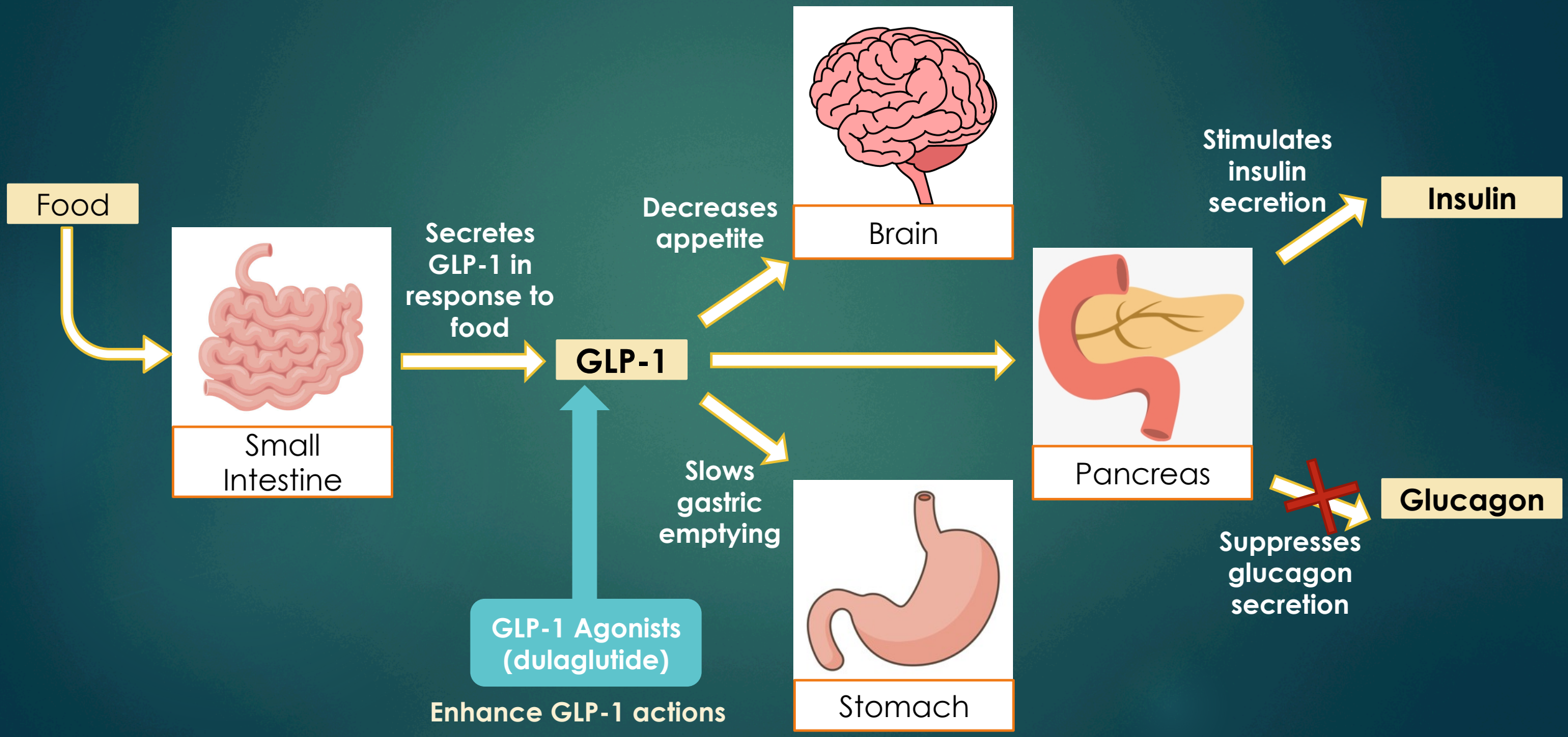
Dulaglutide (Trulicity)

NEW ZEALAND'S FIRST FUNDED

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AGONIST

GLP-1 Agonists – **how do they work?**



GLP-1 Agonists – **Efficacy**

Treatment	Glucose Lowering Efficacy
Lifestyle ➢ Diet ➢ Physical activity ➢ Weight loss	 Intermediate Intermediate Intermediate
Alpha-Glucosidase Inhibitors (acarbose)	Low - Intermediate
SGLT2-Inhibitors (empagliflozin)	Intermediate – High (dependant on eGFR)
DPP4-Inhibitors (vildagliptin)	Intermediate
Biguanides (metformin)	High
Sulphonylureas (gliclazide, glipizide)	High
TZDs (pioglitazone)	High
GLP-1 Agonists (dulaglutide)	**High**
Insulin	Very High

