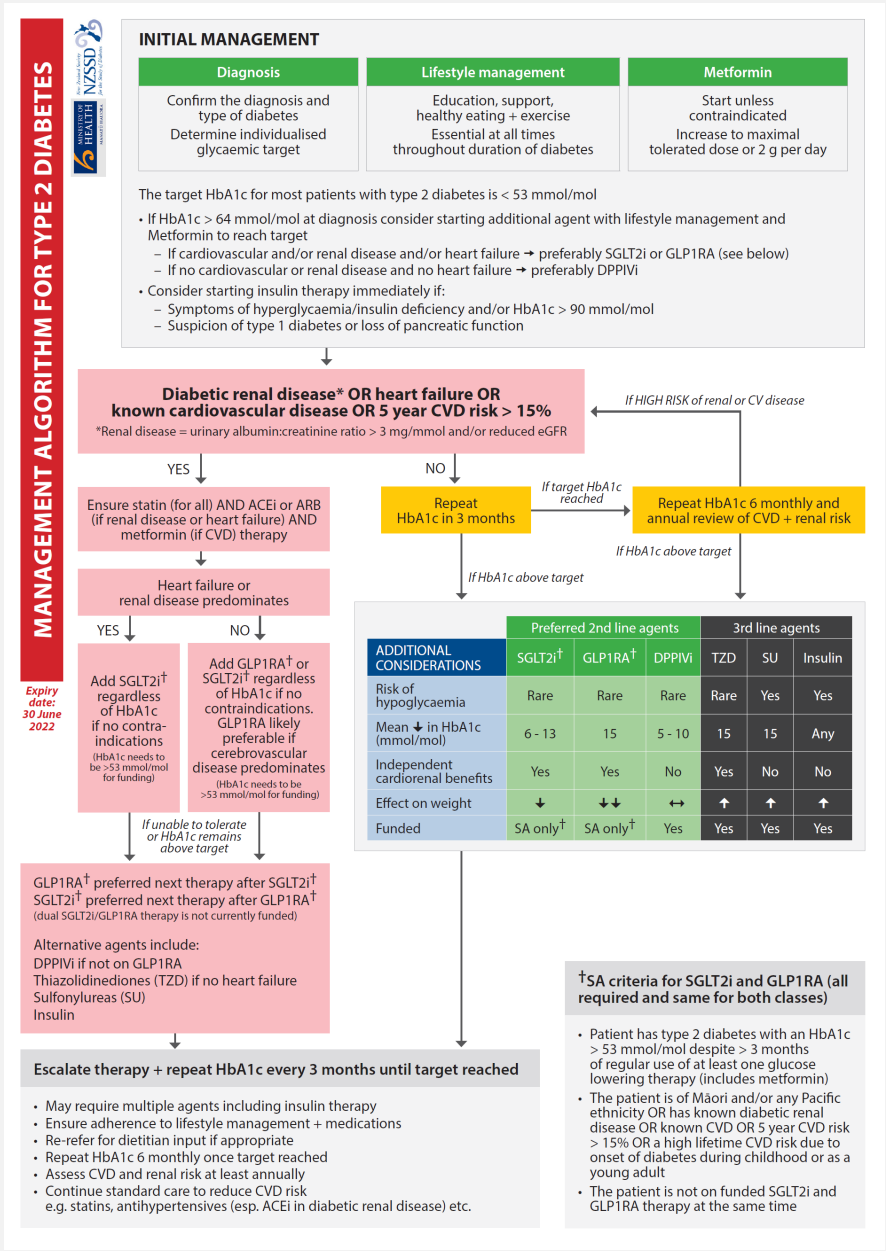
- No safety data so not recommended for use in:
  - Pregnancy + breastfeeding
  - Children < 18 years of age
  - eGFR < 15 mL/min

- Due to risk of adverse effects be very cautious using or do not use if:
  - Significant gastrointestinal disease – particularly gastroparesis or severe gastro-oesophageal reflux
  - Frail and/or > 75 years of age – particularly those on ACEi/ARBs, diuretics, NSAIDs etc.
  - Previous pancreatitis
  - Previous medullary thyroid cancer/multiple endocrine neoplasia 2 (MEN2) syndrome

- No data for dulaglutide in type 1 diabetes to date – use only with specialist approval in this group

WHEN SHOULD I BE USING DULAGLUTIDE?

