This resource has been supported with a grant from Lilly

For Healthcare Professionals:

GLP-1/GIP INJECTABLE THERAPIES: HOW TO OPTIMISE THE BENEFIT OF THESE MEDICATIONS FOR PEOPLE WITH TYPE 2 DIABETES

November 2025

CONTENTS

ABOUT THIS GUIDANCE

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Support

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RATIONAL AND REMIT

It is now over one hundred years since the insulin was developed and introduced for use in the human population. Whilst this has been one of the greatest medical breakthroughs in history (saving millions of lives around the world), it also highlighted the need for medicine and science to work collaboratively and has been a launchpad for many of the interventions and therapies we are able to access today.[1] The GLP-1/GIP therapies are one category of medications for people with type 2 diabetes that have been developed and grown in popularity over the last decade or so. The Glucagon-like peptide -1 receptor (GLP-1/GIP) therapies are a class of medication with significant proven benefits in improvement in glycaemic control, blood pressure, cholesterol, and weight and therefore have high affiliation with cardio/renal protection[2-4] and will be the focus throughout this document.

INTRODUCTION

Research suggests that diabetes is one of the most prevalent chronic diseases people are living with in the UK.[5] National statistics indicate that approximately 4.6 million people live with diabetes and a predict that a further 1.3 million people could be living with the condition who are yet to be diagnosed. Approximately 90% of these individuals will be living with type 2 diabetes.[6] With evidence indicating continued growth in prevalence[5], linked risks associated with metabolic disease processes and the significant impact both on quality of life and micro/macrovascular risk factors.[2-4,7,8] This is also reflected in recent research which continues to indicate an average reduction of 3.4% in all cause motility with each kilogram of weight loss and a 7.6% risk reduction in all-cause mortality rate with each 1% reduction made in Hba1c.[9] It is little wonder that the management of glucose levels and these risks has become a leading factor within national and international consensus guidance.[5,10,11]

Whilst there remains a clear emphasis within the guidance to support people with type 2 diabetes with diet and lifestyle moderations.[5,12] There is also a recognition that adjustment of pharmaceutical interventions may be required if HbA1c levels are not maintained on current therapies (target 48-53mmol/mol) or rise to 58 mmol/mol (7.5%) or higher).[5]

The guidance strongly suggests that adults with type 2 diabetes and established or high risk of cardiovascular or renal disease, should commence medications with demonstrated evidence of benefits to reduce risk. [5,12]

Additional considerations should include:

- The individuals' personal preferences
- Risks associated with complications
- Contraindications and interactions with current therapies
- Efficacy
- Licensing
- Monitoring requirements
- Cost

WHAT IS A GLP1/GIP THERAPY?

GLP-1 agonists are a class of medications that mimic the effects of the naturally occurring hormone glucagon-like peptide-1 (GLP-1) in the body.[4]

GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are both incretin hormones that activate / stimulate insulin secretion after an oral glucose load (a meal) via the incretin effect. These incretin hormones are inactivated by the presence of dipeptidyl peptidase-4 (DPP-4) (another gut hormone). Higher levels of DPP-4 are highly affiliated with type 2 diabetes[13] leading to blunted or absent impact of the GLP-1 &/or GIP incretin responses and impact on glycaemic control.[3]

Structurally, these agents fall into 2 broad categories:

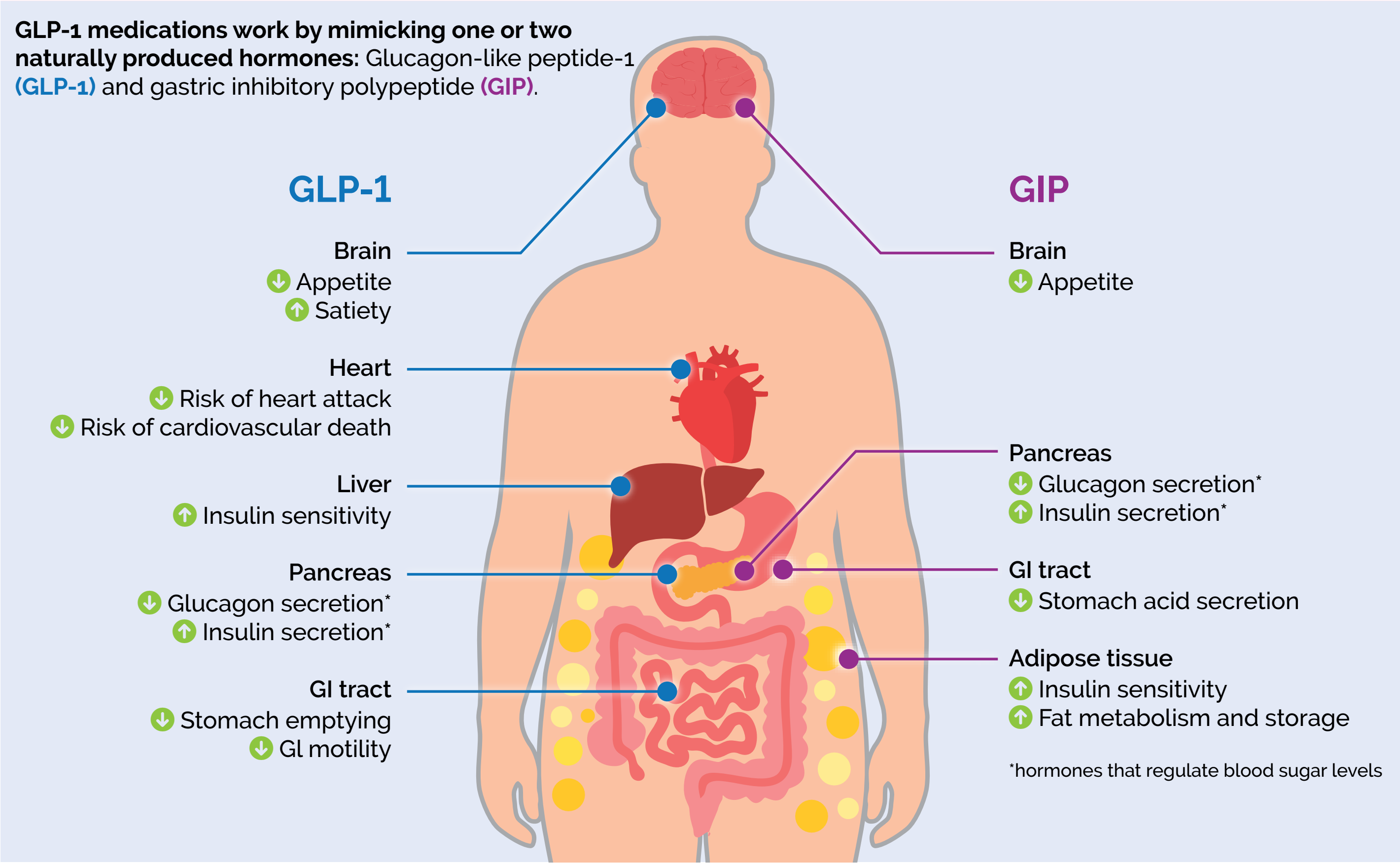
Table 1: GLP-1 Agents on UK formulary.[3,14]

Human GLP-1 agents (artificially adapted peptide chains):	Exendin-4 agents (Exendin-4 is found in the venom of the Gila monster):
• Dulaglutide • Liraglutide • Semaglutide	• Exenatide (2 formulations) • Tirzepatide is a GIP analogue that activates both the GLP-1 and GIP receptors.

