North Central London
Joint Formulary Committee

Antihyperglycaemic agents for Type 2 diabetes

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Document control

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June 2016	1.0	NA
August 2016	1.1	Typo corrected (canagliflozin 10mg → canagliflozin 100mg)

Document management

Groups / Individuals who have overseen the development of this guidance:	Camden IPU, RFL Diabetologists, Haringey and Camden Medicines Management Team, JFC Support Pharmacists
Groups which were consulted and have given approval:	All NCL Diabetologists, Diabetes Consultant and Specialist Nurses, GPs, Commissioners
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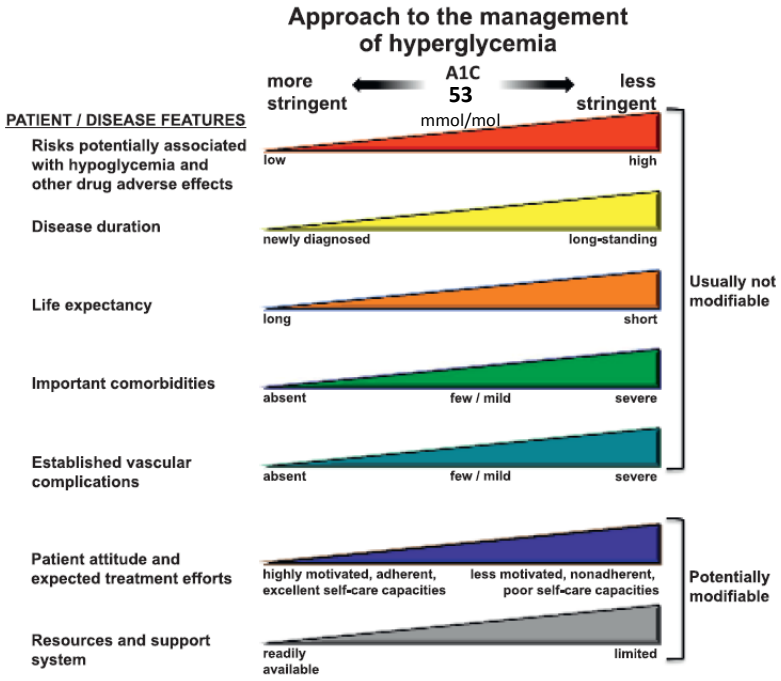
Contents

Personalised HbA1c targets

Involve adults with type 2 diabetes in decisions about their individual HbA1c target, the patient decision aid on page 13 may facilitate these discussions.

Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life.

Offer dietary advice (see NICE NG28, section 1.3) and drug treatment to support adults with type 2 diabetes to achieve and maintain their HbA1c target.



In adults with type 2 diabetes, measure HbA1c levels at:

- 3–6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy
- 6-monthly intervals once the HbA1c level and blood glucose lowering therapy are stable

Patients group	**Target HbA1c presumption (this must be individualised)**
Patients managed by lifestyle and diet	< 48 mmol/mol (6.5%)
If **all** the following apply: • Younger patients < 60 years within 10 years of diagnosis • Without established macrovascular disease (IHD, CVA, PVD) • Taking a ***single oral agent*** which is not associated with risk of hypoglycaemia (metformin, gliptin, SGLT2-i, pioglitazone)	48 mmol/mol (6.5%)
If **all** the following apply: • Younger patients < 60 years within 10 years of diagnosis • Without established macrovascular disease (IHD, CVA, PVD) • Without CKD on dialysis • Low risk for serious consequences of hypoglycaemia • Taking SU/repaglinide/insulin/GLP-1RA ***OR*** on more than one oral agent • Without significant comorbidities	53 mmol/mol (7.0%)
If life-expectancy > 10 years and **any** of the following apply: • Age > 60 years or duration diabetes > 10 years • Established macrovascular disease (IHD, CVA, PVD) • CKD on dialysis • Tight control poses a high risk of the consequences of hypoglycaemia (e.g. risk of falling, impaired awareness of hypoglycaemia, people who drive or operate machinery as part of their job) • Experiences recurrent hypoglycaemia on SU/insulin • Significant comorbidities	58 mmol/mol (7.5%)
Patients who are frail and elderly (>80 years), dementia and/or life-expectancy < 10 years	69 mmol/mol (8.5%)

Advantages and disadvantages of treatment combinations in adults with type 2 diabetes <u>eligible for METFORMIN</u>

<u>Metformin</u> (with active dose titration) – refer to Algorithm 1 on page 6.