NZSSD MANAGEMENT ALGORITHM OF T2D



ALGORITHM FOR TYPE 2 DIABETES

New Zealand Society for the Study of Diabetes NZSSD

MINISTRY OF HEALTH MANATŪ HAUORA

INITIAL MANAGEMENT

Diagnosis	Lifestyle management	Metformin
Confirm the diagnosis and type of diabetes Determine individualised glycaemic target	Education, support, healthy eating + exercise Essential at all times throughout duration of diabetes	Start unless contraindicated Increase to maximal tolerated dose or 2 g per day

The target HbA1c for most patients with type 2 diabetes is < 53 mmol/mol

- If HbA1c > 64 mmol/mol at diagnosis consider starting additional agent with lifestyle management and Metformin to reach target
  - If cardiovascular and/or renal disease and/or heart failure → preferably SGLT2i or GLP1RA (see below)
  - If no cardiovascular or renal disease and no heart failure → preferably DPPIVi
- Consider starting insulin therapy immediately if:
  - Symptoms of hyperglycaemia/insulin deficiency and/or HbA1c > 90 mmol/mol
  - Suspicion of type 1 diabetes or loss of pancreatic function

↓

Diabetic renal disease* OR heart failure OR known cardiovascular disease OR 5 year CVD risk > 15%

*Renal disease = urinary albumin:creatinine ratio > 3 mg/mmol and/or reduced eGFR

MANAGEMENT ALGORITHM

Expiry date: 30 June 2022

Diabetic renal disease* OR heart failure OR known cardiovascular disease OR 5 year CVD risk > 15%

*Renal disease = urinary albumin:creatinine ratio > 3 mg/mmol and/or reduced eGFR

YES

Ensure statin (for all) AND ACEi or ARB (if renal disease or heart failure) AND metformin (if CVD) therapy

Heart failure or renal disease predominates

YES

Add SGLT2i† regardless of HbA1c if no contra-indications
(HbA1c needs to be >53 mmol/mol for funding)

NO

Add GLP1RA† or SGLT2i† regardless of HbA1c if no contraindications. GLP1RA likely preferable if cerebrovascular disease predominates
(HbA1c needs to be >53 mmol/mol for funding)

If unable to tolerate or HbA1c remains above target

GLP1RA† preferred next therapy after SGLT2i†
SGLT2i† preferred next therapy after GLP1RA†
(dual SGLT2i/GLP1RA therapy is not currently funded)

Alternative agents include:
DPPIVi if not on GLP1RA
Thiazolidinediones (TZD) if no heart failure
Sulfonylureas (SU)
Insulin

NO

Repeat HbA1c in 3 months

If target HbA1c reached

Repeat HbA1c 6 monthly and annual review of CVD + renal risk

If HIGH RISK of renal or CV disease

If HbA1c above target

If HbA1c above target

	Preferred 2nd line agents			3rd line agents		
ADDITIONAL CONSIDERATIONS	SGLT2i†	GLP1RA†	DPPIVi	TZD	SU	Insulin
Risk of hypoglycaemia	Rare	Rare	Rare	Rare	Yes	Yes
Mean ↓ in HbA1c (mmol/mol)	6 - 13	15	5 - 10	15	15	Any
Independent cardiorenal benefits	Yes	Yes	No	Yes	No	No
Effect on weight	↓	↓↓	↔	↑	↑	↑
Funded	SA only†	SA only†	Yes	Yes	Yes	Yes

Escalate therapy + repeat HbA1c every 3 months until target reached

- May require multiple agents including insulin therapy
- Ensure adherence to lifestyle management + medications
- Re-refer for dietitian input if appropriate
- Repeat HbA1c 6 monthly once target reached
- Assess CVD and renal risk at least annually
- Continue standard care to reduce CVD risk
  e.g. statins, antihypertensives (esp. ACEi in diabetic renal disease) etc.

BEST PRACTICE WHEN TO USE DULAGLUTIDE

- Lifestyle management + metformin remain 1st line management for all with T2D
  - Lifestyle changes required to maximise weight loss with dulaglutide

- Clinical indications are the same as for empagliflozin:
  - 2nd line management in all with T2D + renal disease OR CVD OR 5 year CV risk > 15% OR **regardless of HbA1c**
  - 2nd line management if overweight or obese with **HbA1c above target** on metformin
  - 3rd line management if normal weight with **HbA1c above target** on metformin + vildagliptin

- **NB: MISMATCH with special authority criteria + need to choose between dulaglutide + empagliflozin**

- **Dulaglutide will be a better option than empagliflozin for many patients**
  - Dual dulaglutide/empagliflozin therapy likely preferable to other treatment in above scenarios if HbA1c remains above target