AWARD trials summary:

Table **Pivotal efficacy trials of dulaglutide in type 2 diabetes**

Trial (comparator)	Total number of patients (number treated with dulaglutide 1.5 mg weekly)	Total duration	Time of primary endpoint assessment	Reduction in HbA1c from baseline in mmol/mol (%) at primary end point		Proportion of patients achieving an HbA1c below 53 mmol/mol (7%) at primary end point
AWARD-1[4] (exenatide)	976 (279)	52 weeks	26 weeks	Dulaglutide	16.5 (1.51%)	78%
				Exenatide	10.8 (0.99%)	52%
AWARD-2[5] (insulin glargine)	810 (273)	78 weeks	52 weeks	Dulaglutide	11.8 (1.08%)	53.2%
				Insulin glargine	6.9 (0.63%)	30.9%
AWARD-3[2] (metformin)	807 (269)	52 weeks	26 weeks	Dulaglutide	8.5 (0.78%)	62%
				Metformin	6.1 (0.56%)	54%
AWARD-4[6] (insulin glargine)	884 (295)	52 weeks	26 weeks	Dulaglutide	17.9 (1.64%)	68%
				Insulin glargine	15.4 (1.41%)	57%
AWARD-5[3] (sitagliptin)	1098 (304)	104 weeks	52 weeks	Dulaglutide	12.0 (1.1%)	58%
				Sitagliptin	4.3 (0.39%)	33%

REWIND trial

- Investigated the effect of dulaglutide on Major Adverse Cardiovascular Events (MACE)
- Double-blind, RCT, multi-centred, placebo-control group
- >50yr T2DM with previous CV event or high CV risk
- Primary outcome = 1st occurrence non-fatal MI / stroke, death
- Duration =5.4 yrs (mean), followed-up every 6 months

	Primacy composite outcome	All Cause Mortality	Gastrointestinal Adverse effects
Dulaglutide 1.5mg weekly	**12.0%**	10.8%	47.4%
Placebo	**13.4%**	12.0%	34.1%
	p = 0.026	p = 0.067	p < 0.0001

- Reduction in non-fatal stroke (2.73% vs 3.5%, p=0.017)

Dulaglutide –**Benefits**

- Further reduction in HbA1c when added to metformin by ~7-15 mmol/mol
- Low rates of hypoglycaemia (monotherapy, combined with metformin)
- Positive CV benefits

  - mild systolic BP reduction (~2.8 mmHg)
- Reduced adverse CV outcomes (especially stroke)
- Weight loss ~1.3 – 3 kg

Dulaglutide – **Adverse effects**

Common:

- Nausea (most common), vomiting, decreased appetite, diarrhoea (usually transient and improve with continue treatment)
- Injection site reactions

Other:

- GI pain, burping, dyspepsia
- Hypoglycaemia (particularly with sulphonylureas / insulin)
- Increases heart rate & slightly reduces BP

Rare:

- Pancreatitis

Dulaglutide - **Contra-indications**

- Personal or family history of medullary thyroid carcinoma

- Dulaglutide is not recommended for people:
- Aged < 18 years
- Who are pregnant or breastfeeding
- With severe gastrointestinal disease, including gastroparesis
- With previous pancreatitis

Dulaglutide – **Effect on other Drugs**

- DPP-4 Inhibitors (vildagliptin) – see next slides
- Prokinetic agents (metoclopramide, domperidone, erythromycin)
  - → Stimulate gastric emptying
  - → GLP-1 agonists delay gastric emptying
  - → = theoretical opposing action
- No expected renal elimination or cytochrome P450 enzyme interactions
- May worsen existing diabetic gastroparesis

Not approved / recommended

GLP-1 agonist plus DPP-4 inhibitor combination

- Unlike endogenous incretin, GLP-1 agonists are designed to resist the activity of DPP-4 enzyme
- In one study, combination only had a 0.3% reduction in HbA1c
- Contributes to unnecessary polypharmacy
- Increased patient / supply costs
- Similar adverse effects profile → unclear if risk of additive effects
- Stop DDP-4i if starting GLP-1 agonist

