Guidelines for the Management of Type 2 Diabetes in Adults

Document history

Version	Date updated	Main changes/comments	Created/updated by
1	September 2020	Kent and Medway guidelines created to include NICE NG28, EASD-ADA guidelines and existing guidance documents from east Kent, west Kent, DGS and Medway Swale localities.	Tapan Shah Yiki Chi Sola Akeremale
2	September 2021	Updated as per new NICE guidelines (draft consultation)	Amali Gamaarachchi
3	March 2022	Updated as per NICE 2022 update, removed references to ADA/EASD guidelines	Amali Gamaarachchi Tapan Shah
4	April 2022	Further updates and clarification on use in SGLT2i in CKD, formulary status for SGLT2i and GLP-1.	Amali Gamaarachchi Tapan Shah
5	June 2022	Changes made from comments received- SGLT2i recommendations and counselling points, formulary changes, GLP-1 PITstop templates, pioglitazole for NALFD, guidance on m/r gliclazide, algorithm comments. GLP-1 use in pathway	Tapan Shah Amali Gamaarachchi
6	June 2022	Further update in algorithm to include SGLT2i choices based on evidence, GLP-1 use in pathway, language around oral semaglutide based on comments.	Tapan Shah
7	July 2022	Updates on name change of organisation, comments from DGS MOG, DVH, EKHUFT, M&S MOG and preferred metformin m/r preps	Tapan Shah Amali Gamaarachchi

Acknowledgements to Medway & Swale, DGS, West and East Kent localities for their input into and sharing their guidance. The information below is correct to best intentions when agreed through governance routes. This document is for use within the NHS only and not for commercial purposes . This document serves and guidance and shares best practice it is not intended to replace clinical judgement.

Approved by JPC Ratified by Kate Langford
Ratified Date: Aug 2022
Review Date: Aug 2024

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INTRODUCTION

The aim of this guideline is to bring together the latest evidence in the pharmacological management of type 2 diabetes (T2DM) across Kent and Medway. This covers the treatment algorithm, formulary choices and safe prescribing of these agents.

The goals of treatment for type 2 diabetes are to prevent or delay complications and maintain quality of life. This requires control of glycaemia and cardiovascular risk factor management, regular follow-up and, importantly, a patient-centred approach to enhance patient engagement in self-care activities.

Careful consideration of patient factors and preferences must inform the process of individualising treatment goals and strategies. Failure to manage T2DM can put patients at higher risk of developing cardiovascular disease (CVD), renal dysfunction, and other microvascular and macrovascular complications. Diabetes is likely to account for up to 10% of NHS expenditure with the prevalence of adult (aged 17 years or above) diabetes across Kent, Surrey and Sussex estimated at 7.3% of the population.[1]

Typically, a patient with T2DM will spend less than an hour with a healthcare professional each year and will spend the remaining 8000+ hours managing their condition alone. It is therefore imperative that each patient is offered appropriate education, and a comprehensive diabetes review, to ensure concordance to medication and lifestyle measures.

Every week in the UK, diabetes leads to 169 amputations, 680 strokes, 530 heart attacks, and almost 2000 cases of heart failure (HF). Over 500 people with diabetes die prematurely each week. 12.3 million people are at risk of developing T2DM in the UK emphasising the importance of a good glycaemic control.[2]

People with diabetes who are at the end of life have a specific set of care needs including those relating to health and social care. End of life diabetes care has been recognised as an area lacking quality standards and guidance on best clinical practice. Therefore, this document produced by Diabetes UK provides a high quality approach towards end of life care for people with diabetes by providing a series of clinical care recommendations.

Guidelines around T2DM management are changing as new risks and/or benefits come to light. These guidelines have been updated to consider the 2022 NICE guidelines as the primary reference point for the pharmacological management of type 2 diabetes. Formulary choices will change over time and the formulary choices should be checked against latest information on the various Kent and Medway formulary webpages. Local clinicians have been asked for their view on these guidelines as well as an practical points and these are captured in the document below.

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1. RECOMMENDATIONS FOR TYPE 2 DIABETES MEDICATION REVIEW

In preparation for the review sufficient time should be arranged to help facilitate a thorough review. A good quality review will reduce time spent for future reviews if sufficient time allows for better understanding and management of the diabetes.

At all appointments the following points should be discussed with the patient. (See appendix 1 for a checklist).[3] This is not an exhaustive list of points which should be covered during the review. NICE have also produced a visual aid (see p6) that supplements the points below [4]

- Offer all patients structured education and integrate dietary advice with a personalised diabetes management plan, including other aspects of lifestyle modification, such as increasing physical activity and losing weight. A collaborative care plan should be devised with individual targets including some of the points below. This should be reviewed and reinforced at every review at least annually.
- Please provide patients with the Diabetes UK Patient Information Prescriptions which outlines further lifestyle and diabetes management advice to patients. These patient information prescriptions contain information on HbA1c, blood pressure, cholesterol, foot care, being active, eating well and much more.
- Check medication adherence and discuss any concerns with diabetes or medication with the patient.
- Review current medication ensuring side effects and effectiveness are considered and discussed. Advice should be given on how to identify and manage hypoglycaemia if this may occur. Measure HbA1c levels in adults with type 2 diabetes every:
    - 3 to 6 months (tailored to individual needs) until HbA1c is stable on unchanging therapy
    - 6 months once the HbA1c level and blood glucose lowering therapy are stable.
- Patients who are using insulin must have their insulin passport/safety card checked and updated at every diabetes review. For further recommendations on insulin see section 3.

    - NICE has produced a patient decision aid on agreeing HbA1c targets, which also covers factors to weigh up when discussing HbA1c targets with patients.
    - Discuss and agree an individual HbA1c target with adults with type 2 diabetes. Encourage them to reach their target and maintain it, unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target impair their quality of life. Think about using the NICE patient decision aid on weighing up HbA1c targets to support these discussions as well as the characteristics of each medication class (appendix 2).
    - For adults whose type 2 diabetes is managed either by lifestyle and diet, or lifestyle and diet combined with a single drug not associated with hypoglycaemia, support them to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, support them to aim for an HbA1c level of 53 mmol/mol (7.0%)
    - In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:
      reinforce advice about diet, lifestyle and adherence to drug treatment and
    - support the person to aim for an HbA1c level of 53 mmol/mol (7.0%) and Intensify drug treatment.

- Consider relaxing the target HbA1c level on a case-by-case basis and in discussion with adults with type 2 diabetes, with particular consideration for people who are older or frailer, if:
    - they are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy
    - tight blood glucose control would put them at high risk if they developed hypoglycaemia, for example, if they are at risk of falling, they have impaired awareness of hypoglycaemia, or they drive or operate machinery as part of their job
    - intensive management would not be appropriate, for example if they have significant comorbidities.

- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia, is pregnant/planning to become pregnant or there is evidence of hypoglycaemic episodes.
- Driving advice: this should be an individualised decision by the clinician, using the DVLA guidance (https://www.gov.uk/government/publications/at-a-glance) and advice from diabetes.org.uk. Discussions around this with the patient should be clearly documented.
    - Note on Group 2 drivers: clinicians should discuss with patients who are Group2 drivers that starting insulin would not invalidate their driving license. It should also be reminded that isCGM ("flash") or rtCGM devices are no permitted for the purposes of group2 driving and licensing- group 2 drivers must continue to monitor finger prick capillary blood glucose levels. ***The provision of CGM/Flash for people with type 2 diabetes on insulin is under review and a separate guidance will be issued in due course.***
- The 8 key care processes[5] should be reviewed in order to reduce overall risk of disease progression and complications.
- It is important to consider the psychological impact which diabetes can have on the patient. This should be explored with the patient and managed in line with current national guidelines.
- SICK DAY RULES- See appendix (It is important that sick day rule advice is given to patients on managing episodes of intercurrent illness (see appendix 9 below). Information for patients is available here from diabetes UK.

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RECOMMENDED APPROACH FOR GLUCOSE-LOWERING MEDICATION SELECTION IN TYPE 2 DIABETES[4]- adapted from NG28

For rescue therapy: For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review use when blood glucose control has been achieved

ASSESS

FIRST LINE THERAPY

(refer to SPCs for drug details and relevant sections within this guidance)

FURTHER INTERVENTIONS

(refer to SPCs for drug details and relevant sections within this guidance)

Lifestyle advice (diet and physical activity) should be tailored to the individual at all stages

Assess HbA1c, cardiovascular risk and kidney function

Not at high risk CVD risk	Chronic heart failure or established atherosclerotic CVD	High risk of CVD (QRISK2 of 10% or higher)	Type 2 diabetes in adults with CKD take ARB or ACE inhibitor (titrated to highest licensed tolerated dose)
Offer Metformin (or if GI disturbance Metformin MR)	**Offer** Metformin (or if GI disturbance Metformin MR)	**Offer** Metformin (or if GI disturbance Metformin MR)	**Consider** SGLT2i in addition to ARB or ACE if ACR between 3 and 30 mg/mmol- see section 2.2 below for further information **Offer** SGLT2i in addition to ARB or ACE if ACR > 30mg/mmol
If metformin contraindicated **Consider DPP4i, TZD*, SU or SGLT2i**	Once metformin tolerability is confirmed **Offer** SGLT2i with proven cardiovascular benefit (see below for further information) If metformin contraindicated offer SGLT2i alone	Once metformin tolerability is confirmed **Offer** SGLT2i with proven cardiovascular benefit (see below for further information) If metformin contraindicated offer SGLT2i alone	

Information on SGLT2i choices

Patients with T2DM and CVD, HF or risk evidence suggests in no specific order- dapagliflozin, canagliflozin and empagliflozin

Patients with T2DM and CKD in no specific order- dapagliflozin and canagliflozin

Ertugliflozin remains an option but is not licensed for where CKD, ASCVD or HF are co-morbidities with type 2 diabetes

At any point: Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

HBA1c not controlled below individually agreed threshold	If a person has or develops chronic heart failure or established atherosclerotic CVD	Person has or develops a high risk of CVD (QRISK2 of 10% or higher)
Switching or adding treatments **Consider** DPP4i, TZD or SU SGLT2i in **dual** or **triple** therapy	**Switching or adding treatments** **Offer** SGLT2i (if not already prescribed) (also see note re GLP-1 mimetics below)	**Switching or adding treatments** **Consider** SGLT2i (if not already prescribed) (also see note re GLP-1 mimetics below)

Further interventions

Consider insulin therapy, when dual therapy has not continued to control HbA1c to below the person's individually agreed threshold (with or without other drugs). See notes below regarding prescribing points around insulin

NB ADA/EASD guidelines discuss earlier use where established CVD or risk of CVD in patients with type 2 diabetes. See notes below

Consider GLP-1, 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.

Use of GLP-1 mimetics also as per clinician and patient discussion

NB: Boxes with dashed outline are adapted from the algorithm from NICE guidelines- these boxes are based on feedback from local clinicians rather than an extract from NICE guidelines

Notes on the algorithm above

- Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.
- At each point follow the prescribing guidance.
- Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
- In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label.
- NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:
  • who cannot have metformin
  • for whom diet and exercise alone do not provide adequate glycaemic control.
  - The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

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2.1 Metformin

Metformin standard release is the drug of choice for first line treatment of adults with type 2 diabetes. Some evidence shows that it may have a greater effect than sulfonylureas for reduction in diabetic complications including cardiovascular effects, stroke, and all-cause mortality.

The dose of metformin should be titrated gradually to minimise the risk of gastrointestinal side effects. This should be done over several weeks. If a patient develops side effects at any stage during this process they should remain on that dose for a further week before increasing the dose further.

For those patients who still cannot tolerate metformin standard release despite slow titration, a trial of modified release metformin should be considered in line with NICE recommendations. It may be more cost effective to prescribe metformin MR by brand. **At the current time Sukkarto SR or generic m/r metformin are the preferred preparations across NHS Kent and Medway.**

In NHS Kent and Medway there is a higher proportion use of modified release preparations of all metformin items compared to that seen nationally. It is important that this guidance from NICE is considered before prescribing modified release preparations 1st line.

NICE Do not do recommendation: In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m2:

- Stop metformin if the eGFR is below 30 ml/minute/ 1.73m2

Give information regarding "sick day rules" for this medication (see appendix 9)

See appendix 3 for further details of metformin.

2.2 Sodium glucose co-transporter-2 inhibitors (SGLT2i)

The glucose lowering effect of SGLT2i is dependent on sufficient renal function. This class of anti-diabetics also has blood pressure and weight lowering effects. Drugs in this class include (in no order) canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.

Within Kent and Medway all SGLT2i are on formulary. They can be initiated in both primary and secondary care with appropriate counselling and monitoring. Please refer to the supplementary Kent and Medway guide on the SGLT2i on type 2 diabetes document for further information. Whilst some agents SPC give specific guidance on monitoring of renal function others do not. Renal function should be measured

- At initiation to ensure correct dose is started (depending upon agent)
- Additional monitoring after starting SGLT2 inhibitors is NOT required but refer to each SPC.
- Routine monitoring of kidney function should continue as part of routine care, frequency guided by national and local guidance for T2DM, and in line with person's other co-morbidities as appropriate, but additional routine tests are not required after starting SGLT2i therapy.

Current evidence shows that for those patients with type 2 diabetes and ASSCVD or HF canagliflozin, dapagliflozin or empagliflozin are preferrable (no preference in order). For those with CKD canagliflozin and dapagliflozin are preferrable (no preference in order). Ertugliflozin remains an option but is not licensed for where CKD, ASCVD or HF are co-morbidities with type 2 diabetes.

Due to mode of action of SGLT2i patients may be more susceptible to urinary tract infections and postural hypotension so SGLT2is must be used with caution in those taking diuretics, ACE inhibitors or angiotensin receptor antagonists.[6] Appropriate advice of these risks should be given along with advice on the risk of diabetic ketoacidosis and the associated signs or symptoms. Please see MHRA guidance below (pg 11).

Before starting an SGLT-2 inhibitor, check whether the person may be at increased risk of diabetic ketoacidosis (DKA), for example if:

- They have had a previous episode of DKA.
- They are unwell with intercurrent illness.
- They are following a very low carbohydrate or ketogenic diet.

