MASTERCLASS 1 : GLP-1 RECEPTOR AGONISTS

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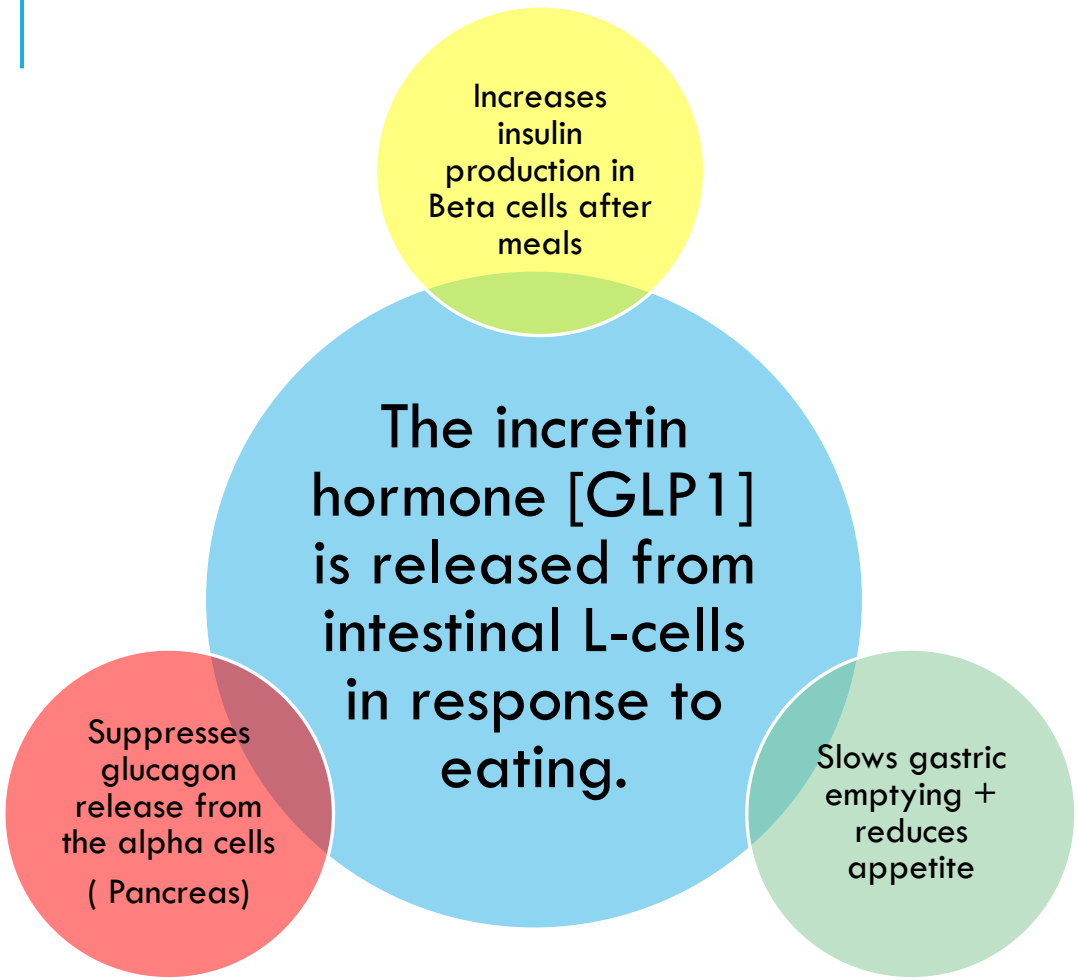
LEARNING OBJECTIVES- GLP1S

- Mode of action
- When to start and current agents on the market
- Administration of injections
- Initiation of s/c GLP-1s and titration
- Oral formulations
- Supply issues

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISTS MECHANISM OF ACTION



The enzyme DPP4 rapidly degrades GLP-1

Using GLP receptor agonists increases GLP1 levels resulting in benefits to the :

- **Pancreas** : Inhibits glucagon secretion from alpha-cell in the presence of high glucose.
- **Brain** : Reduced hunger and energy intake in the brain
- **Stomach** : Increased incretin effects, reduced gastric emptying
- **Liver** : With lower glucagon, hepatic glucose production can be reduced
- **Muscles** : Increased insulin sensitivity

WHEN TO START GLP-1S

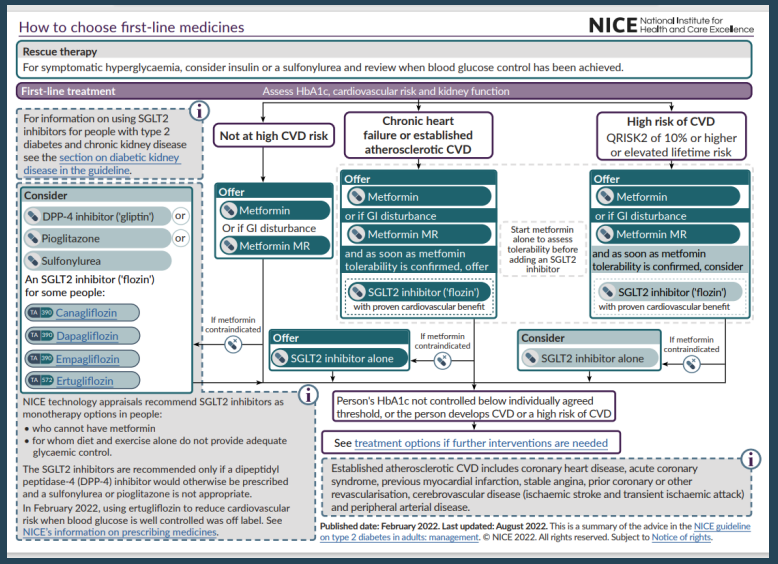
-NICE GUIDELINE [NG28] : UPDATED JUNE 22