HOW DO THEY WORK?

By mimicking endogenous (naturally occurring) GLP-1, these agents stimulate insulin secretion, suppresses glucagon secretion, and slows down gastric emptying. They are also affiliated with weight loss which is linked to their impact on promoting satiety and reducing appetite.[3,4]

Table 2: How do they work?



IMPORTANCE OF DIET AND LIFESTYLE CONSIDERATIONS AND IMPLICATIONS ON NUTRITIONAL BALANCE

Research demonstrates that the use of GLP-1 receptor agonists (GLP-1 RAs) can lead to significant weight loss.[2,3] However, there has been emerging controversy regarding the association in loss of muscle mass (sarcopenia) and potential for malnutrition due to reductions in oral intake, particularly in vulnerable populations.[15,16] Therefore suggesting, that support in the navigation of altered dietary preferences and intake, management of gastrointestinal side effects, preventing nutrient deficiencies, preserving muscle and bone mass through resistance training, adjusted diet and complementary lifestyle interventions is essential and should play a key role in our consultations.[17]

Some supportive strategies to consider:

- Nutritional assessment / screening
- Referral to registered dietitian nutritionist counselling
- Remote consultations
- Include group-based visits for education and support,
- Use of digital platforms / apps for support with food choices [17]

COMPARISON DATA

As discussed above, the GLP-1 therapies are a class of medication with significant evidence correlating with improvements in glycaemic control, blood pressure, cholesterol, and weight with associated impact on cardio/renal protection.[2,3] However, it is important to understand the clinical trial data associated with the individual therapies as this plays a lead role in the development of guidance, local formulary development and most importantly may impact the choice of therapy the individual could choose or benefit from most (Please see comparison data in Table 3).

Table 3: Key results from Cardiovascular outcome trials.

Trial Name	Medication studied V Comparison	Trial population	Primary outcome	Results	Adverse events
LEADER[18]	Liraglutide 1.8mg once daily V Placebo	9340 T2DM with high CV risk (24.7% also had CKD stage 3 or higher)	3P-MACE	Showed superiority. MACE: ↓ CV death: ↓ Nephropathy: ↓ Non- significant ↓ in stroke & Non-fatal MI Average drop in: HbA1c: 0.40% Weight: 2.3kg B/P: 1.2 mmHg	GI effects ↑ (NS) ↑ gall stone disease, allergic reactions, neoplasms and pancreatic carcinoma
SUSTAIN 6[19]	Semaglutide (injectable) 0.5 or 1.0mg once weekly V Placebo	3297 T2DM Established CVD, HF or CKD (10.7% had CKD stage 3 or higher and a further 13.4% had CV and CKD)	3P-MACE	Showed superiority. MACE: ↓ Non-fatal MI: ↓ Stoke: ↓ Nephropathy: ↓ Non- significant ↓ CV deaths, all-cause mortality, HF or unstable angina Average drop in: HbA1c: 0.40% Weight: 2.9-4.3 kg (dose dependant) B/P: 2.2-2.8 mmHg (dose dependant)	Retinopathy ↑ GI effects ↑ (NS) ↑ gall stone disease, allergic reactions, neoplasms and pancreatic carcinoma
EXSCEL[20]	Exenatide extended release 2mg once weekly V Placebo	T2DM 14,752 with or without CVD (73% with CVD, individuals with ESRF were excluded)	3P-MACE	Showed non-inferiority. Non- significant ↓ MACE, CV death, Non-fatal MI, Stoke Average drop in: HbA1c: 0.53% Weight: 1.27kg B/P: 1.57 mmHg	Thyroid papillary carcinomas ↑ (NS) ↑ acute pancreatitis, pancreatic cancer, or medullary thyroid carcinoma.
REWIND[21]	Dulaglutide 1.5mg once weekly V Placebo	T2DM 9901 with CVD or CV RF (included CKD down to ESRF)	3P-MACE	Showed superiority. MACE: ↓ Stoke: ↓ Nephropathy: ↓ Non- significant ↓ CV deaths, Non-fatal MI Average drop in: HbA1c: 0.61% Weight: 1.46kg B/P: 1.70 mmHg	Retinopathy comps ↑ New or worsening nephropathy ↓ (NS) ↑ acute pancreatitis, pancreatic cancer

Trial Name	Medication studied V Comparison	Trial population	Primary outcome	Results	Adverse events
PIONEER 6[22]	Semaglutide (oral) 14mg once daily target dose V Placebo	T2DM 3183 with established CVD, CKD or both or >60yrs with CV RF Excluded: proliferative retinopathy or maculopathy.	3P-MACE	Showed non-inferiority. CV death: ↓ Nephropathy: ↓ (post-hoc analysis of PIONEER 6 and SUSTAIN 6) Non- significant ↓ MACE, Non-fatal MI and Stoke Average drop in: HbA1c: 1.0% Weight: 4.2kg B/P: 2.6 mmHg	GI effects ↑ (NS) ↑ hypoglycaemia (in those receiving concurrent insulin) ↑ Malignant neoplasms ↓ in retinopathy (note exclusions)
SURPASS[23]	Tirzepatide (5 mg, 10 mg or 15 mg) V Semaglutide 1mg	T2DM 1879 Prescribed Metformin, BMI ≥ 25 elevated Hba1c Excluded: CKD (eGFR <45), active eye disease	3P-MACE	Showed superiority. ↓ liver fat ↓ new-onset macroalbuminuria ↓ blood pressure ↓ lipids Average drop in: HbA1c: 2.01 -2.30 % (dose dependant) Weight: 1.9-5.5 kg (dose dependant) B/P: 4.4-6.5 mmHg (dose dependant)	GI effects ↑ (NS) ↑ hypoglycaemia ↑ acute pancreatitis, pancreatic cancer (in those with associated genetic risk factors)
SURPASS -CVOT[23,24]	Tirzepatide (up to 15mg) V Dulaglutide 1.5mg	T2DM 13299 people with CVD or CV RF Excluded: ESRF eGFR <15 mL/min/1.73m, active eye disease	3P-MACE	Showed non-inferiority. CV death: ↓ All-cause mortality: ↓ Nephropathy: ↓ Non- significant ↓ MACE and Stroke Average drop in: HbA1c: 1.73% Weight: 11.43kg B/P: improvement of 4.2-6.8 mmHg (pooled data):	GI effects ↑ (NS) ↑ gall stone disease

Please note: We recognise that some of the heterogeneity in outcome metrics reported may represent the study population selected, the length of study and targeted primary and secondary outcomes observed. However, on review of the data there appears to be stronger evidence regarding efficacy particularly relating to weight reduction and impact on other CV/ renal risk factors with the weekly preparations within this class of therapies. There is even greater efficacy associated with the dual therapy agonist (Tirzepatide) which combines both GLP-1 and GIP (another gut hormone).[25]

Some therapies have not been included in this document due to lack of efficacy and /or withdrawal from national formulary. (i.e. Albiglutide, Bydureon, Lixisenatide).

