Update March 2024: Glucagon-Like-Peptide 1 Receptor Agonist National Shortage

Guidance from the Primary Care Diabetes Society (PCDS) and Association of British Clinical Diabetologists (ABCD)

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Background

There is an ongoing national shortage of glucagon like peptide-1 receptor agonists (GLP-1 RAs) used in the management of Type 2 Diabetes (T2DM). This situation is not expected to resolve until into late 2024. Supplies of some GLP-1 RA preparations may be intermittent or exhausted within this time (see GLP-1 RA table for products affected). The updated Medicines Supply Notification indicates that there are now products available which can be used for new initiation starts and conversions for people with type 2 diabetes unable to obtain their original GLP-1 RA medication.

Scope

This guidance aims to support clinicians in selecting alternative glucose lowering therapies when GLP-1 RAs used in the management of T2DM in adults are unavailable during this period of national shortage. This guidance should be used in conjunction with NICE NG28 Type 2 Diabetes in Adults: choosing medicines.

Children and young people with T2DM prescribed GLP-1 RAs under the care of specialist paediatric services should be directed back to specialist services.

The use of GLP-1 RAs in the management of obesity is outside the scope of this guidance.

Target audience

- Prescribers in all care settings
- NHS Diabetologists/ Endocrinologists
- Specialist diabetes services and associated health care professionals
- People with Type 2 Diabetes, their families, or carers
- Organisations commissioning NHS services
- Providers of NHS services

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

The following advice has been issued from DHSC as a medicines supply notification which supersedes previous National Patient Safety Alerts (NatPSA), until supply issues have resolved:

March 2024 – MSN/2024/

Updated availability can be found here: Prescribing available GLP-1 receptor agonists – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice

Clinicians should:

- only prescribe GLP-1 RAs for their licensed indication;
- continue proactively engaging with patients established on GLP-1 RAs impacted by shortage and consider prioritising for review based on the criteria set out in clinical guidance and:
    - discuss stopping the GLP-1 RA if patients have not achieved treatment goals as per NICE NG28;

- do not double up a lower dose preparation where a higher dose preparation of a GLP-1 RA is not available;
- do not switch between strengths of a GLP-1 RA solely based on availability; and
- do not prescribe more than one month's supply unless there is clear reason to do so in order that the risks to the supply chain are minimised and the needs of patients acknowledged (see supporting information).

Where patients are prescribed Victoza® or Byetta® or where patients are unable to obtain Ozempic® or Trulicity® for 2 weeks or more, prescribers should:

- consider prescribing either Rybelsus® tablets or Mounjaro® KwikPens® (ensuring that the patient is prescribed appropriate needles), which can support the market during this time, if appropriate;
- if prescribing Mounjaro® or Rybelsus®, ensure that the patient is not intolerant to any of the excipients (refer to product SPC) and is counselled on the dose regimen, including administration volumes where applicable (see supporting information); and
- if the above options are not considered appropriate, or if prescribers in primary care require further clinical advice, they should liaise with specialists on management options.

Advice for prescribers

This guidance aims to support clinicians in selecting alternative incretin hormone therapy when a person's prescribed GLP-1 RA is unavailable. This advice should be used in conjunction with NICE NG28 Type 2 diabetes in adults: choosing medicines. When prescribing an alternative GLP-1 RA or dual glucose-dependent insulinotropic peptide / glucagon like peptide-1 receptor agonists (GIP/GLP-1 RA), clinicians are advised to prescribe medications in accordance with the licenced indications.

This guidance does not override the responsibility of the clinician to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Rybelsus® (oral semaglutide) is an oral preparation of semaglutide that is taken once daily on an empty stomach. (Please see below for additional key information for prescribers. – (See Rybelsus® section)

Mounjaro® (Tirzepatide) is a first in class long-acting dual glucose-dependent insulinotropic polypeptide GIP/GLP-1 RA). NICE TA 924 has positioned Mounjaro® the same as single incretin GLP-1 RAs, and the same criteria for prescribing and continuing treatment apply. Please see below for additional key information for prescribers – (see Mounjaro® section)

Clinical review

In most cases, the need to consider alternative glucose lowering therapy will arise when a person with T2DM established on GLP-1 RA therapy is unable to source their regular GLP-1 RA prescription. Where the prescribed GLP-1 RA is available and clinically effective, there is no need to instigate any change in therapy.