Dulaglutide - **Administration**

Dose: 1.5mg

Frequency: ONCE weekly on same day each week

Route: subcutaneous injection (abdomen, thigh, upper arm)

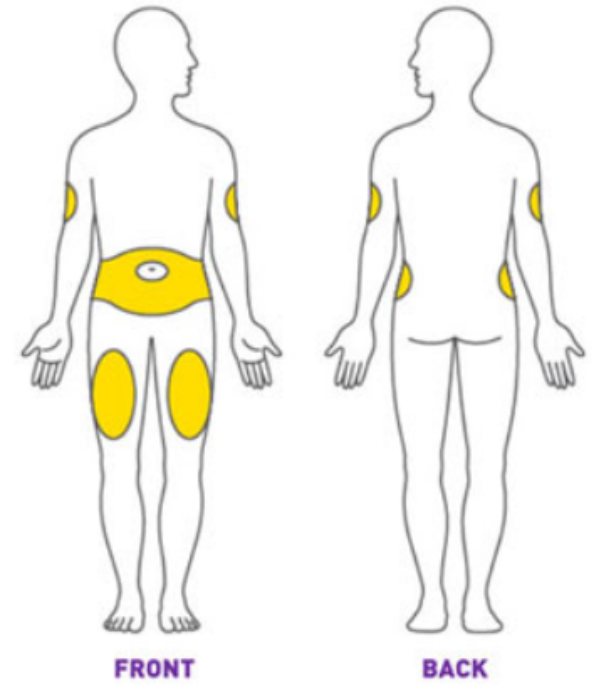
Missed dose: as soon as possible if ≥ 3 days before next scheduled dose