SPECIAL AUTHORITY CRITERIA FOR DULAGLUTIDE

- T2D with an HbA1c > 53 mmol/mol for ≥ 3 months on at least one glucose lowering therapy with:
  - Māori or Pacific ethnicity OR
  - Diabetic renal disease (UACR > 3 mg/mmol and/or eGFR < 60 mL/min) OR
  - Known cardiovascular disease OR
  - Cardiovascular risk > 15% on standardised CV risk calculator OR
  - Onset of T2D at a young age

- **NB: But only empagliflozin OR dulaglutide will be funded**
  - Purely financial situation + not evidence based
  - **Should discuss self-funding when clinically appropriate – dulaglutide is listed for $115 excl. GST**

WHEN SHOULD PATIENTS SELF-FUND EMPAGLIFLOZIN OR DULAGLUTIDE?

- History of diabetic renal disease, CVD or high CV risk who do not meet SA criteria (e.g. HbA1c < 53 mmol/mol)
- For dual empagliflozin/dulaglutide therapy if HbA1c above target + CVD
  - No evidence to date that dual therapy has additional benefits on renal disease
- In non-Māori/non-Pacific who are overweight or obese with HbA1c above target on metformin
- In non-Māori/non-Pacific who are normal weight + HbA1c above target on metformin + vildagliptin

DO I CHOOSE DULAGLUTIDE OR EMPAGLIFLOZIN?

- No head to head studies comparing GLP1RA versus SGLT2i
- Dulaglutide will likely lead to greater decrease in HbA1c + weight & potential role in primary prevention of CVD
- Co-morbidities + patient preference likely most important factors
  - **May need to emphasise that dulaglutide is not insulin**

FACTORS FAVOURING DULAGLUTIDE	FACTORS FAVOURING EMPAGLIFLOZIN
eGFR 15 – 29 mL/min	Heart failure
Cerebrovascular disease	Renal disease
Keto diet/high alcohol/recurrent GU infections	GI disease/medullary thyroid cancer/MEN2
Cannot tolerate empagliflozin	Cannot tolerate dulaglutide
Does not like taking or forgets tablets	Strongly dislikes injections

IMPORTANT CLINICAL POINTS

- Warn of adverse effects + reassure transient
- Instruct patient how to inject dulaglutide
- Stop vildagliptin but continue lifestyle management, metformin + other glucose lowering therapies
  - Reduce insulin and/or sulfonylureas if concerns over hypoglycaemia
- Organise follow up in 3 months or earlier if potential adverse effects
  - Phone follow up in 1-2 weeks in high risk patients reasonable
- Escalate therapy if HbA1c remains above target in 3 months

USEFUL RESOURCES

- **NZSSD guidance** – www.t2dm.nzssd.org.nz
- **He Ako Hiringa information + algorithms** – www.akohiringa.co.nz
- **Health Navigator patient information –** www.healthnavigator.org.nz/medicines/d/dulaglutide

NZSSD GUIDANCE ON T2D

MINISTRY OF HEALTH MANATŪ HAUORA | New Zealand Society NZSSD for the Study of Diabetes

Search

Type 2 Diabetes Management Guidelines

GLP-1 receptor agonists (GLP1RA)

- Is a preferred 2nd line agent in cardiovascular and renal disease as reduces mortality from cardiovascular events and renal disease progression independent of effects on glycaemic control; and leads to the most weight loss of all of the glucose lowering agents available, blood pressure reduction and will not cause hypoglycaemia in or of itself. Therefore, **GLP1 receptor agonists (GLP1RA) should be strongly considered in all patients with diabetic renal disease** (urinary albumin:creatinine ratio > 3 mg/mmol and/or reduced eGFR) **OR known cardiovascular disease OR 5 year CVD risk > 15% regardless of their glycaemic control or other glucose lowering therapies**. In these patients, **GLP1RA are likely preferable to SGLT2i if cerebrovascular disease predominates, but both classes can be used together with likely additional benefits**
- Further evidence is awaited to confirm the role of dulaglutide in primary prevention, as it may prevent cardiovascular events in those with multiple risk factors. Regardless, **in patients with no renal and cardiovascular disease, GLP1RA are a useful 2nd line agent if required for glycaemic control particularly if weight loss is desirable.** Can consider introducing after vildagliptin since vildagliptin in combination with metformin is the only currently known 2nd line agent to delay the need for insulin therapy in type 2 diabetes. But unlike GLP1RA, vildagliptin does not typically lead to weight loss and is a less potent glucose lowering therapy. In these patients, **GLP1RA will likely lead to greater improvements in glycaemic control and weight loss than SGLT2i, but both classes can be used together with likely additional benefits**
- Increase glucose-induced insulin secretion and decrease gastric emptying, appetite and glucagon secretion by activating the GLP-1 receptor (GLP1R)
- Useful alternative to starting basal insulin
- All available GLP1RA in New Zealand are subcutaneous injections (very similar to insulin pens)
- Dulaglutide is the only funded GLP1RA in NZ under special authority criteria ⊞ (likely available 2021)
  - NB: Only the 1.5 mg per week dose of dulaglutide will be available in New Zealand initially
- When starting GLP1RA:
  - Provide ongoing support and education for lifestyle management