Local supply chain issues may be overcome by attending an alternative pharmacy; this should be considered before switching therapies. Should a particular preparation of GLP-1 RA remain unavailable despite this, the following actions are suggested:

GLP-1 RA availability and actions suggested

GLP-1 RA unavailable	Suggested action
Byetta® (exenatide) 5micrograms/0.02ml and 10micrograms/0.04ml pre-filled pens	Byetta® is due to be discontinued March 2024, patients should be identified and if still clinically appropriate should be prescribed either Rybelsus® tablets or Mounjaro® S/C injections
Victoza® (liraglutide) 6mg/ml solution for injection	Victoza® is out of stock until end of 2024, people with T2DM should be identified and if still clinically appropriate should be prescribed either Rybelsus® tablets or Mounjaro® injections
Ozempic®(semaglutide) 0.25mg, 0.5mg and 1mg injection	Ozempic® has intermittent supply throughout 2024 with occasional out of stocks predicted for individual strengths. If a person cannot obtain their medication for more than two weeks, consider prescribing Rybelsus® tablets or Mounjaro® injections
Trulicity® (dulaglutide) 0.75mg, 1.5mg, 3mg and 4.5mg injections	Trulicity® has intermittent supply throughout 2024. If a person cannot obtain their medication for more than two weeks, consider prescribing Rybelsus® tablets or Mounjaro® injections.
Bydureon BCise® (exenatide) 2mg/0.85ml prolonged-release pre-filled pens	There is no predicted supply problem at this time. If a person cannot obtain their medication for more than two weeks, consider prescribing Rybelsus® tablets or Mounjaro® injections.
Rybelsus® (oral semaglutide) 3mg, 7mg and 14mg tablets	There are no predicted supply problems with Rybelsus® at this time.

Rybelsus® (Semaglutide) – Key Information

Please see SmPC for full clinical information – www.medicines.org.uk

Mode of Action

Rybelsus® (oral semaglutide) is a long-acting oral GLP-1 RA that is administered once daily for the treatment of type 2 diabetes mellitus in adults. The medicine has a low bioavailability and therefore requires daily dosing on an empty stomach, however its half-life is the same as injectable semaglutide.

Although there are no head-to-head studies that compared the final approved doses of Rybelsus® (oral semaglutide) to Ozempic®(injectable semaglutide), 14mg of Rybelsus® daily is approximately equivalent to 0.5mg subcutaneously once weekly of Ozempic®.

Common Side effects

GLP-1 receptor agonist drugs lower glucose levels by reducing appetite (cerebral effect and by delaying gastric emptying) and stimulate the release of insulin while also reducing glucagon levels. The delayed gastric emptying can lead to nausea and vomiting, diarrhoea, and reflux symptoms. People with type 2 diabetes, particularly the elderly, should be advised to maintain good hydration should they develop gastrointestinal side effects to avoid dehydration and possible subsequent acute kidney injury (AKI).

Serious Side Effects

Cases of pancreatitis have been reported in people using semaglutide. People with type 2 diabetes should be advised to seek medical advice immediately if they experience **severe** and **persistent** abdominal pain, nausea, or vomiting.

Rybelsus® is a black triangle drug, all side effects should be reported using the yellow card system at: www.mhra.gov.uk/yellowcard

Contraindications

The SmPC lists only hypersensitivity to active substance or excipients listed. However, there is still uncertainty about the role of GLP-1 RA in the development of medullary thyroid carcinomas in humans. Until there is further understanding, and as with all GLP-1 RA, it would be reasonable to consider GLP-1 RAs should be avoided in those with a personal or family history of medullary thyroid carcinoma and in those with multiple endocrine neoplasia syndrome type 2 (MEN 2). This is in line with the US licence for Rybelsus®.

Notable Drug Interactions

Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Rybelsus® specifically contains an absorption enhancer sodium N- (8- [2-hydroxybenzoyl] amino) caprylate (SNAC) which may increase the total exposure of certain medications. Increased monitoring is recommended for:

- Levothyroxine: Total exposure of levothyroxine was increased by 33% following combined administration. Thyroid parameter monitoring should be considered 6-8 weeks after initiation for those on concomitant levothyroxine. (There may be an opportunity to move Levothyroxine to dosing at bedtime as this medicine does not need specifically morning dosing to ensure both continue to be

taken on an empty stomach)

- Warfarin — Did not change the total exposure to warfarin. Manufacturer advice is to monitor INR at initiation. Practically this can occur 5-7 days after initiation of Rybelsus®, and if INR is in range, return to the usual monitoring thereafter.
- Rosuvastatin: The total exposure of rosuvastatin was increased by 41%. For those who have been prone to statin related side effects, they can be asked to watch for this, or pre-emptive dose reduction could be made where suitable, doses could also be reduced where symptoms suggest this is needed.
- Other antidiabetic drugs — due to the increased risk of hypoglycaemia, dose of concomitant sulfonylurea and/or insulin may need to be reduced. For those on sulfonylureas or insulin, a recent HbA1c should be available along with blood glucose readings to support dose adjustment / sulfonylurea cessation and safe initiation of Rybelsus®.