There may also be a small number of individuals who are prescribed combination therapies containing both GLP-1 and insulin products. GLP-1 receptor agonists and insulin have complementary mechanisms of action. Whilst the GLP-1 agonists stimulate insulin release in a glucose-dependent manner, while also suppressing glucagon secretion and slowing gastric emptying. The insulin components of these therapies replace the lack of endogenous insulin and aid reductions in elevated glucose levels. This can lead to improvements in both fasting and postprandial glucose levels[26] and associated cardiovascular risks associated with improvements in glycaemic variance (GV) when compared to mixed -insulin therapies.[27] However, these therapies are associated with difficulties especially during illness where general guidance would be to discontinue / hold GLP-1 therapies and increase insulin.

It is important to note: That this class of therapy is not currently licenced for the use in Type 1 diabetes. However, it is acknowledged that people living with type 1 diabetes may be prescribed these medications "off licence" due to clinical benefits under the direct care of a specialist team or be using these therapies under the direct supervision of bariatric services. These indications are not discussed further as they are beyond the scope of this document.

ELIGIBILITY CONSIDERATIONS: IN PRIMARY AND SECONDARY CARE SETTINGS

Caveat: The information contained in this document Is based on national and international guidance. You may notice that there are some differences within your local guidance. Please familiarise yourself with your local formularies and individual reference SmPC's.

NICE Guidance suggests healthcare professionals Consider triple therapy by switching one drug treatment to a GLP-1 RA/Joint GLP-1 RA and GIP agonist in adults (≥ 18years) with type 2 diabetes when:[5]

BMI ≥ 35kg/m^2 (adjust accordingly for ethnicity) and specific psychological or other comorbidities associated with obesity

OR

BMI < 35kg/m^2

OR

Where insulin would have significant occupational implications

OR

Weight loss would benefit other significant cardio/renal risk factors or obesity related co-morbidities (Table 4)

OR

HbA1c > 58mmol/mol (7.5%) or greater than individually agreed threshold for intensification

AND

When Triple therapy with metformin and two other oral anti-hyperglycaemic drugs is not effective, not tolerated or contraindicated

The guidance also suggests GLP-1/GIP therapy may also be prescribed by the specialist team (Consultant or GP with specialist interest or appropriately trained diabetes specialist practitioner or nurse) in any one of the following three scenarios below if target HBA1c is not achieved or maintained and / or there is a high risk of associated cardio/renal complications:[5]

1. In combination with two oral anti-hyperglycaemic drugs e.g., one oral antihyperglycemic medication maybe switched for a GLP-1 analogue (Please Note: sulfonylureas may be withdrawn where clinically necessary e.g., due to hypoglycaemia risk)
2. In combination with insulin
3. In weight loss / metabolic disease management.

WEIGHT LOSS MANAGEMENT

Caveat: We are aware that many areas have devised local prescribing guidance affiliated with their local service provisions. We are also aware that national guidelines and implementation are currently under review. Please familiarise yourself with your local guidance.

In the UK guidance[28] suggests people living with type 2 diabetes are referred to specialist weight management services for weight management assessment and support alongside other diet and lifestyle interventions if;[5,29]

They have a body mass index (BMI) greater than or equal to 40kg/m^2

OR

BMI 35-40kg/m^2 and living with qualifying comorbidities (Table 4).

OR

Those with a body mass index (BMI) greater than or equal to 35kg/m^2 and 1 weight related comorbidity (not restricted to qualifying co-morbidities) and one of the below criteria:

- Active malignancy and need for urgent weight loss for planned therapy e.g., radiotherapy or surgery
- Urgent weight loss needed for organ transplant
- Idiopathic intracranial hypertension (IIH), needing frequent lumbar punctures and/or visual compromise.
- Undergoing planned time-sensitive surgery for life-limiting conditions, where a high BMI is the main barrier to surgery.
- Under the care of NHS fertility service and weight loss is needed for assisted conception
- Obesity hypoventilation syndrome (OHS)

Table 4: Qualifying co-morbidities

Qualifying co-morbidities:
Cardiovascular disease
Hypertension
Dyslipidaemia
Obstructive sleep apnoea
Type 2 Diabetes

Please Note: A lower body mass index threshold should be used (usually reduced by 2.5 kg/m^2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean ethnic background.[28] You may also use the QRISK-3 score that automatically adjusts for ethnicity when correct sections are Completed.[30]

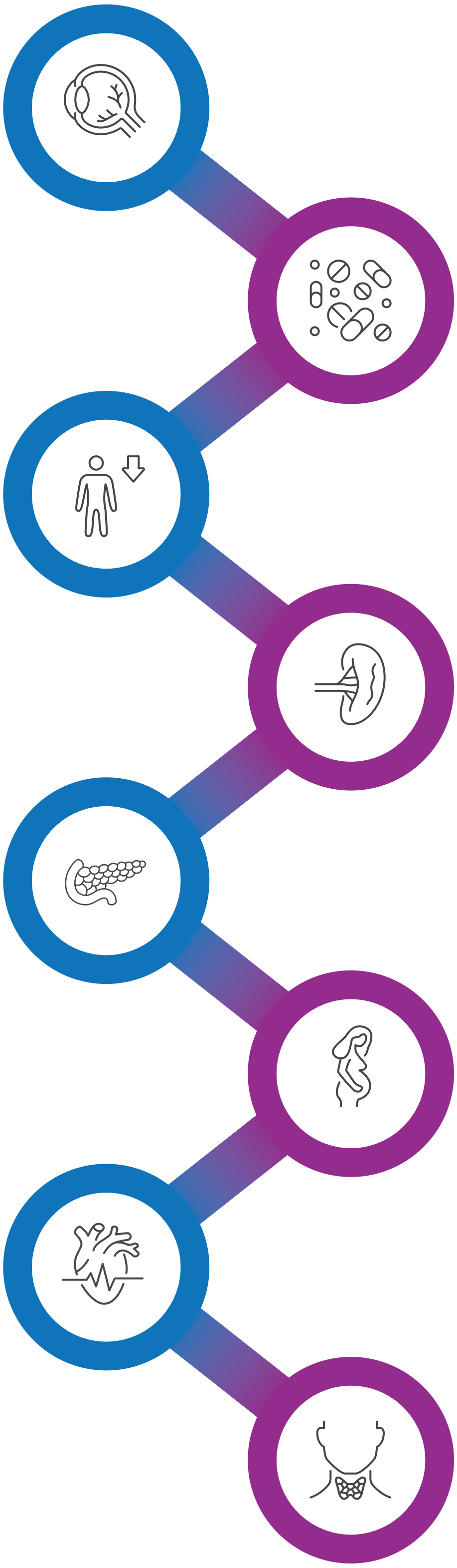
People who would <u>**not**</u> be considered eligible:

According to the guidance[28] and reference SmPC's for each medication in this class, the individual risk factors listed below would indicate non-eligibility for the GLP-1/GIP class of medications.