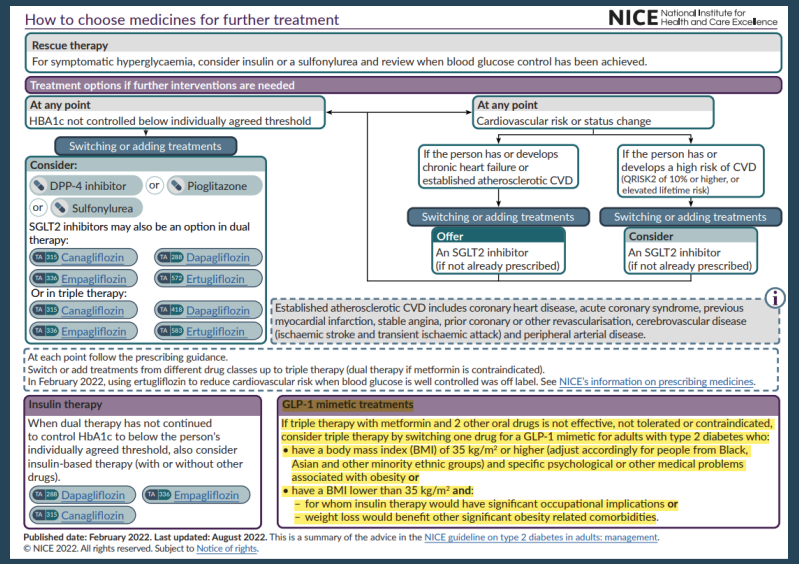
If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity

or

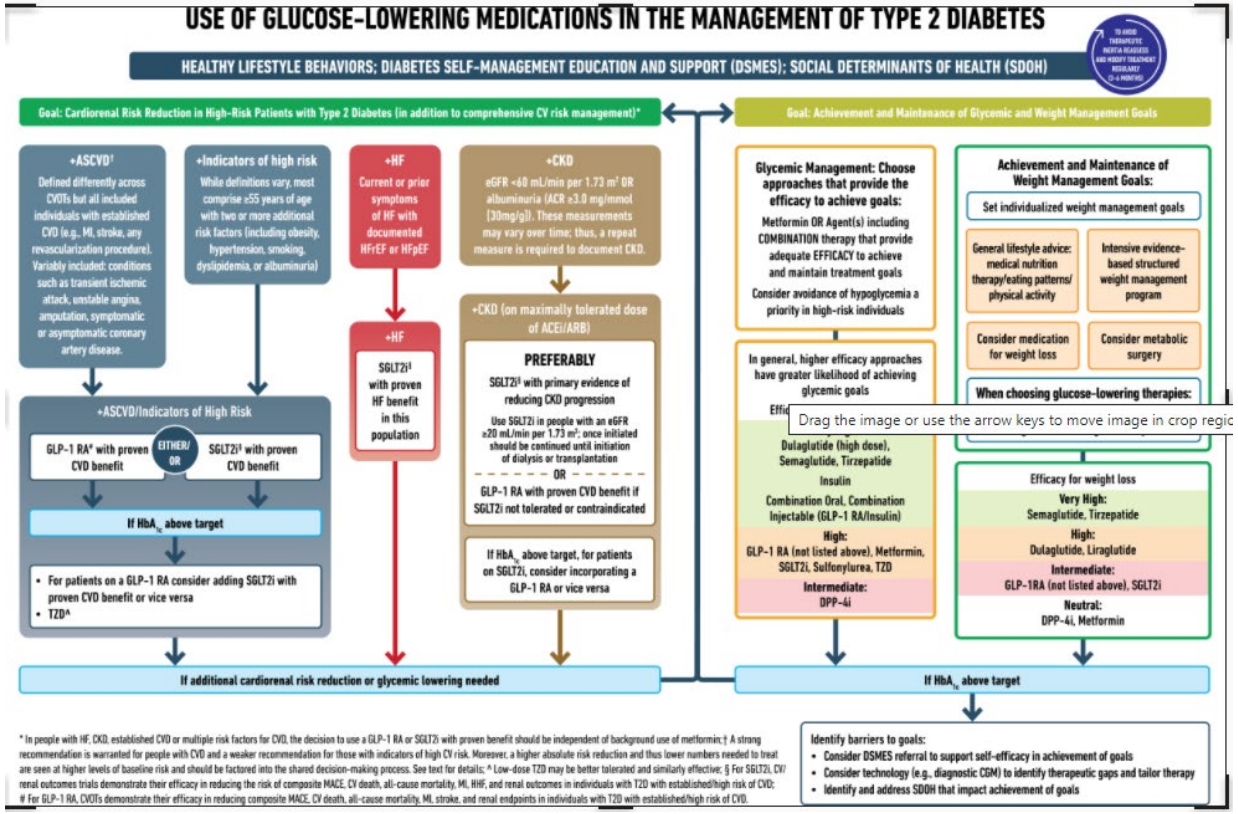
- have a BMI lower than 35 kg/m2 and: – for whom insulin therapy would have significant occupational implications or – weight loss would benefit other significant obesity related comorbidities