Initial prescribing

Dosing Regimen	• Take 3mg once daily for 1 month, • then 7mg once daily for at least 1 month, • where if tolerated the dose can be increased to 14mg once daily thereafter. • **Do not use two 7mg tablets to achieve the 14mg dose.**
Administration instructions	• Ensure tablets are taken on an empty stomach (at least 2 hours after previous oral intake) • Take tablets with a sip of water only. Up to 120ml can be used, but more than this reduces absorption. • Wait at least 30 minutes before eating or drinking or taking any other medicines. Waiting less than 30 minutes reduces absorption.

Administration and Practical advice for people with T2DM

- Rybelsus® (oral semaglutide) is a long-acting oral GLP-1 RA that is administered once daily, that takes 5-6 weeks to reach steady state in the body
- Rybelsus® (oral semaglutide) is available in 3mg, 7mg and 14mg tablets
- The tablets need to be taken on an empty stomach, away from food or other medications.
- The tablets need to be taken with only a small amount of water – this is stated as up to 120ml (half a glass), but a sip is enough and is preferred.
- Tablets should not be split, crushed, or chewed.
- Concomitant medications should be checked and if possible, interaction highlighted, increased monitoring put in place as described above.
- Ensure sick day guidance given (ensure adequate fluid intake through any acute dehydrating illness and when to seek advice)
- Give side-effect minimisation advice:
    - Reduce portion size
    - Respond to feeling of fullness and stop eating rather than clear the plate
    - Avoid overly fatty or fried foods
    - Maintain adequate fluid intake
    - Reassure that symptoms are often mild and transient
    - Most people are able to continue medication despite initial nausea.

Storage

Rybelsus® (oral semaglutide) should not be included in a 'dosette' box due to the need to protect from light and moisture.

Retinopathy

In a pooled analysis of glycaemic control trials with Rybelsus®, people reported diabetic retinopathy related adverse reactions during the trial (4.2% with Rybelsus® and 3.8% with comparator). In a 2-year trial with semaglutide injection involving people with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in those treated with semaglutide injection (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among those with a history of diabetic retinopathy at baseline than among those without a known history of diabetic retinopathy.

Rapid improvement in glucose control has been associated with a worsening of diabetic retinopathy and cannot be excluded as a mechanism. Until further UK/international consensus guidelines are available, we suggest the following for initiation of Rybelsus® (oral semaglutide). (see figure 1 for visual representation)

- Those with an HbA1c **less than** 86mmol/mol (10%) with normal eye screening (R0M0) or background changes (R1) in the last 2 years can continue with usual interval for eye screening - Discuss/educate person about risks, including asking them to report significant visual changes prior to initiation of treatment, and prompt importance of continued attendance for eye screening.

- Significantly elevated HbA1c, e.g. 86mmol/mol (10%) **or higher**, in a person with normal eye screening (R0M0) in the last 2 years can continue with usual interval for eye screening- Discuss/educate person about risks, including asking them to report significant visual changes prior to initiation of treatment, and prompt importance of continued attendance for eye screening.

- Significantly elevated HbA1c, e.g. 86mmol/mol (10%) **or higher**, in a person with established background retinopathy (R1) - consider discussion (or Advice & Guidance) with local diabetes team prior to initiation of treatment.

- Those with active eye disease (R2/R3 or M1) or equivalent*, under specialist ophthalmology services - should be discussed with their specialist team prior to initiation to allow an individualised risk/benefit approach to treatment and monitoring to be formulated.

*if document is used outside of England and Wales

Mounjaro® (Tirzepatide) – Key Information

Please see SmPC for full clinical information – www.medicines.org.uk

Mode of Action

Mounjaro® (Tirzepatide) is a first in class long-acting dual glucose-dependent insulinotropic polypeptide GIP/GLP-1 RA) for the treatment of type 2 diabetes mellitus in adults. NICE TA 924 has positioned Mounjaro® the same as GLP-1 RAs, and the same criteria for prescribing and continuing treatment apply.