- Hypersensitivity to the active substance or to any of the excipients of GLP-1 analogues
- Acute pancreatitis (always check history)
- Severe gastrointestinal disease (included gastroparesis and irritable bowel syndrome)
- Treatment of diabetic ketoacidosis
- Use in pregnancy/those planning pregnancy
- Use in Type 1 Diabetes Mellitus
- Women who are breast feeding

CONSIDERATIONS PRIOR TO PRESCRIBING

This guidance[28] and additional research[31] also suggests that caution is needed when prescribing GLP-1/GIP therapies for people with the following risks:



Eye retinopathy: Particularly if they have pre-existing or previous diabetes related eye disease

Drug interactions: i.e., Caution with anti-hyperglycaemic agents that are associated with hypoglycaemia (Insulin/SU), individuals prescribed blood thinning agents may experience an increase in efficacy and should be advised regarding screening processes.

Eating disorders: Suspected or diagnosed, it is advisable to check with eating disorder team before initiation

Renal consideration: Particularly in end stage renal failure due to lack of clinical evidence[11,28]

Hepatic impairment: Linked to pancreatitis and gallstones

Women of childbearing potential: There is a lack of data on safety profile

People with severe heart failure: Lack of data with some agents

People with thyroid disease: particularly those with a history of medullary thyroid cancer or multiple endocrine neoplasia

SIDE EFFECTS AND SAFETY CONSIDERATIONS

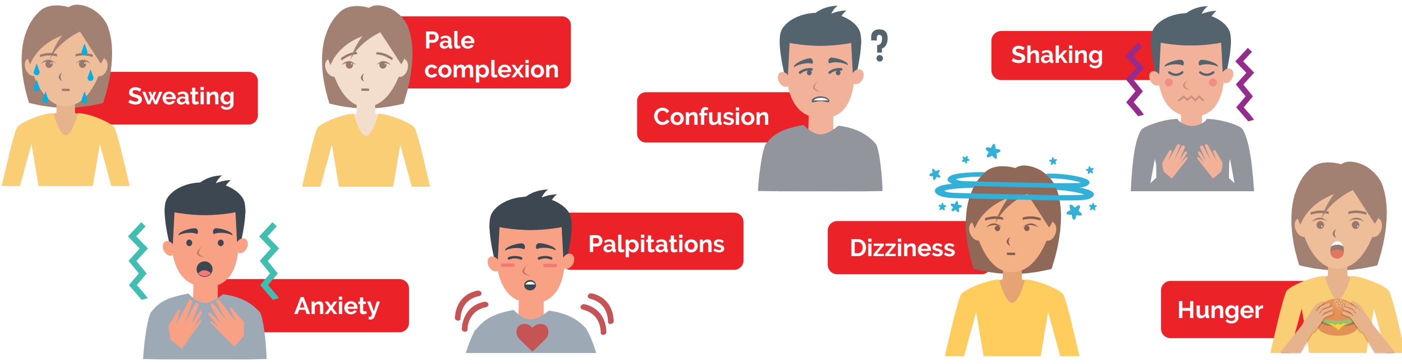
Since GLP-1/GIP therapies mimic the action of a peptide produced in the GI tract, the most reported side effects are gastrointestinal (GI) these include; nausea, vomiting, and diarrhoea.[31] However, the GI side effects experienced appear to be dose-dependent, hence the general consensus advice for slow titration of doses.[5,10,28] Individuals should therefore be educated that this drug slows gastric emptying, and associated feelings of early satiety. They should also be advised that nausea can occur if attempting to eat when already full. Other side effects associated with these therapies are listed below (Table 5)

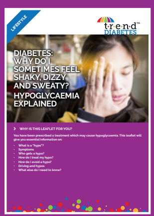
Table 5: Side effects / Risks[14]

Side effect / Risk	Implication
Acute pancreatitis (Rare)	Give direct advise to the person to seek urgent medical advice if symptoms such as severe upper abdominal pain, nausea, and/or vomiting develop. Advise to discontinue treatment if pancreatitis is suspected. ⚠ **THIS IS A MEDICAL EMERGENCY** **Please Note:** cholecystitis and cholelithiasis are also rare risks associated with this class of therapy
Gastrointestinal	Decreased appetite, altered taste, nausea, vomiting, dyspepsia, burping, gastro-oesophageal reflux, constipation, diarrhoea, gallbladder disorders, delayed gastric emptying **Please Note:** Intestinal obstruction has been associated with this therapy (although rare and exact figures are unknown)
Headache	Usual therapy advised, however if ongoing or persistent the individual is advised to seek medical advice
Dizziness	Monitoring of hydration status, B/P and renal status is recommended, particularly during illness or up titration of therapies.
Fatigue / drowsiness / lack of energy	May relate to altered oral intake. Seeking nutritional advice and support is recommended. If ongoing / persistent individuals should see their health care provider.
Alopecia	If symptoms occur, the individual should be advised to hold medications and see their health care provider.
Hyperhidrosis	If present and excessive even during rest periods. The individual should be advised to withhold the medication and seek medical attention.
Cardiac arrythmias	The individual should be advised to withhold the medication and seek urgent medical attention. **Please note:** If suspected heart attack / life threatening symptoms they should seek urgent medical attention / should call 999
Skin reactions	Including rash, angioedema, cutaneous amyloidosis, urticaria, and pruritus. The individual should be advised to withhold the medication and seek medical attention. **Please note:** If suspected anaphylaxis they should seek urgent medical attention / should call 999

Specific advice:

The guidance suggests that HCPs should Inform individuals when prescribing or increasing the dose of GLP-1/GIP therapies, about the common risk of gastrointestinal side effects which may affect more than 1 in 10 patients[5,14,28,31] and provide education regarding the appropriate management of these and the other risk factors mentioned above (Table 5). Additional advice needs to be provided on the potential of hypoglycaemia. This can occur in people living with Type 2 diabetes using concurrent medications with hypoglycaemia effect (i.e., Insulin / Sulfonylurea) and people using GLP-1/GIP therapies for weight management.[5,10,11,14,28] HCP's should ensure individuals are aware of the symptoms and signs of hypoglycaemia / how this should be managed and know to urgently seek medical advice should they occur.[32]