Other risk factors for DKA include[13]

- very high level of HbA1c >86 mmol/mol
- Body mass index under 25 kg/m2 (under 23 kg/m2 in South Asian patients)
- People diagnosed with or at risk of frailty (due to not being able to recognise symptoms)
- people you suspect may have slowly developing Type 1 (LADA)

Address modifiable risks for DKA before starting an SGLT2 inhibitor. For example, for people who are following a very low carbohydrate or ketogenic diet, they may need to delay treatment until they have changed their diet.
Advise adults with type 2 diabetes who are taking an SGLT2 inhibitor about the need to minimise their risk of DKA by not starting a very low carbohydrate or ketogenic diet without discussing it with their healthcare professional, because they may need to suspend SGLT-2 inhibitor treatment.

There is an increased risk hospital admissions for patients on SGLT2i with DKA so appropriate and continued reiteration of the advice above is paramount along with sick day guidelines.

NICE Recommendations
Assess the person's cardiovascular status and risk to determine whether they have congestive heart failure or established atherosclerotic cardiovascular disease or are at high risk of developing cardiovascular disease. Based on the person's cardiovascular risk assessment:
• If they have congestive heart failure or established atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor in addition to metformin.
• If they are at high risk of developing cardiovascular disease, consider an SGLT2 inhibitor in addition to metformin.
When starting dual therapy with metformin and an SGLT2 inhibitor as first-line therapy, introduce the drugs sequentially, starting with metformin, checking their tolerability.
If metformin contraindicated, SGLT2i may be offered alone.

See appendix 6 for further details of SGLT2i and renal function dosing.

Give information regarding "sick day rules" for this medication (See appendix 9)

Please ensure that the strength of SGLT2i is appropriate for the patient. Examples include

- Dapagliflozin is prescribed at 10mg once a day. Only when there is severe hepatic impairment should 5mg strength be used before increasing to 10mg once a day if tolerated. There is an increasing trend in the use of 5mg dapagliflozin. Health care professionals in Kent and Medway should be aware of this and not to use the 5mg strength inappropriately, should only be used in severe hepatic impairment. This is a recommended audit area.
- Other SGLT2i can start on lower doses and then increase if needed. Please check product literature for further details

For type 2 diabetes and CKD and information on SGLT2i

For adults with type 2 diabetes and CKD who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), *consider* an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if:

- ACR is between 3 and 30 mg/mmol and
- they meet the criteria in the marketing authorisation (including relevant eGFR thresholds)

For adults with type 2 diabetes and CKD who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), *offer* an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if:

- ACR is over 30 mg/mmol and
- they meet the criteria in the marketing authorisation (including relevant estimated glomerular filtration rate [eGFR] thresholds).
- In November 2021, not all SGLT2 inhibitors were licensed for this indication

Information regarding the NICE TA for dapagliflozin in CKD is available here.

SGLT2i information here has been produced in relation to the management of type 2 diabetes. For the management of other indications (heart failure or chronic kidney disease) where a person does not have type 2 diabetes, please see advice on Kent and Medway formulary pages and NICE guidelines.

Kent and Medway recommended action: the indication for the SGLT2i should be documented in the patients notes in primary care and made clear from trusts when initiating or recommending their use

Also note that the glucose lowering action of SGLT2i reduces with a reduction in renal function. Whilst patients can remain on SGLT2i at lower renal function ranges in line with SPC recommendation other interventions may be needed to ensure glucose metabolic control is maintained.

MHRA alerts for SGLT2i- click on links for full information

SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis: risk of ketoacidosis in both type 1 and type 2 even if plasma glucose level are near normal. Inform patients inform them of the signs and symptoms of diabetic ketoacidosis (DKA) and advise them to seek immediate medical advice if they develop any of these.

SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes): Canagliflozin may increase the risk of lower-limb amputation (mainly toes) in patients with type 2

diabetes. Evidence does not show an increased risk for dapagliflozin and empagliflozin, but the risk may be a class effect. Preventative foot care is important for all patients with diabetes.

SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum): If Fournier's gangrene is suspected, stop the SGLT2i and start treatment urgently (including antibiotics and surgical debridement). Fournier's gangrene is a rare but potentially life-threatening infection that requires urgent medical attention.

SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness:

SGLT2 inhibitors should be temporarily stopped in patients who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured (preferably in blood rather than urine). Treatment may be restarted when the ketone values are normal and the patient's condition has stabilised.

2.3 Glucagon like peptide 1 mimetics

There are currently 3 GLP-1 mimetics on the formulary: liraglutide, dulaglutide, semaglutide (sc and oral). Lixsenatide and Exenatide are no longer on formulary for new initiations. Patients currently prescribed these preparations can remain on them until seemed suitable for a change at clinical decision.

NICE 2022 update

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

• have a 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

ADA/EASD guidelines recommend the use of GLP-1 mimetics 2nd or 3rd line especially where established CVD disease or high risk of CVD. This is reflecting some of the current practice as the ADA/EASD consensus was also in place before the latest NICE update and local clinical view. The formulary choices reflect this as GLP-1 mimetics with some cardiovascular benefit (apart from oral semaglutide)

Reviewing patients currently prescribed of GLP-1 mimetics

- GLP- 1 mimetics should only be continued if the individual has a beneficial metabolic response (a reduction of at least 11mmol/mol (1%) HbA1c AND a weight loss of at least 3% of initial body weight at 6 months).

When initiating GLP-1 mimetics consider keeping this medication available on acute to ensure review. Health care professionals initiating GLP-1 mimetics must have a process in place to ensure a review of GLP-1 mimetics occur at 6 months after prescribing.

When initiating GLP-1 mimetic particular attention is needed to those that require titration of dose (liraglutide, semaglutide and lixisenatide). Patients should be reviewed accordingly to ensure they do not remain on initiation doses. Quantities of GLP-1 mimetic should reflect monthly use of item. (See appendix 7).

GLP1 mimetics should be initiated by clinicians who have received appropriate training (eg PITSTOP training). Adequate training on the use of the injectables and follow up reviews should be provided to patients initiated on GLP-1 mimetics. GLP-1 mimetics across Kent and Medway have a green status so can be initiated in primary, community or secondary care. Where MDT support is also possible (not for all of Kent and Medway) this can be utilised. In primary care Arden's templates are available in EMIS to support the initiation of GLP-1 mimetics and are encouraged to be used.

Oral Semaglutide has been approved as an option for insufficiently controlled type 2 diabetes, especially when an injectable GLP-1 mimetic where an injectable GLP-1 mimetic may not be preferrable. GLP-1 mimetic would be considered as part of this pathway. Oral semaglutide is not a replacement for injectable GLP-1 mimetics and should still be initiated by a clinician with PITSTOP or equivalent training. It can be prescribed alongside other diabetes medications (apart from DPP-4 inhibitors and other GLP-1 mimetics).