AMERICAN DIABETES ASSOCIATION (ADA) AND THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD) CONSENSUS REPORT – UPDATED SEPTEMBER 2022

MANAGEMENT OF HYPERGLYCEMIA IN TYPE 2 DIABETES



Advantages of using GLP-1s

- ❑ Low risk of hypoglycaemia
- ❑ Can be used in moderate to severe renal impairment
- ❑ Some agents have shown CV protection
- ❑ Potent with 12-20mmol/mol expected reduction in HBA1c
- ❑ Weight loss of around 2.5-5kg

Disadvantages of using GLP-1s

- ❑ Tolerance issues – GI side-effects common, greater than 10% of pts
- ❑ Injectable (usually)
- ❑ Expensive
- ❑ Risk of pancreatitis
- ❑ Risk of Gall stones
- ❑ Risk of Thyroid tumours
- ❑ Possible early worsening of retinopathy

CURRENT GLP-1S ON THE MARKET – S/C

Name of GLP-1	Dose
Exenatide  	<u>Standard-release formulation:</u> 5 micrograms twice daily, increased if necessary, after at least 1 month to a maximum dose of 10 micrograms twice daily. It should be administered within 1 hour before two main meals (at least 6 hours apart). It should not be administered after a meal. <u>Modified-release formulation:</u> 2 mg once weekly on the same day each week (at any time, with or without meals). The day of weekly administration can be changed if necessary, as long as the next dose is administered at least 24 hours later.
Liraglutide 	0.6 mg once daily, increased after at least 1 week to 1.2 mg once daily. This can be further increased if necessary, after an interval of at least 1 week to a maximum dose of 1.8 mg once daily.
Lixisenatide 	10 micrograms once daily for 14 days, to be taken within 1 hour before the first meal of the day or the evening meal, increased to 20 micrograms once daily thereafter. ** Discontinued – supplies to end Dec 23
Dulaglutide 	1.5 mg once weekly; increased if necessary to 3 mg once weekly after at least 4 weeks, then increased if necessary to 4.5 mg once weekly after another 4 weeks, a starting dose of 0.75 mg once weekly may be considered for potentially vulnerable patients; maximum 4.5 mg per week.
Semaglutide 	0.25 mg once weekly for 4 weeks, then 0.5 mg once weekly for at least 4 weeks, then increased to 1 mg once weekly if needed.

ADMINISTRATION OF INJECTION

Injection self-administered by subcutaneous injection in the:

thigh,

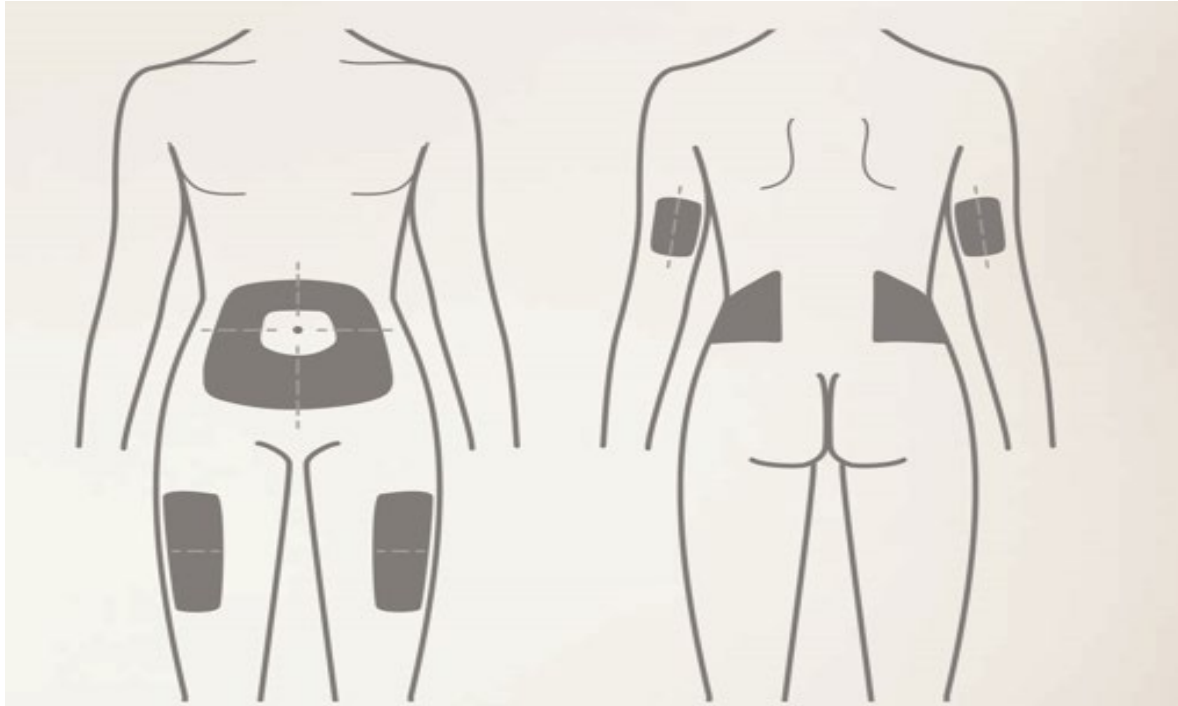
abdomen,

upper arm,

Ensure patients understand to rotate the injection sites from one injection to the next and use a new needle each time.