Peak plasma concentrations reached in 48 hrs

Half life: 4.7 days Steady state: 2-4 weeks

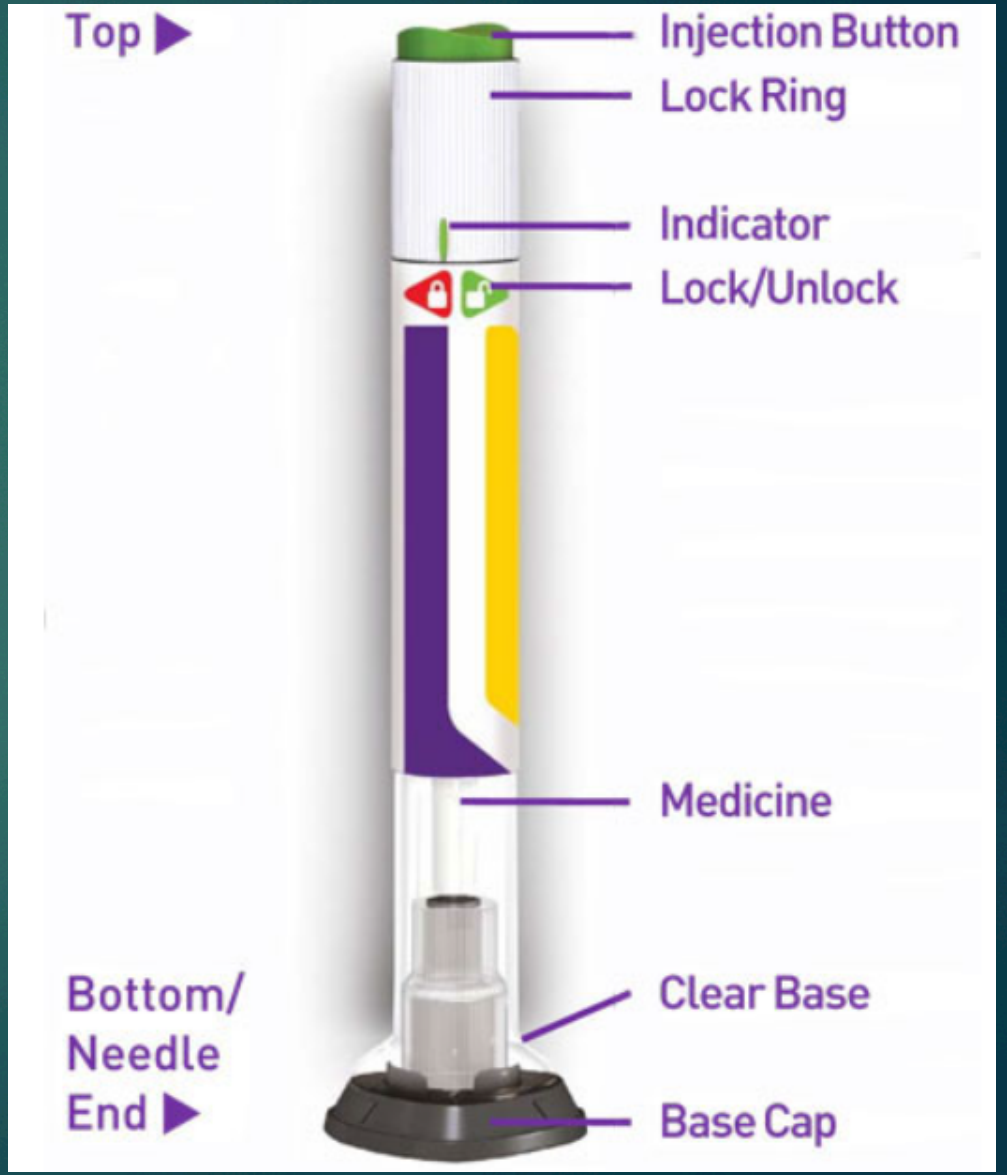
Storage: 2 - 8 °C Protect from light

30 °C for up to 14 days

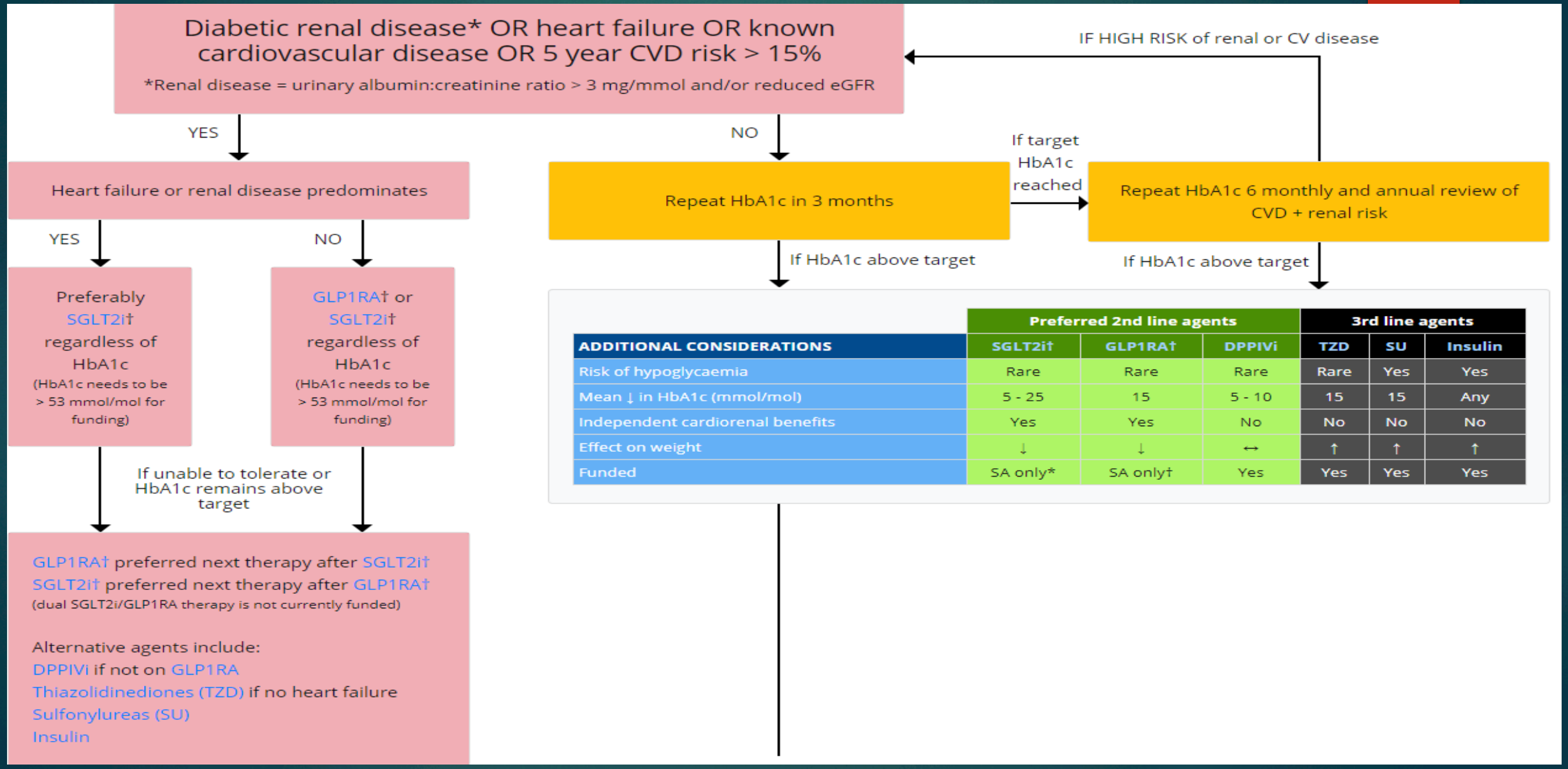


Dulaglutide – **Injection Technique**

1) Uncap pen
2) Place on site and unlock
3) Press and hold (5-10 sec)
4) Remove pen
5) Dispose of used pen safely



NZSSD Guidance



	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)	5 - 25	15	5 - 10	15	15	Any
Independent cardiorenal benefits	Yes	Yes	No	No	No	No
Effect on weight	↓	↓	↔	↑	↑	↑
Funded	SA only*	SA only†	Yes	Yes	Yes	Yes

Dulaglutide - **Funding from ????**

Fully funded subject to the following Special authority criteria:

- T2DM **AND** HbA1c > 53 despite 3 months of at least one glucose lowering medicine
- **AND** any of:
  - Māori or Pacific ethnicity **OR**
  - Pre-existing cardiovascular disease or 5-year cardiovascular risk > 15% **OR**
  - Microalbuminuria (ACR ≥ 3 mg/mmol in at least 2 out of 3 samples over 3 to 6 months), and / or eGFR < 60 ml/min/1.73m^2 **OR**
  - High lifetime cardiovascular risk due to diabetes diagnosis during childhood or as young adult
- Treatment will not be funded for both a SGLT-2i **and** a GLP-1 agonist in combination

Prescribing considerations

- Stop vildagliptin before initiating GLP-1 agonist