Administration advice

Oral Semaglutide should be taken on an empty stomach at any time of the day. It should be swallowed whole with a sip of water (up to half a glass of water equivalent to 120 ml). Tablets should not be split, crushed or chewed, as it is not known whether this impacts absorption of semaglutide. Patients should wait at least 30 minutes before eating or drinking or taking other oral medicinal products. Waiting less than 30 minutes decreases the absorption of semaglutide.

DPP4i's should be stopped when started GLP-1 mimetics as they work on the same pathway
See appendix 7 for further details of GLP-1 mimetics.

Consideration should be given to the potential risk of diabetic retinopathy with semaglutide. This is listed as a common side effect with oral and subcutaneous semaglutide in the SPC. There is also a potential risk of diabetic ketoacidosis when used in combination with insulin – please see MHRA guidance (below (pg 13)). 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 as per NICE recommendations. Abrupt improvement in glycaemic control has been associated with temporary worsening of retinopathy, especially when semaglutide is added to insulin therapy. Avoid adding in semaglutide to patients with active proliferative or pre-proliferative diabetic retinopathy, and/or active maculopathy or macular oedema.

Kent and Medway action point: care should be taken when prescribing semaglutide injectable(Ozempic) around the quantity of pens prescribed. One pen is enough for 4 weeks. There are many examples of practices continuing to prescribe 4 pens each month which is a significant cost pressure to the system. Dulaglutide required 4 pens per month. Both semaglutide and dulaglutide do not require pen needles to be prescribed.

See table below around which preparations require needles to be prescribed.

Give sick day advice for these patients (see appendix 9)

MHRA alerts for GLP1s- click on link for full information

GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued:

Diabetic ketoacidosis has been reported in patients with type 2 diabetes on a combination of a GLP-1 mimetic and insulin that had doses of concomitant insulin rapidly reduced or discontinued. GLP-1 mimetics are not substitutes for insulin, and any reduction of insulin should be done in a stepwise manner with careful glucose self-monitoring. Abrupt discontinuation or reduction in insulin doses can lead to poor glycaemic control, with a risk of diabetic ketoacidosis.

2.4 Dipeptidyl peptidase-4 inhibitor (DPP4i)

There are currently five DPP4i's licensed for use in Type 2 diabetes. **Sitagliptin (generic) is the preferred DPP4i across Kent and Medway.** DPP4i will be coming of patent gradually over the next few years. Sitagliptin is now preferred due to this reason. Consideration should be made where if a patient still requires a DPP4i that sitagliptin is prescribed instead. Other formulary choices include alogliptin and linagliptin (reserved to those with renal impairment eGFR<45ml/min)

Prescribing of DPP4i is based on renal function (apart from linagliptin). It is important to ensure that renal function is monitored to ensure that the dose is appropriate for that person as part of annual checks required for type 2 diabetes. This is a recommended audit area along with ensuring that those patients prescribed gliptins have seen a metabolic benefit from DPP4i.

See appendix 4 for further details of DPP4 inhibitors.

MHRA alerts for DPP4i- click on links for full information
Dipeptidylpeptidase-4 inhibitors: risk of acute pancreatitis

An increased risk of acute pancreatitis has been reported for all DPP-4 inhibitors. Patients should be advised of the characteristic symptoms of acute pancreatitis (such as acute abdominal pain) and to inform a healthcare professional. The DPP4i therapy should be discontinued if pancreatitis is suspected.

2.5 Sulfonylureas (SU)

Gliclazide is the preferred first choice sulfonylurea although glimepiride and glipizide are also on the formulary.

A sulfonylurea is an option in place of metformin in patients not at high CVD risk in whom metformin is contraindicated or not tolerated. They are also an option if monotherapy has not continued to control HbA1c to below the person's individually agreed threshold for further intervention for use in dual therapy and in triple therapy. The advantages of using a sulfonylurea include efficient glycaemic control and long term safety data however there is a risk of hypoglycaemia and weight gain.[7]

Patients commenced on a sulfonylurea may need to monitor blood glucose in line with local blood glucose testing guidelines and DVLA guidelines. Aim to support patients on a sulfonylurea to aim for

HbA1c of 53mmol/mol (7.0%). Group 2 drivers will be required to test in line with DVLA guidelines and a blood glucose testing machine should be provided.

Sulfonylureas can also be used as first line therapy if rapid response is required due to symptomatic hyperglycaemia. The following should be considered in discussions with the patient:

- Educate the person about the risk of hypoglycaemia, especially in the presence of renal impairment
- Caution is advised in patients who are elderly, housebound and in certain occupations (e.g. operating heavy machinery)
- Educate the person that SUs can cause weight gain
- Check HbA1c after patient has been on SU for 3 months

It is generally recommended that the following groups of patients may not be suitable for treatment with a sulfonylurea due to the increased risk of hypoglycaemic attacks[6]:

- Group 2 drivers (those who hold a licence to drive heavy goods vehicles or public service vehicles)
- Professional drivers (e.g. taxi drivers)
- Occupations where safety is critical, e.g. construction workers, steeplejacks
- Frail, elderly patients who live alone
- Those with severe renal impairment (eGFR less than 30mls/min)

Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems. See Fitness to Drive document and http://www.diabetes.org.uk/ website for the latest recommendations.

When SUs are used in combination with SGLT2is and DPP4is care should be taken with dosing. To reduce risks of hypoglycaemia the dose of the SU may need to be reduced.

CV safety – SUs are considered safe however avoid aggressive up titration which may lead to hypoglycaemia and cardiovascular risk (Action to Control Cardiovascular Risk in Diabetes -ACCORD).

Give sick day advice for people on this medication (see appendix 9)

See appendix 5 for further details of SUs.

2.6 Thiazolidinediones (TZD)

The only thiazolidinedione licensed in the UK is pioglitazone. NICE recommends to the use of pioglitazone as per the guidance above.

In adults with type 2 diabetes, do not offer or continue pioglitazone[4] if they have any of the following:

- heart failure or history of heart failure
- hepatic impairment (see note below on NAFLD)
- diabetic ketoacidosis
- current, or a history of, bladder cancer
- uninvestigated macroscopic haematuria

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA_{1c}). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained.

Caution is advised when considering use in cardiovascular disease or in combination with insulin, or in those with an increased risk of bone fractures or risk factors for bladder cancer. Pioglitazone may cause weight gain of 2-3kg on average over 12 months, so it is not recommended in overweight patients.[8]

No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 45 mL/min).

Pioglitazone may be an option in non-alcoholic fatty liver disease- this use is off-label as per NICE[14]

Before starting treatment, monitor liver function

- If alanine aminotransferase (ALT) is more than 2.5 times the upper limit of normal, or there is any other evidence of liver disease, do not start treatment

Following treatment, monitor liver enzymes periodically based on clinical judgement

- If ALT levels are increased to three times the upper limit of normal during treatment, promptly reassess liver enzyme levels.
- If ALT levels remain more than 3 times the upper limit of normal, discontinue treatment with pioglitazone
- If the patient develops symptoms suggesting hepatic dysfunction (such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine), check liver enzymes and use clinical judgement to decide whether to continue treatment

For further details see SPC here.