Consider trial of <u>modified release metformin</u> ONLY if GI tolerability prevents continuing metformin despite gradual titration.

If metformin is contraindicated or patient intolerant refer to Algorithm 2 on page 7.

Impact on HbA1c: High
Other advantages: ↓CV events
Hypo risk: Low
Weight: -0.5Kg
Disadvantage: GI, lactic acidosis (rare), vitamin B12 deficiency
Cost (£): Low

FIRST INTENSIFICATION if uncontrolled on monotherapy. Aim for HbA1c of 53mmol/mol (7.0%) or individually agreed target.
Reinforce lifestyle measures, confirm medication adherence, optimise dose and refer to structured education programme if patient has not already attended.

<u>Metformin + gliclazide</u>

Impact on HbA1c: High
Other advantages: ↓microvascular risk, no cardiovascular risk
Hypo risk: Moderate
Weight: +1.5 to +2Kg
Disadvantage: hypos, low durability
Cost (£): Low

<u>Metformin + sitagliptin</u>

Impact on HbA1c: Moderate
Other advantages: Nil
Hypo risk: Low
Weight: Nil
Disadvantage: ?↑HF hospitalisation
Cost (£): High

<u>Metformin + SGLT2-i 'flozin'</u>

Impact on HbA1c: Moderate
Other advantages: ↓BP, ↓CVD events
Hypo risk: Low
Weight: -3 to -4Kg
Disadvantage: GU infections, polyuria, volume depletion, ↑risk of AKI, DKA, bone fractures, ? lower limb amputation
Cost (£): High

<u>Metformin + pioglitazone</u>

Impact on HbA1c: High
Other advantages: ?↓CVD events, durability, ↑HDL-C, ↓TG
Hypo risk: Low
Weight: +3 to +4Kg
Disadvantage: Oedema, HF hospitalisation, bladder Ca, bone fractures
Cost (£): Low

<u>Metformin + insulin</u>

Impact on HbA1c: Highest
Other advantages: ↓microvascular risk, near universal response, no cardiovascular risk
Hypo risk: High
Weight: +4 to +5Kg
Disadvantages: Injection, need for titration
Cost (£): Variable

SECOND INTENSIFICATION if uncontrolled on dual therapy. Aim for HbA1c of 53mmol/mol (7.0%) or individually agreed target.
Reinforce lifestyle measures, confirm medication adherence, optimise dose and refer to structured education programme if patient has not already attended.

<u>Metformin + gliclazide</u>

+ sitagliptin *or*
+ SGLT2-i *or*
+ insulin *or*
+ pioglitazone *or*
+ GLP-1RA (in line with SCG only)

<u>Metformin + sitaglitpin</u>

+ gliclazide *or*
+ SGLT2-i[†] *or*
+ insulin *or*
+ pioglitazone

<u>Metformin + SGLT2-i</u>

+ gliclazide *or*
+ sitagliptin[†] *or*
+ pioglitazone (not with dapagliflozin)
+ **insulin**

<u>Metformin + pioglitazone</u>

+ gliclazide *or*
+ sitagliptin *or*
+ SGLT2-i (not with dapagliflozin) *or*
+ insulin *or*
+ GLP-1RA (in line with SCG only)

<u>Metformin + insulin</u>

+ gliclazide *or*
+ sitagliptin *or*
+ SGLT2-i *or*
+ pioglitazone *or*
+ GLP-1RA (in line with SCG only)

[†]Combination not included in NICE NG28. RCT evidence to support this combination is very limited therefore only consider if other combinations are cautioned or contraindicated.

Algorithm 1: Blood glucose lowering therapy in adults with type 2 diabetes eligible for METFORMIN

If the person is symptomatically hyperglycaemic, exclude a diagnosis of T1DM and initiate metformin + gliclazide. Consider withdrawing gliclazide when glycaemic control is achieved.
Up to 12 weeks trial of lifestyle changes including healthy eating, weight loss, smoking cessation, blood pressure control, alcohol consumption and increased physical activity.
Aim for HbA1c of 48mmol/mol (6.5%) or individually agreed target for as long as possible after diagnosis.
Refer for Structured Diabetes Education programme

INITIATE THERAPY if HbA1c is above 48mmol/mol (6.5%) or individually agreed target.