Common Side effects

Dual GIP/GLP-1 receptor agonist drugs lower glucose levels by reducing appetite (cerebral effect and by delaying gastric emptying) and stimulate the release of insulin while also reducing glucagon levels. The delayed gastric emptying can lead to nausea and vomiting, diarrhoea, and reflux symptoms. People with type 2 diabetes, particularly the elderly, should be advised to maintain good hydration should they develop gastrointestinal side effects to avoid dehydration and possible subsequent acute kidney injury (AKI).

Serious Side Effects

Cases of pancreatitis have been reported in people using tirzepatide. People with type 2 diabetes should be advised to seek medical advice immediately if they experience **severe** and **persistent** abdominal pain, nausea, or vomiting.

Tirzepatide is a black triangle drug, all side effects should be reported using the yellow card system at: www.mhra.gov.uk/yellowcard

Contraindications

The SPC lists only hypersensitivity to active substance or excipients listed. However, there is still uncertainty about the role of GLP-1 RA and GIP/GLP-1 RA in the development of medullary thyroid carcinomas in humans. Until there is further understanding and as with all GLP-1 RA, it would be reasonable to consider GIP/GLP-1 RAs should be avoided in those with a personal or family history of medullary thyroid carcinoma and in those with multiple endocrine neoplasia syndrome type 2 (MEN 2). This is in line with the US licence for this tirzepatide.

Notable Drug Interactions

Tirzepatide delays gastric emptying and has the potential to impact the rate of absorption of oral medicines administered at the same time. No dose adjustments are expected to be required for most concomitantly administered oral medicinal products. However, it is recommended to monitor persons on:

- Narrow Therapeutic Index Medicines: oral medicinal products with a narrow therapeutic index (e.g., warfarin, digoxin), especially at initiation of tirzepatide treatment and following dose increases.
- Warfarin — may possibly enhance the anticoagulant effect of warfarin. Manufacturer advice is to monitor INR at initiation. Practically this can occur 5-7 days after initiation of tirzepatide, and if INR is in range, return to the usual monitoring thereafter.
- Rapid Onset Effect: The risk of delayed effect should also be considered for oral medicinal products for which a rapid onset of effect is of importance.
- Other antidiabetic drugs — due to the increased risk of hypoglycaemia, dose of concomitant sulfonylurea and/or insulin may need to be reduced. For those on sulfonylureas or insulin, a recent HbA1c should be available along with glucose levels to support dose adjustment / sulfonylurea cessation and safe initiation or tirzepatide.

- Oral Contraceptives: No dose adjustment of oral contraceptives is required in women with normal BMI. There is limited information about the effect of tirzepatide on oral contraceptives in women with obesity or who are overweight. Since reduced efficacy of oral contraceptives cannot be excluded, it is advised switching to a non-oral contraceptive method or add a barrier method of contraception upon initiating tirzepatide therapy (for 4 weeks), or after each dose escalation (for 4 weeks).

Initial prescribing

Device	Mounjaro® (tirzepatide) KwikPen 2.5mg/0.6ml solution for injection 2.4ml pre-filled pen (1 pen/4 doses) * *This may need to be a free typed or handwritten prescription whilst prescribing systems are updated
Delivery	4mm insulin pen needles (or any other 4mm insulin pen needles costing < £3 per 100) x 1 box
Destruction	1 Litre Sharpsguard container

Administration and Practical advice to people with T2DM

- Mounjaro® (tirzepatide) is a long-acting injection that takes approximately four weeks to reach steady state in the body
- Mounjaro® KwikPen is a disposable multi-dose single-patient-use pre-filled pen. Each pen contains 4 doses of Mounjaro® either 2.5mg, 5mg, 7.5mg, 10mg, 12.5mg or 15mg.
- The pen contains 3ml of solution of which 2.4mls is used for administration (0.6ml x 4 doses). Excess solution in the pen after use should be discarded.
- Mounjaro® is a clear, colourless to slightly yellow solution.
- Each pen dials one specified dose (designated by a 1 on the dial and the dose can be seen on the label and is colour co-ordinated) and allows you to prime the pen using an 'air-shot', which is two clicks from 0 on the dial and designated by an extended line (-).
- Increased monitoring is needed for people who are initiating or switching onto this medication. Adjustments may be needed in sulphonylurea and insulin doses.
- Good injection technique should be followed: trendDiabetes – Injection technique matters -
- The day of weekly administration can be changed, if necessary, as long as the time between two doses is at least 3 days.
- The dose can be administered at any time of day, with or without meals, and should be injected subcutaneously in the abdomen, thigh, or the upper arm. If a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day.
- No dose adjustments are needed for renal impairment (including ESRD) or hepatic impairment. (Please note advice around benzyl alcohol content below.)
- The pharmaceutical manufacturer recommends swabbing the pen prior to use in its device user manuals. This practice is not something that is universally recommended or commonly part of injection education in the UK for other non-insulin and insulin injectable pen devices. Should there be a wish to follow the user manual, please ensure an alcohol swab is advised, and note that these cannot be provided on prescription.