MHRA alerts for pioglitazone - click on links for full information

Pioglitazone: risk of bladder cancer: There is a small increased risk of bladder cancer with using pioglitazone. Prescribers are advised to make careful selection of patients suitable to have pioglitazone and to follow the cautionary advice in the Drug Safety Update.

Insulin combined with pioglitazone: risk of cardiac failure: If pioglitazone is used in combination with insulin patients should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if there are signs of cardiac deterioration.

2.7 Meglitinides

The meglitinides class of antidiabetics includes nateglinide and repaglinide. Nateglinide was discontinued in December 2019.

Cardiovascular safety of repaglinide has not been extensively analysed however cardiovascular disease is listed as a rare side effect. Other more common side effects include abdominal pain, diarrhoea and hypoglycaemia. There is a lack of studies with use in those with hepatic insufficiency and over 75 years of age. Although it is not considered to be affected by renal disorders it should be

used with caution in severe renal impairment due to increased insulin sensitivity in severe renal impairment. See SPC here for further details.

2.8 Acarbose

Acarbose is not commonly prescribed however is available on formulary. Acarbose has a small but significant effect in lowering blood glucose and is used either on its own or as an adjunct to metformin or to sulfonylureas when they prove inadequate. It can be considered for a person unable to use other oral glucose lowering medications. Flatulence deters some from using acarbose although this side effect tends to decrease with time.

Acarbose delays the digestion and absorption of starch and sucrose. For this reason it is contraindicated in disorders of digestion or absorption, hernia and inflammatory bowel disease. Timing of doses is crucial and therefore tablets should be chewed or swallowed whole with the first mouthful of food.

For further details please refer to SPC here.

3. INSULIN

If a patient is unable to achieve glycaemic control with three oral medications, then it will be necessary to consider the initiation of insulin. Insulin initiation should be undertaken by a competent clinician who has undertaken a suitable training course, for example the PITSTOP programme.

Patients should be involved in the decision to start insulin and should always be given a choice of device to suit their needs.
An individual HbA1c target should be agreed taking into account lifestyle, age, co-morbidities risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity.

The National Patient Safety Agency (NPSA) safety recommendations state:

- Always write the term "**units**" in full when prescribing to prevent errors in administration.
- Always write the full name of the insulin, to prevent prescribing and dispensing errors, and ensure insulin is **prescribed by brand**.
- The brand name must be cross-referenced against the patient's insulin safety card/passport and patient records to ensure the correct insulin is being prescribed.
- All adult patients on insulin should receive an insulin passport (these can be ordered from www.nhsforms.co.uk or downloaded from https://www.england.nhs.uk/improvement-hub/publication/safe-use-of-insulin-and-you or www.trend-uk.org).

The principles of insulin safety must be considered at all times when insulin is included in therapy. A summary of the principles (the 6Rs) is outlined below.

Right person
Right insulin (brand)
Right strength

Right dose
Right time
Right device

Please be aware that there are various biosimilar insulins in the UK market. Biosimilar products are **not** necessarily bio-equivalent to the generic version despite having the same active insulin. Although the quality, safety and efficacy of biosimilar products should have no clinically meaningful difference to the generic medicine, the molecular structure of the product may be more complex than the original generic product.[9] It is therefore important that **all insulins are prescribed by brand**.

Patients being switched from one biosimilar to another must be dose adjusted and carefully monitored.

When starting insulin, review the continued need for other blood glucose lowering therapies.

NICE recommends the below with regard to biosimilar insulins

- When starting an insulin for which a biosimilar is available, use the product with the lowest acquisition cost
- Ensure the risk of medication errors with insulins is minimised by following the Medicines and Healthcare products Regulatory Agency (MHRA) guidance on minimising the risk of medication error with high strength, fixed combination and biosimilar insulin products, which includes advice for healthcare professionals when starting treatment with a biosimilar
- When people are already using an insulin for which a lower cost biosimilar is available, discuss the possibility of switching to the biosimilar. Make a shared decision with the person after discussing their preferences[4]

Guidance will be shared regarding biosimilar insulins within Kent and Medway

NICE also recommends the following when initiating insulin:

- education around injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites
- patients should be empowered to have an active involvement with insulin treatment
- continuing telephone support
- self-monitoring
- dose titration to target levels
- dietary advice
- DVLA guidance
- management of hypoglycaemia
- continue metformin for people without contraindications or intolerance.

In primary care Arden's templates are available in EMIS to support the initiation of insulin and are encouraged to be used.

3.1 Neutral Protamine Hagedorn (NPH) insulin

Insulatard and Humulin I are on formulary as intermediate acting insulins. Pre-mixed (biphasic) preparations on formulary include Humulin M3, Humalog Mix25, Humalog Mix50 and Novomix 30.

Current recommendations are to initiate with NPH insulin either at bedtime or twice daily. A short acting insulin can be started, particularly if HbA1c>75mmol/mol. This can be in the form of separate devices or in a pre-mixed (biphasic) formulation.[4]

NICE recommends that human NPH insulin, injected at bedtime or twice daily, is used first line except for the following groups who may benefit from a long-acting insulin (section 3.2):

- A patient needing assistance from a carer or healthcare professional to inject insulin, and in whom the use of an analogue would reduce injections from twice to once a day
- Whose lifestyle is significantly restricted by hypoglycaemia
- Who would otherwise need twice daily NPH insulin injections plus oral hypoglycaemic drugs
- Who cannot use their device to inject insulin.

In addition the following groups may be considered for a long acting analogue first line[6]:

- Group 2 drivers (those who hold a licence to drive heavy goods vehicles or public service vehicles)
- Professional drivers (e.g. taxi drivers)
- Frail, elderly patients who live alone
- Those with severe renal impairment(eGFR less than 30ml/min)
- Those who have a history of hypoglycaemic episodes whilst on a sulfonylurea.

3.2 Long acting insulin analogues

(Glargine - Abasaglar, Semglee, Lantus, Toujeo; Detemir – Levemir; Degludec - Tresiba)

Insulin glargine (Abasaglar) is the most cost effective long acting insulin analogue and is considered the first choice long acting analogue across the majority of Kent and Medway with the exception of Dartford, Gravesham and Swanley locality having a preference for Semglee.

Evidence shows that glargine and detemir are equivalent to NPH (and to each other) in terms of glycaemic control. Long-acting insulin analogues have only a modestly lower absolute risk for hypoglycaemia compared with NPH insulin.[9]

There is no evidence to demonstrate that either detemir or glargine is superior to the other. Some studies claim that weight gain is less with detemir rather than glargine. Generally there is no clinical justification for the use of twice a day Levemir in type 2 diabetics.

The most cost effective agent within the class should be used unless there is a strong clinical reason to use an alternative agent.

Toujeo®

Toujeo® is a high strength formulation of insulin glargine (300 units per ml) and its use is restricted to patients requiring doses of insulin which exceed the end of their current delivery device (typically 60 to 80 units per day). Patients who experience difficulty with injections at doses greater than 40 units per day may also be considered for Toujeo® on an individual patient basis.

Toujeo® is not bioequivalent to Lantus® and is not directly interchangeable. Dose adjustment and close monitoring are needed when switching from Lantus or other basal insulins to Toujeo®.