Prior to injecting , advise patient:

- ✓ Remove the Pen from the refrigerator. Leave the Base Cap on until ready to inject.
- ✓ Check the Pen label to make sure you have the correct medicine and it has not expired.
- ✓ **Check the Pen to make sure that it is not damaged** and inspect the medicine to make sure it is not cloudy, discoloured or has particles in it.
- ✓ Wash hands.



Adapted from: FIT UK Forum for Injection Technique UK. The UK Injection and Infusion Technique Recommendations 4th Edition, 2016. Available at: http://fit4diabetes.com/files/4514/7946/3482/FIT_UK_Recommendations_4th_Edition.pdf. Accessed April, 2019.

CONTRAINDICATIONS

Do not prescribe a GLP-1 receptor agonist to people with

- Ketoacidosis.
- Pancreatitis.
- Renal impairment:
  - Avoid exenatide standard-release and liraglutide injection if estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73 m^2.
  - Avoid exenatide modified-release injection if eGFR is less than 50 mL/min/1.73 m^2.
  - Avoid liraglutide and semaglutide in end-stage renal disease.
- Severe hepatic impairment — avoid liraglutide.
- Severe gastrointestinal disease — avoid exenatide, liraglutide (for example if diabetic gastroparesis or inflammatory bowel disease), lixisenatide, and dulaglutide.

CAUTIONS

People with a history of **pancreatitis** — discontinue if symptoms of acute pancreatitis occur.

People with **renal impairment** — if eGFR is 30–50 mL/min/1.73 m^2 use standard-release exenatide and lixisenatide with caution.

People with **hepatic impairment** — caution with semaglutide.

Elderly people — may cause weight loss (exenatide).

Women of childbearing potential — advise that effective **contraception** should be used:

People with severe **heart failure** — use liraglutide and semaglutide with caution.

People with **thyroid disease** — history of medullary thyroid cancer or multiple endocrine neoplasia (MEN) type 2 disease (for liraglutide).

People with **retinopathy** — use semaglutide with caution.

WHICH AGENT TO START AND WHEN TO REVIEW

If patient meets NICE criteria to commence a GLP-1- Choose an agent that is tailored to their individual need [existing CVD / weight loss a priority / adherence an issues]

Initial consultation : record baseline HBA1c / weight. Demonstrate technique . Give Information on dosage , side effects, safe storage and disposal of needles. Give sharps bin. Educate on potential side effects and when to seek medical advice. Re-iterate lifestyle advice.

Interim assessment at 3 months – HBA1c and weight : are things moving in the right direction? Tolerating ok ? Any side –effects concerns? Issues with injecting?

Reassess at 6 months : Update weight = loss of 3%?, HBA1c= reduction of 11 mmol/mol? . Side effects / tolerance issues?

0 targets achieved : refer to specialist service . STOP GLP-1

1 of 2 targets achieved : Increase to max dose for further trial for 3 months or switch to other GLP1 for 3 month trial.

2 of 2 targets achieved : continue and assess annually thereafter that GLP1 is making positive contribution to disease control.

CONSIDERATION FOR SPECIAL POPULATIONS

Patients on **insulin** , ensure they are initiated under specialist care.

Cardiovascular history : Both semaglutide and dulaglutide are suitable for patients with established cardiovascular disease (secondary prevention). Consider Dulaglutide for patients with risks for cardiovascular disease (primary prevention)

Consider Semaglutide where **weight** of concern.

DULAGLUTIDE

Brand : Trulicity

Frequency of administration : s/c injection weekly – same day , same time of day – regardless of meals.

Dosage regimen : 1.5 mg once weekly; increased if necessary to 3 mg once weekly after at least 4 weeks, then increased if necessary to 4.5 mg once weekly after another 4 weeks,
Starting dose of 0.75 mg once weekly may be considered for potentially vulnerable patients; maximum 4.5 mg per week.

How to administer: - Trulicity® Pen: confirmation of dose (kaltura.com)

Step 1: Uncap

· Make sure the pen is locked.

· Pull off and discard the grey base cap. Do not put the base cap back on – this could damage the needle. Do not touch the needle.1

Step 2: Place and unlock

· Place the clear base flat and firmly against the skin at the injection site. · Unlock by turning the lock ring.1

Step 3: Press and hold

· Press and hold the green injection button; a loud click will be heard.

· Continue holding the clear base firmly against the skin until a second click is heard. This occurs when the needle starts retracting in about 5-10 seconds. · Remove the pen from the skin

Needles required? No –lubricated needles built into pen [needle depth of 5mm/29G]

Storage : Refrigerator, once removed must be used within 14 days

Missed dose :< 72hrs until next dose- skip. >72hrs- take as soon as possible and resume usual dosing schedule

Special Warning – Black box warning
Trulicity may cause tumours in the thyroid, including thyroid cancer.
Advise patients to watch for possible symptoms, such as a lump or swelling in the neck, trouble swallowing, hoarseness, or shortness of breath.
C/I : personal or FHx of Medullary thyroid carcinoma (MTC) or Multiple Endocrine neoplasia syndrome (MEN 2)

SEMAGLUTIDE

OZEMPIC®
semaglutide injection

Brand : Ozempic (3 different strengths – 0.25mg, 0.5mg and 1mg)

Frequency of administration : s/c injection weekly – same day, same time of day- regardless of meals

Dosage regimen : Initially 0.25 mg once weekly for 4 weeks, then increased to 0.5 mg once weekly for at least 4 weeks, then increased if necessary to 1 mg once weekly.