- Concomitant medications should be checked and if possible, interaction highlighted, increased monitoring put in place as described above.
- Ensure sick day guidance given (ensure adequate fluid intake through any acute dehydrating illness and when to seek advice)
- Give side-effect minimisation advice:
    - Reduce portion size
    - Respond to feeling of fullness and stop eating rather than clear the plate
    - Avoid overly fatty or fried foods
    - Maintain adequate fluid intake
    - Reassure that symptoms are often mild and transient
    - Most people are able to continue medication despite initial nausea.

Storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Mounjaro® may be stored unrefrigerated for up to 30 days at a temperature not above 30 °C and then the pre-filled KwikPen must be discarded.

Retinopathy

Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular oedema, and should be used with caution in these patients with appropriate monitoring. Rapid improvement in glucose control has been associated with a worsening of diabetic retinopathy so we understand that there may be some concern over this with initiation of Mounjaro® (tirzepatide) in primary care. The clinical trials to date have excluded patients with retinopathy so we are lacking clear clinical evidence on the topic. While clinical experience is gained and in the absence of a UK/international consensus guidelines, we suggest the following for initiation of Mounjaro® (tirzepatide). (see figure 1 for visual representation)

- Those with an HbA1c **less than** 86mmol/mol (10%) with normal eye screening (R0M0) or background changes (R1) in the last two years can continue with usual interval for eye screening. Discuss/educate person about risks, including asking them to report significant visual changes prior to initiation of treatment, and prompt importance of continued attendance for eye screening.

- Significantly elevated HbA1c, e.g. 86mmol/mol (10%) **or higher**, in a person with normal eye screening (R0M0) in the last 2 years - discuss/educate person about risks, including asking them to report significant visual changes prior to initiation of treatment, and prompt importance of continued attendance for eye screening.

- Significantly elevated HbA1c, e.g. 86mmol/mol (10%) **or higher**, in a person with established background retinopathy (R1) - consider discussion (or Advice & Guidance) with local diabetes team prior to initiation of treatment.

- Those with active eye disease (R2/R3 or M1) or equivalent*, under specialist ophthalmology services - should be discussed with their specialist team prior to initiation to allow an individualised risk/benefit approach to treatment and monitoring to be formulated.

*if document is used outside of England and Wales

Excipients – Benzyl Alcohol

The tirzepatide (Mounjaro) Kwikpen contains benzyl alcohol as a preservative. Since 2017 the EMA has required patient information leaflets (PIL) for products containing benzyl alcohol to contain the additional wording:

Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis")

In addition to these requirements the manufacturer has stated in its summary of product characteristics (SmPC):

Patients with hepatic or renal impairment should be informed of the potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time.

Tirzepatide Kwikpen formulation contains 5.4mg of Benzyl Alcohol per 0.6ml dose. Benzyl alcohol is a common excipient used in medications often at significantly higher dose exposures. For comparison Amiodarone intravenously contains 20mg/ml with a single 300mg loading dose containing 120mg of Benzyl Alcohol.

In adults the presence of this excipient has a theoretical risk only, where there is no guidance currently as to what degree of hepatic or renal impairment is significant, and the minimum amount at which toxicity may occur is not known. The ongoing documented concerns are with using significantly large dose exposures, in newborn babies (pre- and full-term) and those under the age of 3 years old due to metabolic immaturity.

If a person asks about metabolic acidosis concerns with tirzepatide, it would be reasonable to explain that in adults, this is a theoretical risk only. It can be explained that metabolic acidosis is where your body fluids contain too much acid, either making too much or not getting rid of enough. Not everyone will have any signs of symptoms, but they include, long and deep breaths, fast heartbeat, headache and/or confusion, or nausea and/or vomiting.