Metformin if eGFR>30mL/min (titrate dose using regimen on page 8).
Consider metformin MR if standard metformin causes gastrointestinal side effects

→ If metformin not tolerated or contraindicated, go to Algorithm 2.

FIRST INTENSIFICATION if uncontrolled on monotherapy. Aim for HbA1c of 53mmol/mol (7.0%) or individually agreed target.
Reinforce lifestyle measures, confirm medication adherence, optimise dose and refer to structured education programme if patient has not already attended.

High risk or occupational impact of hypoglycaemia, frail, or medical issues related with obesity

- Y → Weight loss would be beneficial **and** SGLT2-i is suitable (check cautions)
  - Y → **Metformin + SGLT2-i**
  - N → **Metformin + sitagliptin**
- N → **Metformin + gliclazide *or* Metformin + repaglinide** if irregular meals / fasting

SECOND INTENSIFICATION if uncontrolled on dual therapy. Aim for HbA1c of 53mmol/mol (7.0%) or individually agreed target.
Reinforce lifestyle measures, confirm medication adherence, optimise dose and refer to structured education programme if patient has not already attended.

Weight loss would be beneficial **and** SGLT2-i is suitable (check cautions)

- N → add **sitagliptin *or* pioglitazone** (check cautions)
- Y → add **SGLT2-i**

High risk or occupational risk of hypoglycaemia

- N → add **insulin** (usually NPH) ***or*** **gliclazide**
- Y → add **SGLT2-i** if suitable (check cautions, not included in NICE NG28) ***or*** **pioglitazone** (check cautions)

Weight gain would be detrimental to obesity-related comorbidities

- N → *Low hypo risk*: add **insulin** (usually NPH) ***or*** **gliclazide**
  Hypo risk: add **pioglitazone** (check cautions)
- Y → add **sitagliptin** (not included in NICE NG28)

THIRD INTENSIFICATION Aim for HbA1c of 58mmol/mol (7.5%) or individually agreed target.
Reinforce lifestyle measures, confirm medication adherence, optimise dose and refer to structured education programme if patient has not already attended.

BMI >35Kg/m^2 (or >30Kg/m^2 if South Asian) and psychological or medical issues related with obesity, or BMI <35Kg/m^2 (or <30 Kg/m^2 if South Asian) in whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities

- N → start **insulin** (usually NPH)
- Y → **MET ± SU + GLP-1RA**

On insulin-based treatment? → History of problematic hypoglycaemia or BMI >35Kg/m^2 (or >30Kg/m^2 if South Asian) and psychological or medical issues related with obesity-related comorbidities

- N → **intensify insulin** based treatment
- Y → **Insulin + GLP-1RA**

Definitions:
High risk of hypos: elderly, dementia, CKD 3+, significant drug or alcohol use, erratic lifestyle, low body weight, significant liver disease

Significant obesity-related comorbidities:
- Sleep apnoea
- CKD due to obesity
- Non-alcoholic fatty liver disease
- Musculoskeletal issues relating to obesity

NICE continuation criteria
- DPP-4i (gliptin), SGLT2-i, pioglitazone: reduction of 5.5mmol/mol (0.5%) or more within 6 months
- GLP-1 RA: reduction of >11 mmol/mol (1%) AND 3% weight loss within 6 months of initiation (see GLP-1 RA GP Fact Sheet)

If continuation criteria is not met, withdraw treatment and recheck HbA1c at 2 months.

Consider earlier referral for 'Third intensification' if morbidly obese with significant obesity-related comorbidities

Algorithm 2: Blood glucose lowering therapy in adults with type 2 diabetes IF METFORMIN IS CONTRAINDICATED OR NOT TOLERATED

If the person is symptomatically hyperglycaemic, exclude a diagnosis of T1DM and initiate gliclazide. Review treatment when blood glucose control has been achieved.
Up to 12 weeks trial of lifestyle changes including healthy eating, weight loss, smoking cessation, blood pressure control, alcohol consumption and increased physical activity.
Aim for HbA1c of 48mmol/mol (6.5%) or individually agreed target for as long as possible after diagnosis.
Refer for Structured Diabetes Education programme

INITIATE THERAPY if HbA1c is above 48mmol/mol (6.5%) or individually agreed target.