A leaflet about hypoglycaemia for people with diabetes called **Diabetes: Why do I sometimes feel shaky, dizzy and sweaty? Hypoglycaemia explained** is available on the Trend Diabetes website: https://trenddiabetes.online/portfolio/diabetes-why-do-i-sometimes-feel-shaky-dizzy-and-sweaty-hypoglygaemia-explained/

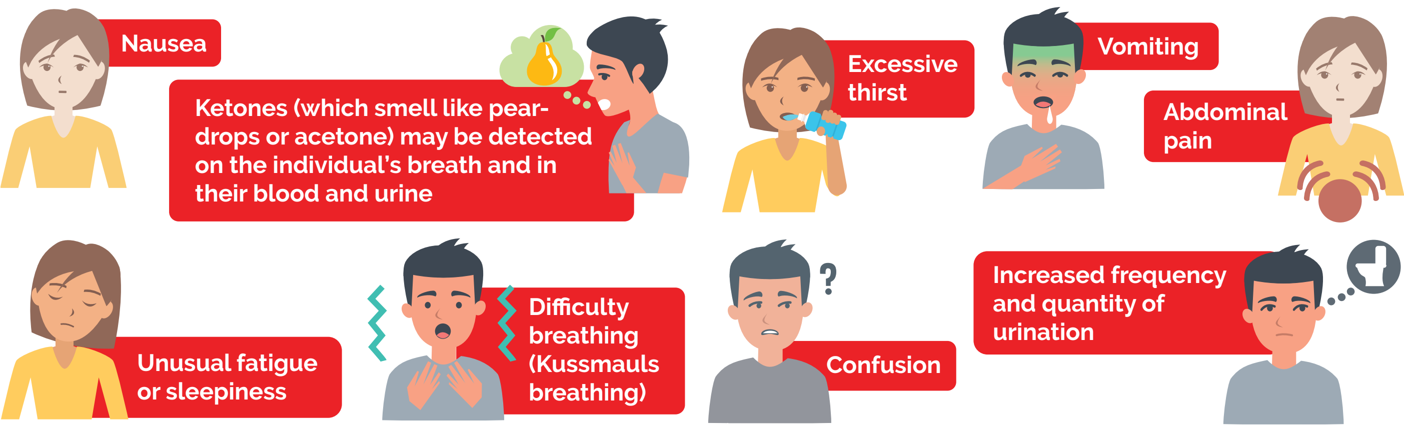
Risk of Diabetic Ketoacidosis (DKA)

Serious and life-threatening cases of diabetic ketoacidosis have been reported in relation to medications in this class, particularly after discontinuation or rapid reduction of concomitant insulin.[33] It is important to remember that these medications do not replace the individual's endogenous insulin production. Therefore, if insulin production / reserve is low (+/- any metabolic risk factors which will be particularly present in illness), this will increase the risk of insulin deficiency and speed up the process of ketosis.[3] When coupled with diabetes this ultimately increases the risk of DKA. Guidance[5,28,33] suggests that individuals should be supported to:

- Blood Glucose Monitor: Increasing monitoring when adjusting the dose of insulin, or initiating / altering GLP-1/GIP therapies.
- Titrate doses of GLP-1/GIP therapies slowly
- Understand and be able to identify risk factors for and signs and symptoms of diabetic ketoacidosis and appropriate management (Including emergency contact or management strategies)[34]
- Report suspected adverse drug reactions to health care providers ASAP in order for teams to submit Yellow Card information.

Guidance for healthcare professionals and carers working in primary care and the community called **Managing Diabetes During Intercurrent Illness** is available on the Trend Diabetes website: https://trenddiabetes.online/portfolio/managing-diabetes-during-intercurrent-illness/

Signs and symptoms of diabetic ketoacidosis: (DKA)



HOW TO ADMINISTER

Guidance suggests that HCPs should ensure that people living with diabetes receive detailed education and support when starting any new therapy.[5,10,12,28,35] They also suggest that monitoring and follow-up support are crucial in improving adherence, understanding and ultimately improving clinical outcomes and safety. It is suggested that HCP's revisit this during each contact. They also suggest that individuals should also be supplied supportive literature and tools to support their education and understanding of the therapies prescribed. These may include:

- Medication specific videos
- Online materials
- Medication specific SmPC's
- Patient information leaflets (from recognised Diabetes organisations)

A leaflet about GLP-1/GIP injectable therapies for people with diabetes called GLP-1 RA, GIP/GLP-1 RA and Type 2 Diabetes is available on the Trend Diabetes website:

They should include advice regarding:

- What is the drug and how it works – including the drug name (both trade and generic), preparation being prescribed, dosage, timing, intended plan for titration and checking of expiry dates.
- Discuss targets and aims – including HbA1c targets, weight targets, screening requirements.
- The regime - including common side effects, less common side effects and risks (red flags) and risk (red flag) management.
- What to do if a dose is missed.
- What to do if something changes with regimen - e.g., stopping, swapping or reduction in dose.
- Discuss risk of hypoglycaemia, management and when to seek help if needed.
- Advice and training regarding injection technique – including priming of devices, sites for injection, site rotation, injection technique (relating to device), sharps disposal, storage and disposal of devices, how to self-check injection sites and who to contact if support is needed.
- Specific recommendations on ceasing treatment if any sudden and acute abdominal pains occur.

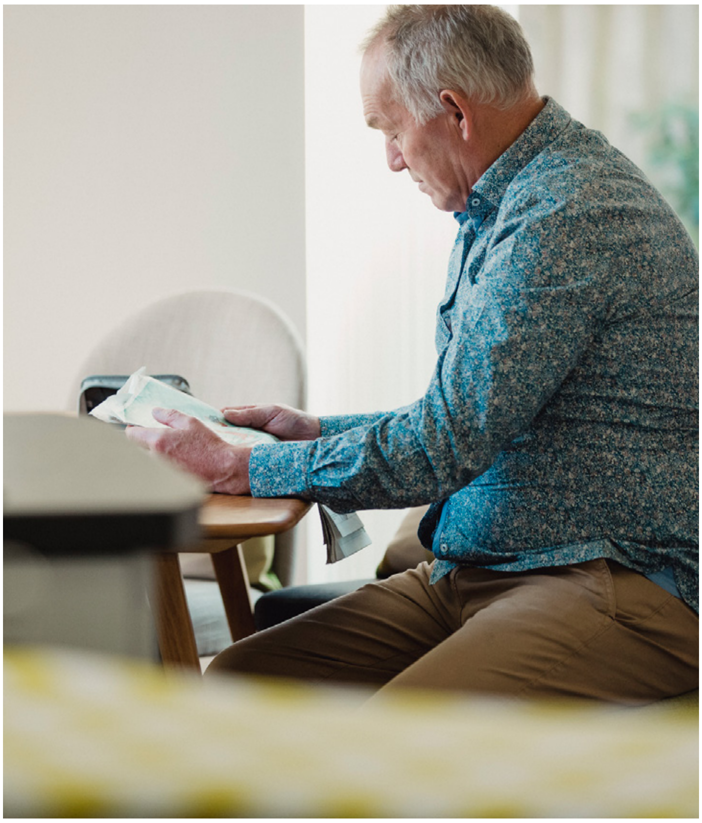


Table 6: Dosing Schedules:[14]