Considerations for Muslims and those of other faiths that prohibit alcohol: The following information is specifically relating to Islam, but the core principles remain when considering alcohol within other religions. Benzyl alcohol is a synthetic alcohol which can raise questions regarding the use of an alcohol in a medicine taken (injected) internally and whether it is considered Halal (permissible). Benzyl alcohol is not the same as ethanol, would be considered non-intoxicating, not sourced from dates of grapes, and is commonly used in cosmetics that are widely considered as Halal (permissible). There may still be a difference of opinion on the issue, along with personal preference and therefore for some people, other alternatives should be considered first should they be available. It should never be assumed that every individual is compliant with all of the practices within Islam, therefore healthcare professionals are advised to consult with each person as an individual to ascertain their views and beliefs.

Further information regarding Benzyl Alcohol can be found here:

Questions and answers on benzyl alcohol used as an excipient in medicinal products for human use (europa.eu)

Switching to Rybelsus® (oral semaglutide) or Mounjaro® (Tirzepatide)

It may now be appropriate to switch people with T2DM to an alternative GLP-1 RA or GIP/GLP-1 RA who are unable to obtain supply of their usual GLP-1 RA medication and who still meet the continuation criteria as outlined in NICE NG28. A clinical review of the patient case should still take place prior to consideration of switching where a clinical decision should be made as to whether a GLP-1 RA or GIP/GLP-1 RA is the most appropriate choice in the circumstances. There may be an alternative therapy more appropriate, or the possible need for insulin.

There are very little data for switching between different GLP-1 RA or switching to a GIP/GLP-1 RA, therefore in most cases it would be reasonable to follow the licenced dose initiation for each product given the need for them all to gradually reach steady state. The exception to this would be converting from Ozempic® (semaglutide) to Rybelsus® (oral semaglutide) with less than two doses missed, where an approximate equivalent dose can be given.

	Switch to Mounjaro® (Tirzepatide)	Switch to Rybelsus® (oral semaglutide)
• Byetta® (exenatide) 5micrograms/0.02ml and 10micrograms/0.04ml pre-filled pens • Victoza® (liraglutide) 6mg/ml solution for injection • Trulicity® (dulaglutide) 0.75mg, 1.5mg, 3mg and 4.5mg injections • Bydureon BCise® (exenatide) 2mg/0.85ml prolonged-release pre-filled pens	Start at 2.5mg once weekly and titrate up according to product licence **NB** – please note that the majority of glucose reduction occurs with the 5mg treatment dose.	Start at 3mg once daily dose and titrate up according to product licence
Ozempic®(semaglutide) 0.25mg, 0.5mg and 1mg injection **(Two or more doses missed)**	Start at 2.5mg once weekly and titrate up according to product licence **NB** – please note that the majority of glucose reduction	Start at 3mg once daily dose and titrate up according to product licence

	occurs with the 5mg treatment dose.	
Ozempic®(semaglutide) 0.25mg, 0.5mg and 1mg injection **(Fewer than two doses missed)**	Start at 2.5mg once weekly and titrate up according to product licence **NB** – please note that the majority of glucose reduction occurs with the 5mg treatment dose.	Can convert over to approximate equivalent dose: • Ozempic® 0.25mg = 7mg once daily Rybelsus® • Ozempic® 0.5mg = 14mg once daily Rybelsus® • Ozempic® 1mg = 14mg once daily Rybelsus®

Where insulin therapy is required

Where insulin therapy is clinically indicated, clinicians are advised to initiate in accordance with NICE NG28 https://www.nice.org.uk/guidance/ng28/chapter/recommendations - insulin-based-treatments.

The choice of insulin should take account of individual characteristics and clinical needs of the person with T2DM.

Where possible, utilise the full range of insulins and devices available to reduce the risk of further impacting supply chain issues.

Advice for people with T2DM

Counterfeit products

People with T2DM should be advised that GLP-1 RAs should only be obtained on prescription from registered pharmacies. It is not legal to obtain GLP-1 RA without a prescription and there is a risk that the medicine may not be genuine. Please see the governments website for further information.

Structured education

People with T2DM requiring a change to their usual medication may welcome an opportunity to access structured education to support self-management. In addition to local services, offer access to structured education at https://healthyliving.nhs.uk/.