How to administer:

Needles required? No – each box of Ozempic® will contain x 4 NovoFine® Plus needles

Storage : Refrigerator, once removed must be used within 6 weeks.

Missed dose : do not double dose.
< 5 days use it as soon as you remember. Then inject your next dose as usual
>5 days - skip the missed dose and inject your next dose as usual day

LIRAGLUTIDE

Brand : Victoza® (1.2 mg or 1.8 mg injections available)

Frequency of administration : s/c injection Daily

Dosage regimen : Initially 0.6 mg once daily for at least 1 week, then increased to 1.2 mg once daily for at least 1 week, then increased if necessary to 1.8 mg once daily.

How to administer: - Same steps as Ozempic . Demonstration video : https://www.youtube.com/watch?v=K7rdXpiKDtQ

Needles required? Yes, will need separate prescription [NovoFine® 32G 6mm is brand recommended by manufacturer]

Storage : Refrigerator, once removed must be used within 30 days

Missed dose : Skip dose and resume the once -daily dosage at next scheduled dose.
If > 3 days have elapsed reinitiate at 0.6 mg once daily to mitigate any GI side effects.

Special Warning – Liraglutide may cause tumours in the thyroid, including thyroid cancer.
Advise patients to watch for possible symptoms, such as a lump or swelling in the neck, trouble swallowing, hoarseness, or shortness of breath.
C/I : personal or FHx of Medullary thyroid carcinoma (MTC) or Multiple Endocrine neoplasia syndrome (MEN 2)

SIDE EFFECTS

Upper gastrointestinal side effects such as nausea are common with GLP-1 receptor agonist therapy.

Acute pancreatitis in patients using these drugs. GLP-1 receptor agonists should be avoided in patients considered to be at high risk of pancreatitis. Patients and their carers should be told how to recognise signs and symptoms of pancreatitis.

Diabetic ketoacidosis has been reported in patients with type 2 diabetes on a combination of a GLP-1 receptor agonist and insulin who had doses of concomitant insulin rapidly reduced or discontinued.

Changes in vision

Gallbladder problems

Headache, dizziness, drowsiness, alopecia, hyperhidrosis .

Renal impairment (exenatide and liraglutide), worsening of existing renal problems.

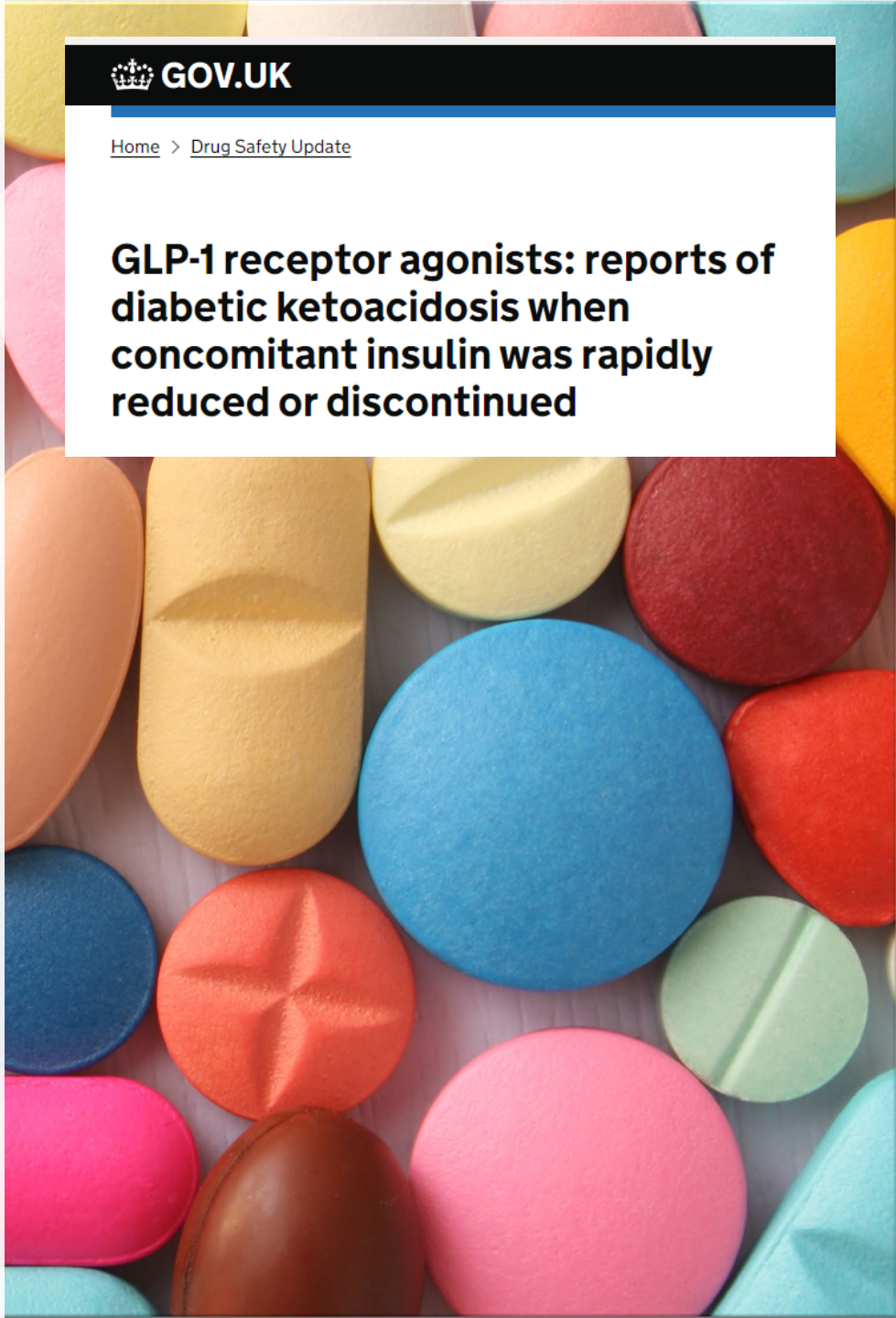
Atrioventricular block, sinus tachycardia, delayed gastric emptying (dulaglutide).
Skin reactions including rash, angioedema, urticaria, and pruritus.