Medication	Dosing schedule:
Liraglutide[36]	**Once daily s/c injection** • Starting dose: 0.6mg • Titration: Wait at least 1 week • Sequential doses: 1.2mg, 1.8mg
Semaglatide[37]	**Once weekly s/c injection** • Starting dose: 0.25mg • Titration: Wait at least 4 weeks • Sequential doses: 0.5mg, 1mg, 2mg*
Semaglatide[38]	**Once daily oral tablet** - Take on an empty stomach at any time of day. Swallow tablet whole (do not split, crush or chew) with a sip of water (up to 120 mL). Wait ≥30 minutes before eating, drinking or taking other oral medicines. Monitor thyroid profile in those also treated with levothyroxine • Starting dose: 1.5mg • Titration: Wait at least 4 weeks • Sequential doses: 3mg, 4mg, 7mg, 9mg, 14mg
Exenatide[39]	**Once weekly s/c injection** • Starting dose: 2mg
Dulaglutide[40]	**Once weekly s/c injection** • Starting dose: 0.75mg • Titration: Wait at least 4 weeks • Sequential doses: 1.5mg, 3mg*, 4.5mg*
Tirzepatide[40]	**Once weekly s/c injection** • Starting dose: 2.5mg • Titration: Wait at least 4 weeks • Sequential doses: 5mg, 7.5mg, 10mg, 12.5mg, 15mg

* Special consideration

Administration technique, advise individuals to:

- Select a day of the week that is convenient to take the injection – set a reminder if required.
- Prepare the device – check it is the correct medication and dose / check the expiry date and the liquid is clear and colourless.
- Ensure the injection site and their hands are clean.
- For devices that contain multiple doses: attach the needle - Tear off the paper tab. Push and turn the needle on until it is attached tightly. Pull off **both** needle caps. For devices that contain a single dose: remove the cap (ℹ **Remember** the Dulaglutide device has an internal needle)
- Turn the dose selector **until the dose counter shows the flow check symbol**. Press and hold in the dose button until the dose counter shows O. Make sure a drop appears at the needle tip (ℹ **Please note:** Some of the devices require this once on commencing a new device, others may require this every time – please check individual SmPC).
- Prepare the injection. Turn the dose selector until the dose counter shows the correct dose for injection (ℹ **This is different for each device** – please check individual SmPC)
- Insert the needle into their skin at a 90-degree angle. For devices that contain multiple doses: Press and hold down the dose button. After the dose counter reaches O, they should count slowly to 10. Then remove the needle from the skin. For devices that contain a single dose: holding the Clear Base firmly against your skin, press the application button and wait until you hear a second click. This happens when the needle starts retracting in about 5-10 seconds.
- For devices that contain multiple doses: After the injection they may need to carefully remove the needle and place it in a sharps container and replace the cap. For devices that contain a single dose: dispose of the device safely in a sharp's container.

Suggested injection sites:

As Injectable GLP-1/GIP therapies are devised to be administered subcutaneously the recommended injection sites remain the same as those for insulin. Please see the attached infographics for advice / guidance.[42]

⚠ **Always inject into correct site.**

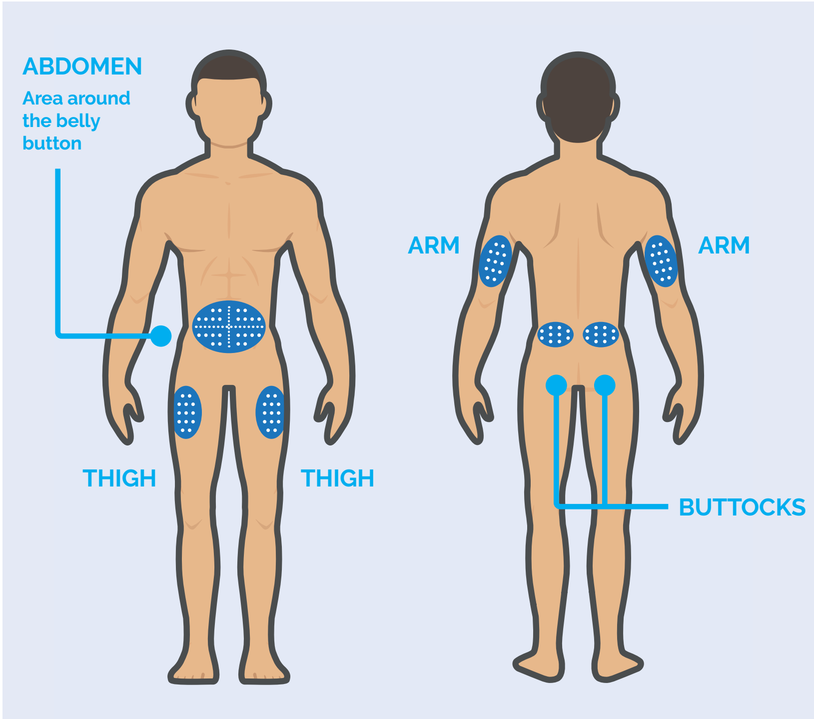
Correct injection sites are:

- Back of upper arms (via 3rd party injector)
- Abdomen
- Upper buttocks
- Upper outer thighs

For GLP-1/GIPs:

✔ All sites suitable

⚠ **Do not use other areas to inject as there is a risk of touching sensitive nerves and larger blood vessels which might lead to some pain or rapid uptake of the insulin or GLP-1/GIP therapy.**

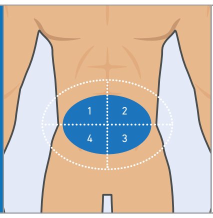


Injection rotation

⚠ **Always follow correct injection rotation**

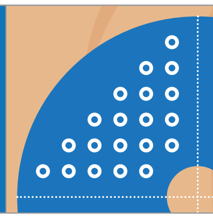
Correct injection site rotation principles:

1



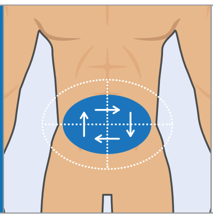
- Inject into one area no more frequently than every 4 weeks

2



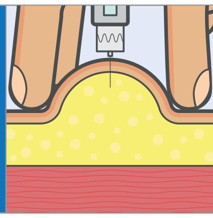
- Each new injection should be given at least 1cm or one finger's width away from the last