Weight management

Eligible people with T2DM who would like support with weight management should be signposted to available weight management programmes. In addition to local pathways, there are several nationally available options, including such as:

- Adult weight management: short conversations with patients
- The NHS Digital Weight Management Programme
- Tier 1 and 2 weight management services
- NHS type 2 diabetes path to remission programme
- https://www.nhs.uk/better-health/lose-weight/

Re-commencing GLP-1 RA therapy when the period of national shortage has passed

The national shortage of GLP-1 RAs is expected to extend into late 2024.

When GLP-1 RAs are regularly and reliably available again, it will be possible re-commence prescribing GLP-1 RAs (excluding Byetta®) for people with T2DM meeting the eligibility criteria as per NICE NG28. Where GLP-1 RA has been prescribed previously, review whether a beneficial metabolic response was achieved. Where there was no beneficial therapeutic response, consider alternative glucose lowering therapies (See Figure 2). Each ICB may take a different stance on the merits of continuity of prescribing Rybelsus® or Mounjaro® versus reverting back to Ozempic or Dulaglutide when available. Please refer to your local prescribing guidance when this is available where continuation is indicated as outlined in NICE NG28.

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 GLP1 mimetic for adults with type 2 diabetes who:

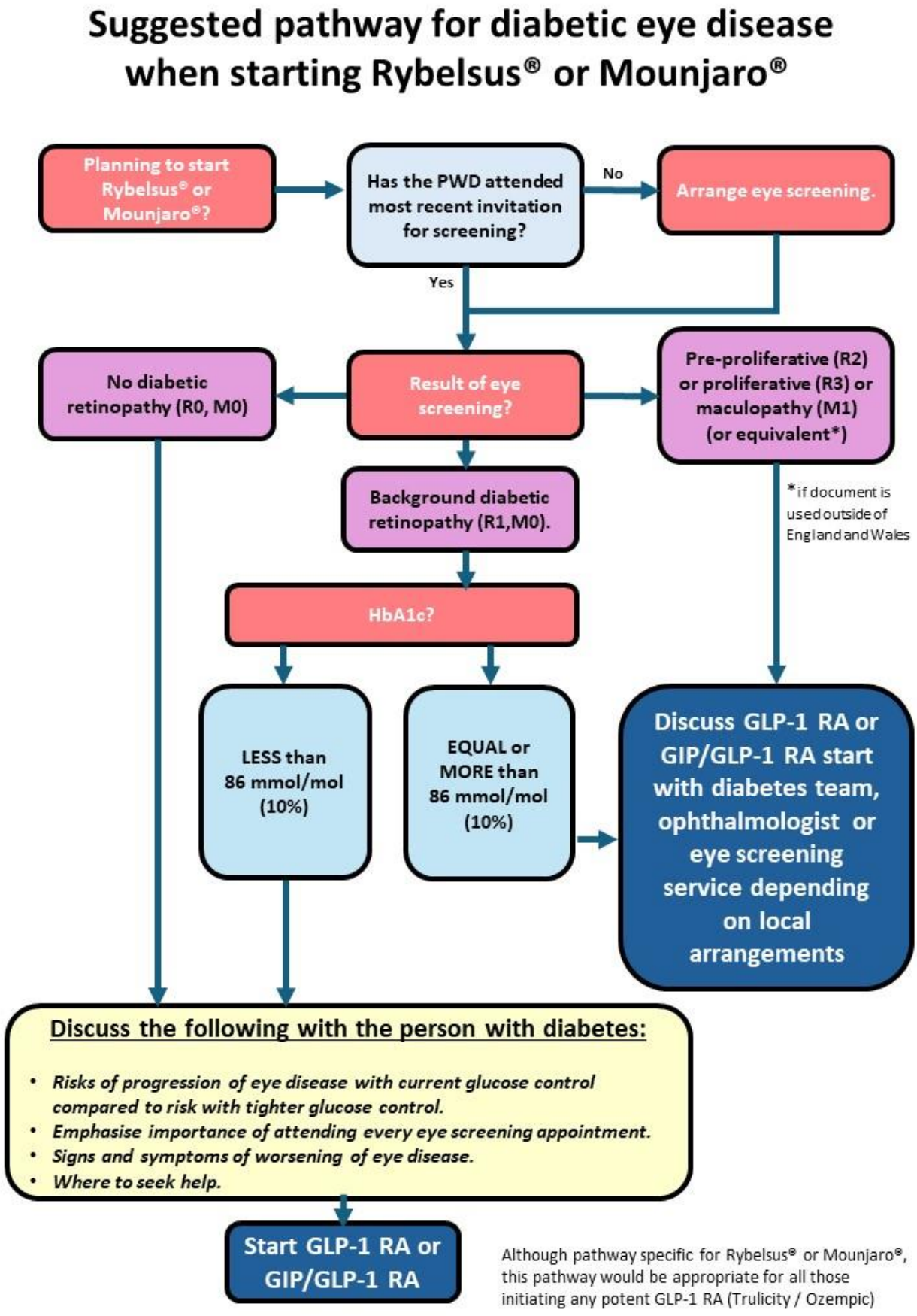
- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian, and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and:**
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity-related comorbidities. **[2015, amended 2022]**