- If HbA1c < 75 mmol/mol (based on BGL), and especially if < 64 mmol/mol:
  - reduce total daily dose of insulin by 15-20%,
  - reduce sulfonylurea dose by 50%
- HbA1c check every 3 months while above target, then every 6 months
- No dose adjustment is needed based on age, gender, race, ethnicity, body weight, or renal or hepatic impairment.

Patient advice and safety information

- Sick day management:

Delay / stop administration if risk of dehydration (diarrhoea/vomiting)

May resume once recovered and eating/drinking normally again.

- Minimise nausea by:

Eating slowly while undistracted and to pay careful attention to the amount eaten

Avoid fried / fatty foods

Nausea peaks during first 2 weeks of treatment then rapidly reduces

Summary

Medicine	Efficacy for lowering HbA_{1c}	Cardiovascular effects		Renal effects: progression of DKD	Effects on weight	Risk of hypoglycaemia	Risk of DKA
		CVD	HF				
Metformin	High	Potential benefit	Neutral	Neutral	Neutral with potential for modest loss	Low	Low
Empagliflozin	Intermediate	Benefit	Benefit	Benefit	Loss	Low	High
Dulaglutide	High	Benefit	Neutral	Benefit	Loss	Low	Low
Vildagliptin	Intermediate	Neutral	Neutral	Neutral	Neutral	Low	Low
Sulfonylureas	High	Neutral	Neutral	Neutral	Gain	High	Low
Pioglitazone	High	Potential benefit	Increased risk	Neutral	Gain	Low	Low

GLP-1 or SGLT-2?