Switching from Lantus® to Toujeo® can be done on a unit for unit basis but a higher Toujeo® dose may be needed to achieve target ranges for plasma glucose levels. For further information on dosing refer to the SPC here.

Insulin Toujeo® is available as 2 devices both the SOLOstar and DOUBLEstar device. Healthcare professionals must be aware of the difference between these devices. When prescribing care must be taken to ensure that the device being prescribed is the device the patient is trained on and is aware of how to use either device. (The SOLOstar device delivers 1 unit of insulin per "click". The DOUBLEstar device delivers 2 units of insulin per click). Toujeo devices also come in packs of **3.**

As with all insulins Toujeo Solostar® or Doublestar® must be prescribed by brand to avoid inadvertent switching to Lantus, Abasaglar, Semglee or any other brand of insulin glargine.

Tresiba®

Degludec is associated with a lower risk of severe hypoglycaemia compared with insulin glargine 100units/ml when targeting intensive glycaemic control in patients with longstanding type 2 diabetes at high risk of CVD.[10] However glycaemic control is similar to glargine. It is available in two strengths so must be initiated with extreme caution to avoid inadvertent prescribing of incorrect strength. Initiation should only be done by specialists with adequate training.

The Kent and Medway Policy Recommendation and Guidance Committee (PRGC) recommends that insulin degludec is not routinely funded on the local NHS for the treatment of type 2 diabetes mellitus in adults unless the following criteria are met:

- It is initiated by a consultant or a GP with an extended role (GPwER) in diabetes AND
- The patient has tried other basal insulin regimens (i.e. NPH insulin and insulin detemir or insulin glargine) and these have been unsuccessful AND
- The patient meets one of the following criteria:
    - Attempts to achieve target HbA1c levels result in recurrent symptomatic hypoglycaemia ***or***
    - There is significant hypoglycaemia on basal insulin irrespective of the level of HbA1c ***or***
    - There is a risk of hypoglycaemia because of reduced awareness ***or***
    - A wide window of timing of administration is essential ***or***
    - There is a diagnosed allergy to either detemir or glargine.

Xultophy (insulin degludec plus liraglutide) is not currently on the formulary following a recommendation by the PRGC that insulin degludec and liraglutide (Xultophy) is not commissioned as the case for cost effectiveness vs. insulin glargine plus liraglutide was not proven.

Suliqua as of April 2022 has not been assessed for prescribing for Kent and Medway

3.3 Rapid/short acting insulin

The rapid acting insulins on formulary include Actrapid, Humulin S, Humalog, Novorapid, Fiasp. See local formulary website for current list.

The BNF advises:

Soluble insulin is usually given 15-30 minutes prior to meals, depending on the insulin preparation used. When injected subcutaneously, soluble insulin has a rapid onset of action (30-60minutes), a peak action between 1 to 4 hours and a duration of action of up to 9 hours.

Insulin aspart, insulin glulisine, and insulin lispro have a faster onset of action (within 15 minutes) and shorter duration of action (approximately 2–5 hours) than soluble insulin.
For maintenance regimens, these insulins should ideally be injected immediately before meals. Rapid-acting insulin, administered before meals, has an advantage over short-acting soluble insulin in terms of improved glucose control, reduction of HbA1c, and reduction in the incidence of severe hypoglycaemia, including nocturnal hypoglycaemia.

The routine use of *post-meal* injections of rapid-acting insulin should be avoided—when given during or after meals, they are associated with poorer glucose control, an increased risk of high postprandial-glucose concentration, and subsequent hypoglycaemia.

> It is important to note that Novorapid and Fiasp are **not** interchangeable. There are differences with bioavailability with Fiasp having a faster onset of action resulting in a greater glucose lowering effect but with a shorter duration of action.

MHRA alerts for insulin - click on links for full information

High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error: health professionals must ensure they are familiar with the different formulations of insulin to ensure safe prescribing of the correct insulin. Due to the availability of biosimilars it is important to note that dosing is not equivalent and care should be taken to prescribe by brand. Particular caution should be taken with the high strength insulins.

Insulins (all types): risk of cutaneous amyloidosis at injection site: there have been reports of cutaneous amyloidosis with the use of insulin which can affect glycaemic control. Patients must be advise to rotate injection sites to minimise the risk of this.

Risk of severe harm and death due to withdrawing insulin from pen devices: health professionals administering insulin for a patient must ensure the availability of the correct devices or equipment to allow for correct administration. Needles and syringes must not be used to withdraw insulin from a pen device.

See appendix 8 for further details of insulin.

Appendix 1 - Type 2 Diabetes Review checklist

The following should be considered when carrying out a clinical review.

Points to cover during review	Tick and date when completed	Comments
Personalised diabetes management plan (include dietary advice, physical exercise/activity)		
Provide patients with the Diabetes UK Patient Information Prescriptions (unless already provided on previous occasion)		
Check medication adherence and discuss any concerns with diabetes or medication taking into account frailty		
Review medication – consider if dose is appropriate, if additional anti-diabetic agents should be added or existing agents stopped as per recommendations, side effects		
Patients who are using insulin must - have their insulin passport/safety card checked and updated at every diabetes review - have their injection technique reviewed - have their injection sites checked		
Agree an individualised HbA1c target and when the HbA1c should be repeated		
If hypoglycaemia is a risk (e.g. if on sulphonylureas or insulin) then discuss how this can be identified and managed. Frailty risk should also be reviewed		
Provide advice on self-monitoring of blood glucose levels if patient is at risk of hypoglycaemia (e.g. if on sulphonylureas or insulin)		
Provide and document driving advice in accordance with DVLA guidance https://www.gov.uk/government/publications/at-a-glance		
Ensure the 9 key care processes have been covered		

Consider the psychological impact which diabetes can have on the patient and discuss		

Appendix 2: summary of medications (BNF links in further detail below)[4]

Medicine	Options and BNF link	Form	Contraindications	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis (not for linagliptin and saxagliptin)	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis (not for dulaglutide) Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid (not for dulaglutide, liraglutide or semaglutide) Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	None	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Metformin	Metformin	Acute metabolic acidosis		None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely

Approved by JPC Ratified by Kate Langford
Ratified Date: Aug 2022
Review Date: Aug 2024

Appendix 3- Metformin

	Metformin	
Drug and SPC link	**Metformin**	**Metformin MR**
Formulary status	**On formulary (1st line)**	**On formulary (if metformin S/R not tolerated)**
Licensed dose	Monotherapy or in combination with other antidiabetic drugs (including Insulin) to improve glycaemic control: Initially 500mg once daily for at least one week (dose to be taken with breakfast), then 500mg twice daily for at least one week (dose to be taken with breakfast and evening meal), then 500mg three times a day (dose to be taken with breakfast, lunch and evening meal). Maximum daily dose is 2g according to BNF but manufacturer's recommended regimen allows titration up to 3g in three divided doses (Please refer to SPC for more guidance).	Monotherapy or in combination with other antidiabetic drugs (including Insulin) to improve glycaemic control: Initially 500mg once daily then increased if necessary to up to 2g ONCE daily. Dose needs to be increased gradually every 10-15 days and dose to be taken with evening meals. Alternatively, can be increased to 1g twice daily to be taken with meals. Alternative dosing only to be used if glycaemic control not achieved with ONCE daily regimen. If control still not achieve, then change to standard release tablets. Reduction in risk or delay of onset of type 2 diabetes: Initially 500mg once daily then increased if necessary to up to 2g ONCE daily. Dose needs to be increased gradually every 10-15 days and dose to be taken with evening meals.
Method of administration	To be given with or after food.	To be given with or after food. Tablets to be swallowed whole.
Other considerations	Pros: High HbA1c efficacy, no weight gain, Extensive experience- Long term safety data (UKPDS study showed significant reduction in microvascular disease and improved cardiovascular outcomes)	