Yellow Card
Making medicines safer

DRUG INTERACTIONS

- **Beta-blockers** — the warning signs of hypoglycaemia (such as tremor) may be masked during concurrent treatment with a beta-blocker.
- **Paracetamol** — lixisenatide possibly reduces the absorption of paracetamol when given 1–4 hours before paracetamol.
- **Warfarin** — exenatide and liraglutide possibly enhance the anticoagulant effect of warfarin. Monitor the international normalized ratio (INR) during concurrent treatment with warfarin. Also consider monitoring INR at the time of initiation or stopping of lixisenatide treatment.
- **Other orally administered drugs** — may need to be taken at least 1 hour before or 4 hours after lixisenatide or exenatide injection or taken with a meal when lixisenatide is not administered, to minimize possible interference with absorption.
- Other antidiabetic drugs — due to the increased risk of hypoglycaemia, the dose of **concomitant sulfonylurea** may need to be reduced.

Limited list – always refer to each GLP-1s SPC / BNF prior to commencing



PRACTICAL ADVICE FOR INITIAL CONSULTATION

- Prior to any prescription – record baseline HBA1c and weight.
- Prescribe GLp-1s by brand
- Ensure appropriate titration schedule and plan in notes – adding date for review / recall for bloods added.
- Give sharps bin . Provide script for needles If appropriate.
- If patient on triple therapy, remember to STOP and remove **one** medication from repeats.
- Ensure patients know how to identify signs of pancreatitis and any change in thyroid .
- Discuss common for GI side-effects in early stages of treatment , best to eat smaller meals.
- To prevent waste, please avoid prescribing large quantities – GLP-1 receptor agonists require refrigeration and are expensive. One month's supply should be adequate for most patients.
- Give information on apps .

SEMAGLUTIDE

Brand : RYBELSUS®

Frequency of administration : Once daily tablet

Dosage regimen : Initially 3 mg once daily for 1 month, then increased to 7 mg once daily for at least 1 month, then increased if necessary to 14 mg once daily

MAO : RYBELSUS® Mechanism of Action | RYBELSUS® (semaglutide) tablets (novomedlink.com)

How to administer:

Take RYBELSUS® by mouth on an empty stomach when you first wake up with a sip of plain water (no more than 4 ounces)

Do not split, crush, or chew. Swallow RYBELSUS® whole

After 30 minutes, you can eat, drink, or take other oral medicines

One 14 mg tablet should be used to achieve a 14 mg dose; use of two 7 mg tablets to achieve a 14 mg dose has not been studied and is therefore not recommended.

Missed dose : If you miss a dose of RYBELSUS®, skip the missed dose and go back to your regular schedule

Special Warning – Possible thyroid tumours, including cancer.

Advise patients to watch for possible symptoms, such as a lump or swelling in the neck, trouble swallowing, hoarseness, or shortness of breath.

C/I : personal or FHx of Medullary thyroid carcinoma (MTC) or Multiple Endocrine neoplasia syndrome (MEN 2)

You should stop using RYBELSUS® 2 months before you plan to become pregnant.

ORAL GLP1S- REVIEW

Dose : 3mg OD for 1 month increasing to 7mg OD maintenance dose. Consider increasing maintenance dose to 14mg OD for further glycaemic control.

Assess for side-effects if not tolerated , STOP and refer back to specialist service.

Only continue if meets NICE criteria at 6 month review : beneficial metabolic response [reduction of at least 11mmol/mol in HBA1c AND a weight loss of 3% initial body weight] .

Continue to assess that GLP-1 analogue is making positive contribution to disease control Annually thereafter.

Due to the lack of available cardiovascular outcome trial data for oral Semaglutide this should only be considered as a second line option for patients suitable for a GLP-1 where the subcutaneous route of administration is not tolerated or advisable.

EVIDENCE OF CARDIOVASCULAR OUTCOMES

Exenatide : EXSCEL Trial (14752 pts over 3.2 years) Median WEEKLY dose: 2mg 73% of participants established Cardiovascular disease NOT Significant - HR 0.91 (0.83 to 1.00) p = 0.06 .