HE AKO HIRINGA RESOURCES

HAH Bulletin

ISSUE #6 AUGUST 2021

Considering the new T2D agents

The two new second-line type 2 diabetes medicines are funded under Special Authority for patients with diabetic kidney disease, known cardiovascular disease or a five ≥15 per cent.[1] Criteria also cover early onset T2D and Māori or Pacific people

But is empagliflozin or dulaglutide better suited to your patient?

Starting injectable medicine: How to prepare your T2D patients

7 minutes to Read

Dulaglutide, a once-weekly injectal second-line treatment of type 2 dia will require an injectable therapy at acceptability early in the patient jou

For type 2 diabetes patients using a sulfonylurea or insulin

Your type 2 diabetes patient has HbA1c >53mmol/mol despite the use of at least one blood glucose-lowering agent for at least three months?

No → Patient not eligibl empagliflozin. It indicated, consider

Yes

Established CVD[F] *or* CKD[G] *or* five-year cardiovascular risk >15% *or* Māori or Pacific *or* diagnosed when a child or young adult?

No → Patient not eligibl empagliflozin. (commencing vilo unfunded empagliflo the cost-benefi with regard to area (eg, weight loss, blo

Yes

Supporting patients to take the new diabete meds: What you need to know

11 minutes to Read

Diabetes clinical nurse specialist Lisa Sparks discusses the place of empagliflozin and dulaglutide in treatment of type 2 diabetes, with emp potential side effects, sick-day management and improving patient adh

Empagliflozin and dulaglutide: Your questions answered

45 minutes to Delve

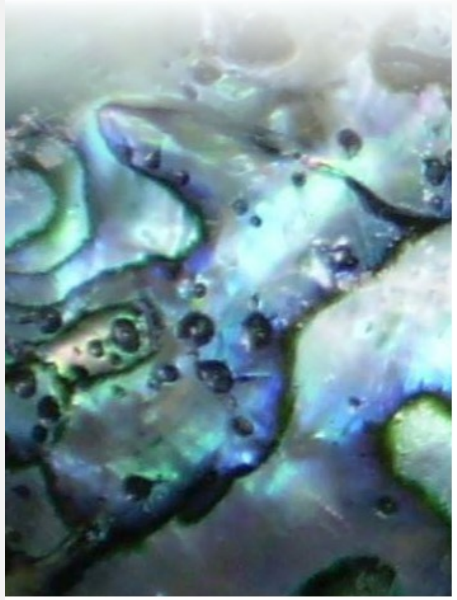
This list of Q&A reflects issues discussed in webinars held early in 2021.

The content has been edited, and reviewed by Waikato DHB endocrinologist/diabetologist Dr Ryan Paul.

Contributor Dr Ryan Paul
23 April 2021

Diabetes

HEALTH NAVIGATOR PAGE



Health A-Z | MEDICINES | Healthy living | Services and support | Clinicians | Apps | Videos | Tools

Medicines / D / Dulaglutide

Dulaglutide

A A A PRINT

Overview

Dulaglutide is used to treat type 2 diabetes. Find out how to take it safely and possible side effects. Dulaglutide is also called Trulicity.

What is dulaglutide?

Dulaglutide is used to treat type 2 diabetes and to protect you from having a heart attack or stroke. Dulaglutide also probably protects your kidneys and may help you to live longer. Read more about type 2 diabetes.

Dulaglutide lowers your blood glucose in several ways, including by helping your pancreas produce more insulin after meals, slowing down how fast food is absorbed and reducing your appetite. This is one reason people on dulaglutide usually lose weight.

Dulaglutide can be used alone or with other diabetes medicines (such as metformin or insulin), along with healthy eating and regular exercise. Dulaglutide is available as an injection that is given under your skin. It comes as a ready-to-use injection pen that contains one dose (1.5 mg).

Is dulaglutide the same as insulin?

Although dulaglutide is an injection, it is NOT insulin.