Appendix 4 - Table of comparison of DPP4 inhibitors

	DPP4i		
Drug and SPC link	**Alogliptin**	**Linagliptin**	**Sitagliptin**
Formulary status	**On formulary**	**On formulary**	**On formulary**
Other considerations	DPP4 inhibitors should not be prescribed in conjunction with GLP-1 agonist since they both work on the same pathway. Alogliptin is not licensed as monotherapy		

Appendix 5 - Table of comparison of sulfonylureas

	Sulfonylureas (SU)		
Drug and SPC link	**Gliclazide**	**Glimepiride**	**Glipizide**
Formulary status	**Formulary**	**Formulary**	**Formulary**
Licensed dose	Immediate release formulation: Initially, 40-80mg daily, adjusted according to response; up to 160mg as a single dose with breakfast. Maximum dose 320mg daily. Increase the dose every 4-6 weeks to achieve glycaemic target or maximal dose is reached.	Initially 1mg daily, adjusted according to response, increased in steps of 1mg every 1-2 weeks to up to 4mg daily. Dose to be taken shortly before or with first main meal. Dose can be increased further in exceptional circumstances to 6mg daily.	Initially 2.5–5 mg daily, adjusted according to response, dose to be taken shortly before breakfast or lunch, doses up to 15 mg may be given as a single dose, higher doses to be given in divided doses; maximum 20 mg per day.

Appendix 6 - Table of comparison of SGLT2 inhibitors

	SGLT2i			
Drug and SPC link	**Ertugliflozin**	**Dapagliflozin**	**Empagliflozin**	**Canagliflozin**
Formulary status	**On formulary**	**On formulary**	**On formulary**	**On formulary**
Dosing information (see BNF and SPC for latest information)	5 mg once daily; increased to 15 mg once daily if necessary and if tolerated, dose to be taken in the morning Avoid initiation if eGFR less than 60 mL/minute/1.73 m2. Frequent monitoring of renal function required if eGFR less than 60 mL/minute/1.73 m2. Avoid if eGFR is persistently less than 45 mL/minute/1.73 m2	10 mg once daily. Consider additional antidiabetic drugs with dapagliflozin if eGFR less than 45 mL/minute/1.73 m2 (reduced efficacy). Avoid initiation if eGFR less than 15 mL/minute/1.73 m2 Initially 5 mg daily in severe hepatic impairment, increased if tolerated to 10 mg daily.	10 mg once daily, increased to 25 mg once daily if necessary and if tolerated. Avoid initiation if eGFR below 60 mL/minute/1.73 m2. Avoid if eGFR is persistently below 45 mL/minute/1.73 m2 Reduce dose to 10 mg once daily if eGFR falls persistently below 60 mL/minute/1.73 m2	100 mg once daily; increased if tolerated to 300 mg once daily if required, dose to be taken preferably before breakfast. Limit dose to 100 mg once daily when eGFR less than 60 mL/minute/1.73 m2; consider addition of other hypoglycaemic agents if further glycaemic control needed. If eGFR falls to less than 30 mL/minute/1.73 m2 during treatment, continue with 100 mg once daily.

Appendix 7 - Table of comparison of GLP-1 mimetics

	GLP-1 mimetic (alphabetical order- not in order of preference)		
Drug and SPC link	**Dulaglutide**	**Liraglutide**	**Semaglutide**
Formulary status	**On formulary**	**On formulary** **Note: Not to be prescribed for weight loss (Saxenda brand)**	**On formulary**
Licensed dose (underline indicates daily dose, bold indicates weekly dose)	0.75mg a **week** (if used as monotherapy) 1.5mg a **week** if add on therapy to other	0.6mg a day increase to maintenance dose of 1.2mg daily after at least a week. Increase to 1.8mg daily if dose intensification is required	S/C: 0.25mg a **week** Increase to maintenance dose of 0.5mg a **week** after 4 weeks. Increase to 1mg a **week** if further intensification is required Oral: 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, dose to be taken on an empty stomach, 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; maximum 14 mg per day.
Other considerations	Take care when prescribing quantities of GLP-1 mimetic in line with dosing above. GLP-1 mimetic should not be prescribed in conjunction with DPP4 inhibitors since they both work on the same pathway. Not to be used in pregnancy or breastfeeding patients. Licensed for adults only. All GLP-1 receptors agonists reduce weight to varied amounts. Head to head trials vary regarding weight loss Nausea and vomiting are adverse events that can be managed through titration where indicated. There is low risk of hypoglycaemia but caution must be used in those patient taking sulfonylureas and or insulin.		
	The needle is within the device therefore disposable needles do not need to be prescribed with this device.	Pen needles need to be prescribed in addition to this device	Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded [4] Needles are supplied in the box therefore do not need to be prescribed Oral semaglutide 14 mg once daily is comparable to subcutaneous semaglutide 0.5 mg once weekly. Due to the high pharmacokinetic variability of oral semaglutide, the effect of switching between oral and subcutaneous semaglutide cannot easily be predicted.

Appendix 8 – Table of comparison of insulins – list not exhaustive and inclusion does not mean on formulary

Type of insulin	Brand	Delivery type and pack size	Image of prefilled pens (not to scale)	Formulary status as of April 2022
NPH (Insulin isophane)	Humulin I 100units/ml	Vials 10ml x1 Cartridges 3ml x5 Kwikpen 3ml x5		On formulary
	Insulatard 100units/ml	Vials 10ml x1 Cartridges 3ml x5 Innolet 3ml x5		On formulary
PRE-MIXED (Insulin isophane biphasic)	Humulin M3 (30/70) 100units/ml	Vial 10ml x1 Cartridges 3ml x5 Kwikpen 3ml x5		On formulary
	Novomix 30 100units/ml	Cartridges 3ml x5 Flexpen 3ml x5		On formulary
	Humalog Mix 25 100units/ml	Vial 10ml x1 Cartridges 3ml x5 Kwikpen 3ml x5		On formulary
	Humalog Mix 50 100units/ml	Cartridges 3ml x5 Kwikpen 3ml x5		On formulary
LONG ACTING (Insulin glargline)	Semglee 100units/ml *Biosimilar*	New pen 3ml x5		On formulary (Dartford, Gravesham and Swale)
	Abasaglar 100units/ml *Biosimilar*	Cartridges 3ml x5 Kwikpen 3ml x5		On formulary (West Kent, East Kent and Medway and Swale)
	Lantus 100units/ml	Vial 10ml x1 Cartridges 3ml x5 Solostar 3ml x5		On formulary