Liraglutide (Victoza®) : LEADER Trial (9340 pts over 3.8 years) Median daily dose 1.78mg 81% of participants established Cardiovascular disease Significantly fewer CV outcomes ay 1.8mg daily dose only – no evidence for improved CV outcomes at 1.2mg dose- HR 0.87 (0.78 to 0.97) p = 0.01

Lixisenatide (Lyxumia®) : ELIXA Trial (6068 pts over 2.1 years) Median daily dose 20mcg 100% of participants established Cardiovascular disease NOT significant—HR 1.02 (0.89 to 1.17) p = 0.81

Semaglutide : SUSTAIN-6 Trial - PATIENT HAS ESTABLISHED CARDIOVASCULAR DISEASE (3297 pts over 2.1 years) Median WEEKLY dose 0.5mg or 1mg. 83% of participants established cardiovascular disease Baseline HbA1c = 72mmol/mol Significantly fewer CV outcomes - HR 0.74 (0.58 to 0.95) p = 0.02

Dulaglutide : REWIND Trial (9901 pts over 5.4 years) Median WEEKLY dose 1.5mg. 68.5% of participants risk factors for cardiovascular disease Baseline HbA1c = 55mmol/mol Significantly fewer CV outcomes - HR 0.88 (0.79 to 0.99) p = 0.026

SUPPLY ISSUES

Association of British Clinical Diabetologists

PCDS Primary Care Diabetes Society

Advice from the Department of Health & Social Care (DHSC)

The following advice has been issued from DHSC for the period of national GLP-1 RA shortages, until supply issues have resolved:

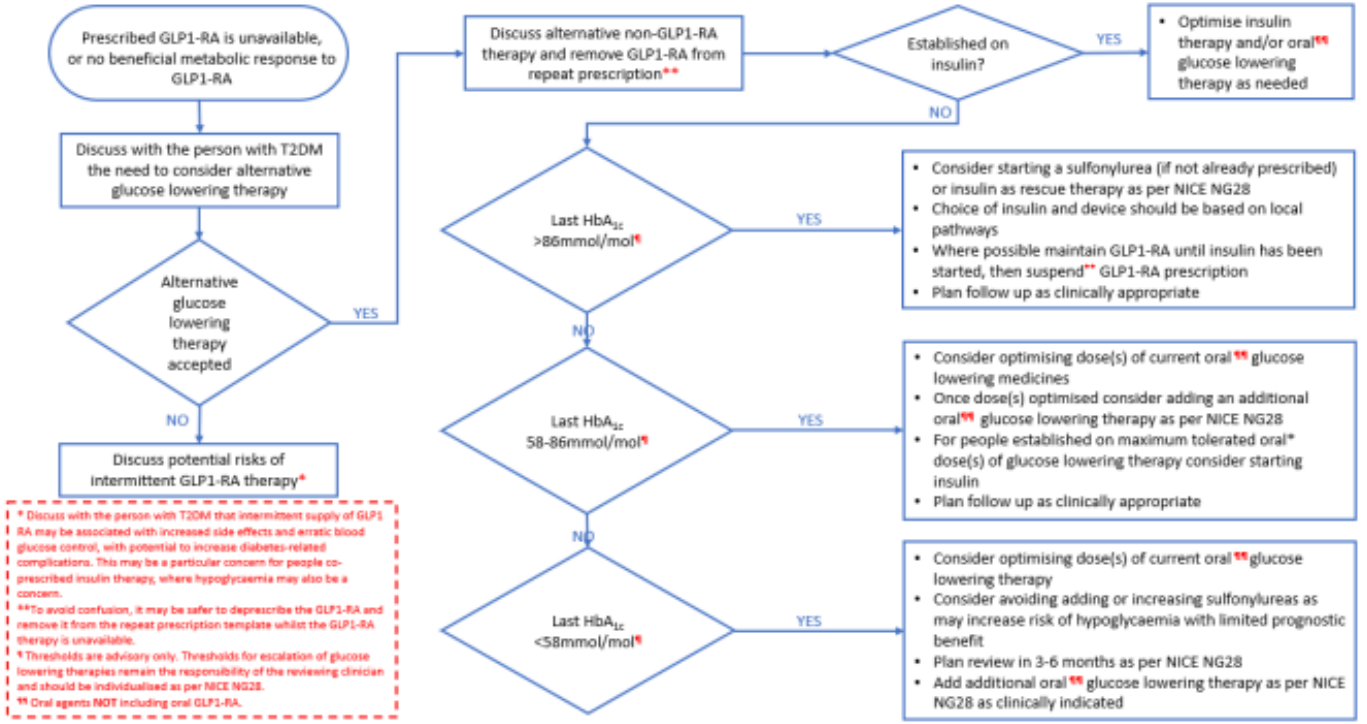
- GLP-1 RAs should only be prescribed for their licensed indication.
- Avoid initiating people with Type 2 Diabetes on GLP-1 RAs for the duration of the GLP-1 RA national shortage.
- Review the need for prescribing a GLP-1 RA agent and stop treatment if no longer required due to not achieving desired clinical effects as per NICE NG28.
- Avoid switching between brands of GLP-1 RAs, including between injectable and oral forms.
- Where a higher-dose preparation of GLP-1 RA is not available, do not substitute by doubling up a lower-dose preparation.
- Where GLP-1 RA therapy is not available, proactively identify patients established on the affected preparation and consider prioritising for review based on the criteria below.
- Where an alternative glucose-lowering therapy needs to be considered, use the principles of shared decision making as per NICE guidelines in conjunction with the **Supporting Information** below.
- Where there is reduced access to GLP-1 RAs, support people with Type 2 Diabetes to access structured education and weight management programmes where available.