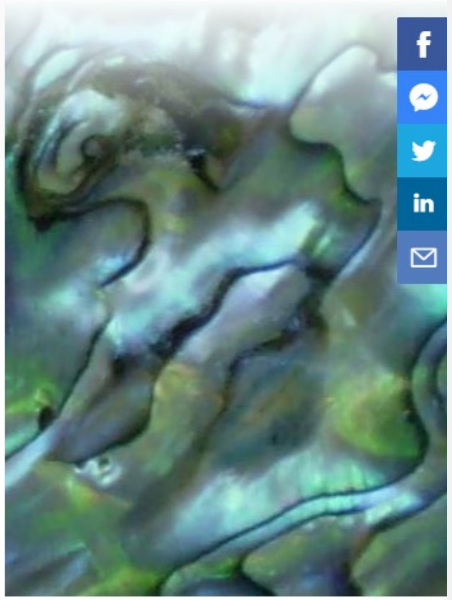
Resources

The Māori Pharmacists' Association Ngā Kaitiaki o Te Puna Rongoā has a free phone line to answer questions whānau have about their medicines. Call **0800 664 688**.
Note: This is a non-urgent service and they will get back to you within 24 hours.
For urgent health advice freephone Healthline 0800 611 116.

Related topics

Medicines for type 2 diabetes

Type 2 diabetes | Mate huka



CASE – MRS W

- 59 year old Māori woman with T2D + a history of:
  - Hypertension
  - Dyslipidaemia
  - Peripheral vascular disease
  - Central obesity (BMI 30.1 kg/m^2)
  - UACR 3.8 mg/mmol with eGFR > 90 mL/min

- HbA1c 63 mmol/mol on current medication regimen:
  - Metformin 1000mg/Vildagliptin 50 mg twice daily
  - Lantus insulin 30 units nocte
  - Atorvastatin 40 mg nocte
  - Perindopril 4 mg daily

- She makes an appointment after seeing the ad on Māori TV about whether she should be on the new diabetes medications. She is very motivated as her whānau all died in their 60's from MIs.

- Should she be on dulaglutide or empagliflozin? Which one is better for her?

CASE – MRS W CONT….

- You discuss that she should be on either dulaglutide or empagliflozin given her peripheral vascular disease + obesity
- She is anxious about injections as her brother died 2 days after starting insulin
- She opts for dulaglutide given the greater potential for weight loss, getting off insulin + preventing a MI
- You switch her Galvumet to metformin alone, reduce her Lantus to 24 units nocte + start dulaglutide 1.5 mg weekly
- You show her the correct injection technique and warn her of the likelihood of nausea and tips to avoid it

CASE – MRS W CONT….

- You organise a phone appointment with your nurses in 1 week + ask Mrs W to check her fasting BGLs daily
- Her fasting BGLs are now 3.8 – 5 mmol/L so you halve her Lantus to 12 units nocte + ask to keep in touch
- Her repeat HbA1c in 3 months is 45 mmol/mol so you stop her insulin + repeat her HbA1c in 3 months
- Her HbA1c is now 50 mmol/mol off insulin so organise further follow up in 6 months
- 18 months later her HbA1c is 58 mmol/mol. Which is the best agent to add in now?
  - A) Vildagliptin
  - B) Pioglitazone
  - C) Glipizide
  - D) Empagliflozin
  - E) Lantus

QUESTION 1

Which one of the following patient groups will not benefit from dulaglutide at present?

- A) HbA1c 46 mmol/mol with BMI 24 kg/m^2 on metformin alone + history of IHD
- B) HbA1c 78 mmol/mol with BMI 29 kg/m^2 on metformin + gliclazide
- C) HbA1c 56 mmol/mol with BMI 30 kg/m^2 on metformin alone
- D) HbA1c 92 mmol/mol with BMI 23 kg/m^2 metformin, vildagliptin, gliclazide + glargine (Lantus)
- E) HbA1c 48 mmol/mol with BMI 32 kg/m^2 on metformin alone

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- **E) HbA1c 48 mmol/mol with BMI 32 kg/m^2 on metformin alone**

QUESTION 2

Which one of the following factors will not favour dulaglutide over empagliflozin?

- A) Keto diet
- B) Heart failure
- C) Central obesity
- D) Primary prevention of CVD
- E) Cerebrovascular disease

QUESTION 2

Which one of the following factors will not favour dulaglutide over empagliflozin?

- A) Keto diet
- **B) Heart failure**
- C) Central obesity
- D) Primary prevention of CVD
- E) Cerebrovascular disease

DISCUSSION