Approved by JPC Ratified by Kate Langford
Ratified Date: Aug 2022
Review Date: Aug 2024

	Toujeo **300units/ml** *High strength*	Solostar 1.5ml x3 Doublestar 3ml x3		On formulary
(Insulin detemir)	Levemir 100units/ml	Cartridges 3ml x5 Flexpen 3ml x5 Innolet 3ml x5		On formulary
(Insulin degludec)	Tresiba 100units/ml **200units/ml** *High strength*	Cartridges 3ml x5 FlexTouch 3ml x5 FlexTouch 3ml x3		Specialist initiation only
SHORT/RAPID ACTING (Soluble human)	Actrapid 100units/ml	Vials 10ml x1		On formulary
	Humulin S 100units/ml	Vials 10ml x1 Cartridges 3ml x5		On formulary
(Insulin Aspart)	Novorapid 100units/ml	Vial 10ml x1 Cartridges 3ml x5 Flexpen 3ml x5		On formulary
	Fiasp 100units/ml *Novel Ultra rapid*	Vials 10ml x1 Cartridges 3ml x5 FlexTouch 3ml x5		Specialist initiaion only
	Trurapi 100 units/ml *Biosimilar*	Cartridges 3ml x5 Solostar 3ml x5		As of April 2022 non formulary
(Insulin Lispro)	Humalog 100units/ml **200units/ml** *High strength*	Vial 10ml x1 Cartridges 3ml x5 Kwikpen 3ml x5 Kwikpen 3ml x5	 	On formulary

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	Admelog® (Insulin lispro Sanofi®) 100 units/ml *Biosimilar*	Vial 10ml x1 Cartridges 3ml x5 Solostar 3ml x5		As of April 2022 non formulary

Appendix 9: Sick day rule guidelines and management of intercurrent illness in adults with type 2 diabetes (NICE CKS)

If an adult with type 2 diabetes is unwell, consider the need to arrange hospital admission or seek specialist advice, depending on clinical judgement, taking into account the person's age, co-morbidities, risk of complications, and the presence of hyperglycaemia and/or ketosis.

- Arrange immediate hospital admission if:
  - There is an immediate risk of diabetic ketoacidosis (DKA), such as moderate ketonuria (2+ on urine dipstick) or ketonaemia (1.5–2.9 mmol/L) with or without hyperglycaemia, and the person cannot eat or drink.
  - There is an immediate risk of hyperosmolar hyperglycaemic state (HHS).
  - There is suspected acute kidney injury (AKI) that cannot be managed in primary care. See the CKS topic on Acute kidney injury for more information.
  - A person treated with insulin does not show signs of clinical improvement with insulin treatment. See the CKS topic on Insulin therapy in type 2 diabetes.
- Consider arranging hospital admission or seeking urgent specialist advice if:
  - The underlying condition is unclear.
  - The person is dehydrated or at risk of dehydration.
  - Vomiting persists beyond 2 hours.
  - The person and their family/carers are unable to keep the blood glucose level above 3.5 mmol/L.
  - The person and their family/carers are exhausted, for example due to repeated night-time waking.
- If admission is not needed and the person can be managed in primary care:
  - Ensure that the person has written contact details of their specialist diabetes team, where appropriate.
  - Assess the person and manage any intercurrent illness(es), as appropriate.
  - Advise on the need to temporarily stop some drug treatments during periods of acute illness. See the section on 'Sick-day rules' for detailed information.
  - Provide the person with clear, individualized advice on 'sick-day rules' to manage diabetes during episodes of intercurrent illness or hyperglycaemia, and reinforce the advice regularly.
    - Advise that intercurrent illness may affect blood glucose control, and there is a risk for worsening hyperglycaemia even if dietary intake is reduced.
  - Ensure the person has sick day foods and drinks supplies readily accessible at home, including:
    - Easily digestible foods and sugary drinks (to provide energy and to prevent further ketosis).
    - Over-the-counter oral rehydration therapy (ORT) sachets (to prevent dehydration).
    - Glucose tablets or oral gel (to prevent hypoglycaemia).

        - Equipment for self-monitoring of blood glucose and ketones (if appropriate).
        - Additional supplies of insulin (if appropriate).
        - A glucagon kit (if appropriate).
        - Note: see the CKS topic on Insulin therapy in type 2 diabetes for information on blood glucose and ketone monitoring meters, glucose oral gels, and other accessories.

'Sick-day rules'

- Provide 'sick-day rules' advice on managing episodes of intercurrent illness.
    - Advise to temporarily stop some drug treatments during acute illness. Medication may be restarted once the person is feeling better and eating and drinking for 24–48 hours, unless there is concern about renal function.
        - On angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (AIIRAs), diuretics, or nonsteroidal anti-inflammatory drugs (NSAIDs) — stop treatment if there is a risk of dehydration, to reduce the risk of acute kidney injury (AKI).
        - On metformin — stop treatment if there is a risk of dehydration, to reduce the risk of lactic acidosis.
        - On sulfonylureas — may increase the risk of hypoglycaemia, particularly if dietary intake is reduced.
        - On SGLT-2 inhibitors — check for ketones and stop treatment if acutely unwell and/or at risk of dehydration, due to the risk of euglycaemic DKA.
        - On GLP-1 receptor agonists — stop treatment if there is a risk of dehydration, to reduce the risk of AKI.
    - If on insulin therapy, do not stop treatment. See the CKS topic on Insulin therapy in type 2 diabetes for more information.
        - Advise the dose of insulin may need to be altered during periods of illness. Seek advice from the specialist diabetes team if there is uncertainty on how to adjust insulin doses.
    - If self-monitoring of blood glucose levels is indicated (for example on insulin therapy), advise:
        - An increase in monitoring frequency may be needed, such as at least every 3–4 hours including through the night and advice to record the results.
        - Insulin doses may need to be adjusted, depending on the results.
        - To continue to self-monitor blood glucose levels carefully when feeling better, until they are back to baseline.
        - Seek urgent medical advice if blood glucose levels remain uncontrolled.
    - Consider the need for blood or urinary ketone monitoring.
        - This should be checked regularly, for example at least every 3–4 hours including through the night, and record the results.
        - If the urine ketone level is greater than 2+, or blood ketone level is greater than 3 mmol/L, the person should seek immediate medical advice. See the section on When to suspect hyperglycaemic emergencies (DKA and HHS) for more information.
    - Advise to maintain their normal meal pattern (including fluids and carbohydrate intake) where possible if appetite is reduced.

- If unable to eat or vomiting, advise to replace normal meals with carbohydrate-containing drinks (such as milk, milkshakes, fruit juices, and sugary drinks).
- If blood glucose levels are high, maintain fluid intake with sugar-free fluids.
- If blood glucose levels are low, encourage regular intake of sugary fluids.

- Advise to seek urgent medical advice if the person:
  - Is unable to eat or drink, is dehydrated or at risk of dehydration.
  - Has persistent vomiting.
  - Has hypoglycaemia that cannot be managed in primary care.
- The Diabetes UK information Diabetes when you're unwell may be helpful.

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