Table 1. Estimated absolute differences in outcomes with SGLT-2 inhibitors and GLP-1 receptor agonists compared with placebo per 1,000 people with type 2 diabetes with moderate and very high cardiovascular risk, treated for five years. Adapted from Palmer et al. (2021).[6]

	CVD risk category*	All-cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure
SGLT-2 inhibitor	Moderate	25 fewer (32 fewer – 18 fewer)	12 fewer (18 fewer – 6 fewer)	13 fewer (21 fewer – 3 fewer)	1 more (11 fewer – 13 more)	6 fewer (9 fewer – 2 fewer)	23 fewer (28 fewer – 17 fewer)
	Very high	48 fewer (61 fewer – 35 fewer)	24 fewer (36 fewer – 12 fewer)	21 fewer (34 fewer – 5 fewer)	2 more (17 fewer – 21 more)	38 fewer (58 fewer – 14 fewer)	58 fewer (73 fewer – 44 fewer)
GLP-1 receptor agonist	Moderate	13 fewer (18 fewer – 6 fewer)	9 fewer (15 fewer – 1 fewer)	8 fewer (15 fewer – 1 fewer)	16 fewer (24 fewer – 7 fewer)	4 fewer (7 fewer – 2 fewer)	4 fewer (11 fewer – 2 more)
	Very high	24 fewer (35 fewer – 12 fewer)	18 fewer (30 fewer – 6 fewer)	13 fewer (24 fewer – 2 fewer)	25 fewer (39 fewer – 11 fewer)	29 fewer (44 fewer – 10 fewer)	11 fewer (28 fewer – 5 fewer)

* Moderate risk defined as people with CVD; very high risk defined as people with both CVD and chronic kidney disease

Case 1

- 55 year old male NZ European
- Type 2 diabetes for 5 years
- 1.74m 122kg BMI 40.3
- HbA1c 62 mmol/mol
- eGFR 70 mL/min/1.73m2, ACR normal
- No CV disease, CVRA 7%

- Metformin 1g twice daily
- Gliclazide 80mg twice daily

Case 2

- 65 year old male NZ European
- Type 2 diabetes for 10 years
- 1.74m 122kg BMI 40.3
- HbA1c 62 mmol/mol
- eGFR 70 mL/min/1.73m2, ACR normal
- Angina

- Metformin 1g twice daily
- Gliclazide 80mg twice daily
- Lantus 30 units at night

Case 3

- 55 year old male NZ European
- Type 2 diabetes for 5 years
- 1.74m 122kg BMI 40.3
- HbA1c 62 mmol/mol
- eGFR 45 mL/min/1.73m2, ACR elevated
- No CV disease, CVRA 7%

- Metformin 1g twice daily
- Gliclazide 80mg twice daily

GLP-1a or SGLT-2i ?

- In most instances probably consider a SGLT2-I first (depending on patient parameters)
- GLP-1a will likely lead to greater improvements in glycaemic control and weight loss than SGLT2i and can be used in more severe renal impairment
- GLP-1a in patients without CVD, low CV risk, diagnosed at an early age, intolerant of SGLT-2i
- Consider GLP-1a as first injectable
- Add-on to SGLT-2i (above and below HbA1c of 53) for patients willing to self fund
- Both classes can be used together with likely additional benefits
- (not funded in combination. Use funded GLP-1a and patient-funded SGLT-2i at $80-$120 per month)

Jardiance and Jardiamet Uptake

- As of 11 July 2021 there have been 27,965 Special Authority number applications approved
- approx. 220,000 T2D in NZ -> prescribed to 12.5% of patients
- FHC = 954 T2D, 140 current SGLT2 patients = 14.5%

SPECIAL AUTHORITY CRITERIA	% OF APPLICATIONS PER CRITERIA
Māori or Pacific ethnicity	46.99%
Pre-existing cardiovascular disease	23.10%
5-year cardiovascular disease risk	29.05%
High lifetime cardiovascular risk (childhood or young adult)	9.05%
Diabetic kidney disease	17.86%

References

i. bpac^{NZ} New diabetes medicines funded: empagliflozin and dulaglutide. March 2021

ii. Lajthia E, Bucheit JD, Nadpara PA, et al. Combination therapy with once-weekly glucagon like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a case series. *Pharm Pract (Granada)*. 2019;17(4):1588.

iii. Gilbert MP, Pratley RE. GLP-1 Analogs and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials. *Front Endocrinol (Lausanne)*. 2020;11:178.

iv. Dulaglutide. Aust Prescr Oct 2018;Vol41:166-8.

v. Asha MZ, Khalil SFH. Pharmacological Approaches to Diabetic Gastroparesis: A systematic review of randomised clinical trials. *Sultan Qaboos Univ Med J*. 2019;19(4):e291-e304.