3



- Use an injection area for approximately one week then move to the next

4



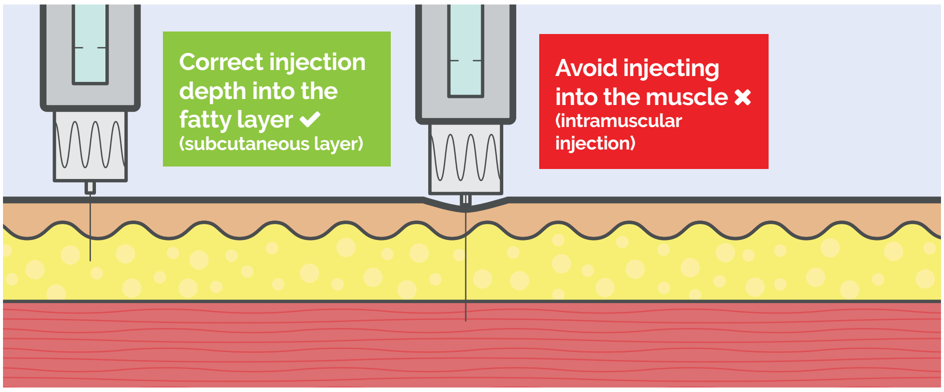
- Never inject into areas affected by lipos
- Use a lifted skin fold in children and slim adults to avoid an intramuscular injection

Injection depth

GLP-1/GIP medication must be injected into subcutaneous layer under the skin.

- **Always** use 4mm needle or a lifted skinfold when required to ensure deposition in fat layer
- **Never** reuse needles

Rationale: People who reuse needles have a high risk of developing lipohypertrophy.



It is important to inject medication into the fatty layer (subcutaneous layer) of the skin for the medication to work correctly.

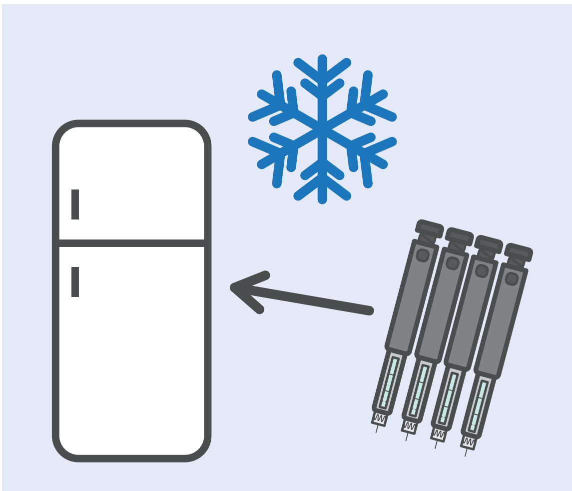
All people who inject insulin and GLP-1/GIP medication should use 4mm pen needles

- GLP-1/GIP medication enters the body correctly when injected into the fatty layer under the skin
- Accidental injections into the muscle layer below the fat can lead to rapid uptake and less predictable duration of action.
- Use 4mm needles for all body types to minimise risk of accidental injection into muscle
- Children, young adults and lean adults even with 4mm pen needle may need to use a lifted skinfold

STORAGE AND HANDLING

Each individual SmPC may have different advice and guidance regarding the storage of their products. However general consensus would suggest that individuals using these products should be advised:

- To store unopened devices in the refrigerator between 36˚F to 46˚F (2˚C to 8˚C).
- To store used devices at room temperature below 86˚F (30˚C) for up to a total of 21 days.
- To avoid freezing devices. If this occurs, they should be advised to discard the device as the integrity of the product will have been compromised.
- To store all products in the original containers
- Protect the device from direct heat and light.
- If the device has glass parts. Advise careful handing. If the device is dropped on a hard surface to discard this device and start a new one.
- To keep all devices / needles and medication out of the reach of children.



MEDICATION RISKS - WHEN TO ADVISE PATIENTS TO SEEK URGENT ADVICE

The prescriber has the responsibility to inform the person living with diabetes of these potential adverse events and when to seek urgent care.

Should a person living with diabetes prescribed GLP-1/GIP therapies attend general practice with the symptoms listed below (or report such events) **an emergency care is required:**[14]

!	Severe or persistent abdominal pain which radiates around to the back. If accompanied by nausea or vomiting, this could signal pancreatitis and requires immediate medical attention.
!	Severe nausea, vomiting, or diarrhoea. High risk of volume depletion/dehydration which can lead to acute kidney injury and require intravenous fluid replacement if unable to tolerate oral fluid intake.
!	Hypoglycaemia (glucose reading below 4 mmol/l) that requires urgent treatment to alleviate symptoms. **Please Note:** A severe hypoglycaemic event is when an individual is in an unconscious state or requires third party assistance to manage their low glucose level.
!	Individuals who are prescribed insulin therapy or sulfonylureas carry a higher risk of hypoglycaemia and may need to reduce or discontinue these types of treatment as directed by a clinician
!	Yellow dis-colouring to skin or the whites of eyes may indicate jaundice. This is a serious condition indicating liver impairment or failure.
!	Signs of allergies. Associated symptoms may include; swelling around the injected site, a rash spreading across a larger surface of the skin with associated itching or pruritus. Angioedema or severe allergic reaction leading to tongue swelling, shortness of breath and rapid pulse rate, indicate a need for urgent medical attention and a ambulance should be called by calling 999.
!	Consider if GLP-1/GIP therapies are being purchased privately. Advise all people living with diabetes to only use GLP-1/GIP therapies which has been prescribed by a registered healthcare professional and dispensed by a reputable pharmacist.

Any adverse events relating to GLP-1/GIP medication will require discontinuation of treatment. The prescriber or emergency clinician are encouraged to report these events to the MHRA and complete an online yellow card.[43]

SAFETY RULES TO MANAGE ILLNESS:

Guidance on how to manage medication during illness is a vital part of education when managing Type 2 diabetes.[5,14,28] There is a wealth of resources, including patient information leaflets that support these conversations in our consultations.[32,34,44] When prescribing GLP-1/GIP therapy, clinicians are responsible for informing individuals on how to manage treatment during illness, in particular the risk of complications and dehydration.

Guidance on whether to continue or cease GLP-1/GIP therapy should be instructed by a clinician or specialist diabetes team and clearly documented. It is important to consider if alternative medication may be required or an increase of Insulin in order to prevent acute hyperglycaemia.[45] Guidance suggests that If Initiation of Insulin during illness is required, the individual will also require access and education in relation to blood glucose monitoring.[14] This guidance also suggests:

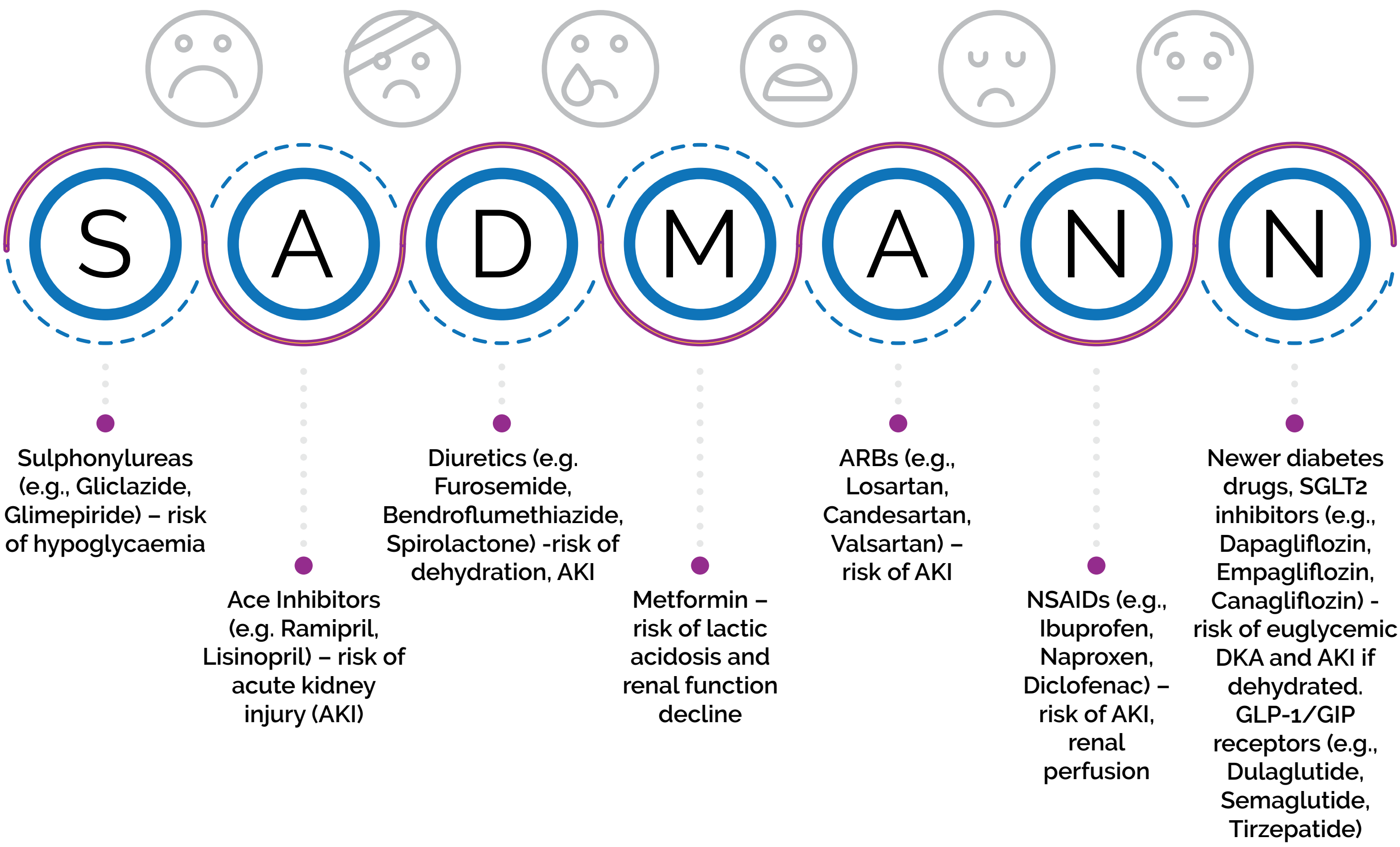
- **GLP-1/GIP therapy can CONTINUE** for mild illness such as cough, cold, minor infection but able to eating drink normally. Nausea or soft stools but not vomiting or experiencing diarrhoea.
- **GLP-1/GIP should be CEASED DURING ACUTE ILLNESS** – developing flu or gastric virus which leads to vomiting and diarrhoea. If unable to keep fluids down there is a high risk of dehydration.

If at any stage GLP-1/GIP medication is stopped during illness, the guidance suggests that this is only restarted when the person is able to tolerate diet and fluid for 24-48hrs. If a GLP-1/GIP is administered via a tablet form (Rybelsus: Semaglutide) or a daily injection guidance suggests that this is only restarted when the person is eating "normally" and If the GLP-1/GIP is a weekly injectable therapy, the individual should revert back to the original chosen day of administration (e.g., injection administered every Friday).[28]

It is important to note that Sick Day guidance may also include other non-diabetes medication as these medications may also carry risks associated with illness, dehydration and possible deterioration of renal function during the phase of acute illness.[6]

Resources such as the document produced by Downs[14,46] highlight the usefulness of the SADMANN acronym (Table 7). This acronym is a useful guide for both people living with diabetes and HCPs to identify which medication to cease during illness. When prescribing GLP-1/GIP therapy or reviewing individuals with diabetes, the prescriber can incorporate this information into the consultation. It is also important to consider alcohol intake and other medications such as, Disopyramide, Monoamine oxidase inhibitors (MAOIs), and hormone replacement therapies such as Testosterone, Oestrogen and Progestogens.[14]

Table 7: SADMANN



SURGERY OR PROCEDURE

Individuals living with type 2 diabetes may be advised to temporarily cease GLP-1/GIP medication for a planned surgical or endoscopy procedure and should be given clear guidance from their surgical/admitting team regarding when to cease treatment for the pre and post-operative stage.[47]

Peri-operative use of these drugs are subject to further exploration due to concerns regarding the delay gastric emptying and correlated risk of pulmonary aspiration on induction of anaesthesia.[48] Research suggests this has the potential to affect the outcome of an endoscopy procedure due to an incomplete bowel preparation and retained gastric content.[47,48]

When a GLP-1/GIP has been temporarily ceased in this scenario, there is a risk of pre and post-operative hyperglycaemia and additional medication may be required or an increase of current anti-hyperglycaemic agents.[47]

PREGNANCY/PRECONCEPTION MANAGEMENT

GLP-1/GIP therapy is not licensed for use during pregnancy

Despite the popularity of GLP-1/GIP therapy in woman with obesity there is limited safety data for this medication during the preconception period and optimal time to discontinue before conception. Patients who have been advised to lose weight during the preconception stage in order to start fertility treatment may have been initiated on GLP-1/GIP therapy and should be advised to seek alternative lifestyle modifications and discontinue GLP-1/GIP receptors.[14] Further studies are required to report on pregnancy, maternal and neonatal outcomes.[49]

Additional education is required if an individual is prescribed oral contraception and a GLP-1/GIP agonist. Should they experience diarrhoea or vomiting, this will reduce the effectiveness of contraception and an alternative contraceptive method should be considered that would not require additional precaution.[50]

SUMMARY

We have come a long way since the invention of insulin (>100 years ago). The rapid growth and development in therapies like the GLP-1/GIP class of medications to support people living with diabetes has been particularly impressive. It is clear that the development of these therapies have had, and will continue to have, a significant impact on glycaemic management, associated reductions in risk factors and quality of life for people living with type 2 diabetes particularly when coupled with effective diet and lifestyle interventions. The future is bright, innovation continues and people lives will continue to be positively impacted by the continued developments being made.

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This resource has been supported with a grant from Lilly

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