1.7.22 Only continue GLP-1 mimetic therapy if the adult with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA_{1c} and weight loss of at least 3% of initial body weight in 6 months). **[2015]**

1.7.23 For adults with type 2 diabetes, only offer combination therapy with a GLP-1 mimetic and insulin along with specialist care advice and ongoing support from a consultant-led multidisciplinary team. **[2015]**

For up-to-date information on current availability and supply issues affecting GLP-1 RAs, see https://www.sps.nhs.uk/home/tools/medicines-supply-tool/ [subscription required] or Prescribing available GLP-1 receptor agonists – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice or contact your local Prescribing Advisor/Medicines Optimisation Team.

Figure 1. Suggested Pathway for Diabetic Eye Disease



Association of British Clinical Diabetologists

PCDS Primary Care Diabetes Society

Figure 2. Oral Glucose Lowering Therapies by Class.

Class	Biguanides	Sodium Glucose Co-Transporter-2 Inhibitors (SGLT2i)- "Gliflozins"	Dipeptidyl Peptidase 4 Inhibitors (DDP4i) - "Gliptins"	Sulfonylureas	Thiazolidinedione
Medicines	Metformin	Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin	Alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin	Gliclazide, glipizide, glimepiride, glibenclamide and tolbutamide	Pioglitazone
When best to use	• Ensure metformin is taken with food. If gastrointestinal side-effects develop consider switching to modified release • If hypoglycaemia is a concern • People concerned about weight gain and wanting an agent that offers some weight loss/weight neutrality	• If hypoglycaemia is a concern • If the person is at high cardiovascular risk • Established heart failure or chronic kidney disease (CKD) consider a SGLT2i licenced for these indications in addition to diabetes • People concerned about weight gain and wanting an agent that offers some weight loss/weight neutrality	• If hypoglycaemia is a concern	• In people with high HbA_{1c} as rescue therapy • Symptomatic hyperglycaemia	• Fatty liver disease • If people have deranged lipid profile it can increase HDL and lower LDL/TG • If hypoglycaemia is a concern • Can be continued in renal impairment
When to be cautious/not use	• If eGFR<45ml/min review dose and stop if eGFR <30ml/min/1.73m^2	• If high HbA_{1c} >86mmol/mol • History of DKA • If renal function is <45ml/min then the SGLT2i will have minimal effect on blood glucose however effects for heart failure and CKD remain • Elderly, risk of volume depletion • History of recurrent urinary tract infection/urosepsis/genital infections • Use "Sick Day Rules" guidance • Preconception/pregnancy • Risk of hypoglycaemia if concomitant use with sulfonylurea or basal insulin therapy. Consider reducing dose of sulfonylurea or insulin (c. 25% insulin dose reduction)	• Dose adjustments required (except linagliptin). See BNF for dosing instructions by product and eGFR • Avoid in patients with a history of pancreatitis • Avoid saxagliptin in heart failure • Preconception/ pregnancy	• Consider alternatives in occupations where hypoglycaemia is likely to cause issues • Use cautious dosing and slower titrations in people with renal impairment • In the elderly where hypoglycaemia may be more concerning (set higher HbA1c targets and titrate cautiously with appropriate monitoring) • Preconception/pregnancy	• Oedema or heart failure • Low bone mineral density (incl. post-menopausal women) • Avoid if current or history of bladder cancer or unexplained haematuria • Be aware of weight gain (lower doses can be used where this is more of an issue) • Significant liver impairment • Preconception/pregnancy
Expected HbA_{1c} drop	• 1-2% (11-22mmol/mol)	• 1-1.5% (11-17mmol/mol)	• 0.5-0.8% (6-9mmol/mol)	• 1-2% (11-22mmol/mol)	• 0.5-1.4% (5-15 mmol/mol)
For further information please refer to NICE guidelines, British National Formerly and the Electronic Medicines Compendium					