Association of British Clinical Diabetologists

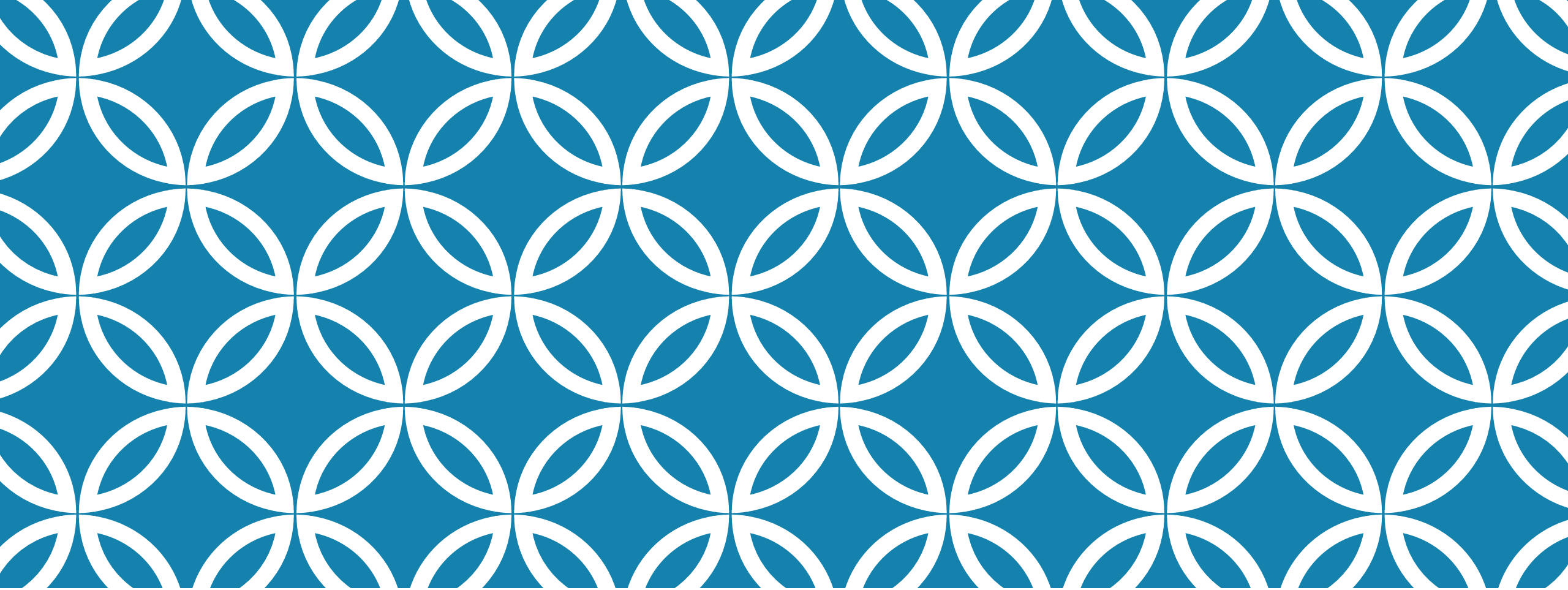
PCDS Primary Care Diabetes Society

Selecting alternative glucose-lowering therapy when GLP-1 RAs are unavailable or where there is no beneficial metabolic response to GLP-1 RA therapy

Figure 1. Choosing alternative glucose-lowering therapies in T2DM when GLP-1 RAs are unavailable or there is no beneficial metabolic response.



Note: Symptomatic hyperglycaemia may indicate clinical need for insulin therapy. If in doubt, discuss with specialist. Symptoms of hyperglycaemia include polyuria, polydipsia, weight loss and fatigue. Think 4Ts – Thirst, Toilet, Thinner, Tired.



THANK YOU FOR YOU TIME

REFERENCES

NG28 Visual summary on choosing medicines for type 2 diabetes in adults (nice.org.uk)

6.1.2.6 GLP-1 Receptor Agonists | NI Formulary (hscni.net)

GLP-1 receptor agonists | Prescribing information | Diabetes - type 2 | CKS | NICE

https://www.pcdsociety.org/pcds-abcd-guidance-glp1-shortage

https://herefordshireandworcestershireccg.nhs.uk/policies/medical/clinical-policies-guidance/endocrine/1097-glp-1-receptor-agonists-in-type-2-diabetes-prescribing-guideline/file

https://www.shropshiretelfordandwrekin.nhs.uk/wp-content/uploads/20211208-GLP-1-Pathway-V4.0.pdf

https://www.diabetes.co.uk/

Hot Topics Diabetes for Primary Care 2023 - Online Course Reference Book.pdf

https://www.medicines.org.uk/emc/product/9750/smpc#gref

Trulicity (dulaglutide) – LillyMedical

Using the Victoza® Pen | Victoza® (liraglutide) injection 1.2 mg or 1.8 mg

Type 2 Diabetes Medicine | RYBELSUS® (semaglutide) tablets 7 mg or 14 mg

https://bnf.nice.org.uk/

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