Confirm that metformin (immediate release and modified release) is contraindicated or not tolerated → If metformin indicated and tolerated, go to Algorithm 1.

High risk or occupational impact of hypoglycaemia, frail, or medical issues related with obesity
- Y → Weight loss would be beneficial **and** SGLT2-i is suitable (check cautions)
  - Y → **SGLT2-i**
  - N → **Sitagliptin**
- N → **Gliclazide *or* Repaglinide** if irregular meals or fasting

FIRST INTENSIFICATION if uncontrolled on monotherapy. Aim for HbA1c of 53mmol/mol (7.0%) or individually agreed target.
Reinforce lifestyle measures, confirm medication adherence, optimise dose and refer to structured education programme if patient has not already attended.

Weight loss would be beneficial **and** SGLT2-i is suitable (check cautions)
- N → add **sitagliptin *or* pioglitazone** (check cautions)
- Y → add **SGLT2-i**

High risk or occupational risk of hypoglycaemia
- N → add **insulin** (usually NPH) ***or*** **gliclazide**
- Y → add **SGLT2-i** if suitable (check cautions, not included in NICE NG28) ***or*** **pioglitazone** (check cautions)

Weight gain would be detrimental to obesity-related comorbidities
- N → *Low hypo risk*: add **insulin** (usually NPH) ***or*** **gliclazide**
  Hypo risk: add **pioglitazone** (check cautions)
- Y → add **sitagliptin** (not included in NICE NG28)

SECOND INTENSIFICATION if uncontrolled on dual therapy. Aim for HbA1c of 53mmol/mol (7.0%) or individually agreed target.
Reinforce lifestyle measures, confirm medication adherence, optimise dose and refer to structured education programme if patient has not already attended.

BMI >35Kg/m^2 (or >30Kg/m^2 if South Asian) and psychological or medical issues related with obesity, or BMI <35Kg/m^2 (or <30 Kg/m^2 if South Asian) in whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- N → start **insulin** (usually NPH)
- Y → **SU + GLP-1RA**

On insulin-based treatment? → History of problematic hypoglycaemia or BMI >35Kg/m^2 (or >30Kg/m^2 if South Asian) and psychological or medical issues related with obesity-related comorbidities
- N → **intensify insulin** based treatment
- Y → **Insulin + GLP-1RA**

Definitions:
High risk of hypos: elderly, dementia, CKD 3+, significant drug or alcohol use, erratic lifestyle, low body weight, significant liver disease

Significant obesity-related comorbidities:
- Sleep apnoea
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- Musculoskeletal issues relating to obesity

NICE continuation criteria
- DPP-4i (gliptin), SGLT2-i, pioglitazone: reduction of 5.5mmol/mol (0.5%) or more within 6 months
- GLP-1 RA: reduction of >11 mmol/mol (1%) AND 3% weight loss within 6 months of initiation (see GLP-1 RA GP Fact Sheet)

If continuation criteria is not met, withdraw treatment and recheck HbA1c at 2 months.

Consider earlier referral for 'Third intensification' if morbidly obese with significant obesity-related comorbidities

Drug summary table

	Month cost	Instructions for use	Side effect	Cautions and contraindications	Monitoring & stopping criteria
Metformin	Low	Start 500mg OD (immediate release) with or after food ↑by 500mg as tolerated (usually weekly) Usual MAX = 1000mg BD (or 850mg TDS if patient has three large starchy meals per day) Consider trial of modified release metformin **ONLY** if GI tolerability prevents the person continuing with metformin despite gradual titration. Discontinue if not tolerated. A switch back to standard release should be considered once titration complete and patient on stable dose. Do not use metformin MR in an attempt to improve compliance as there is no evidence	Gastro-intestinal side effects such as wind, diarrhoea and nausea initially Rarely lactic acidosis (withdraw treatment) and decreased vitamin B_{12} absorption	Contraindicated in ketoacidosis, renal failure (eGFR <30 ml/min/1.73m^2) If the person has mild to moderate liver dysfunction or cardiac impairment, discuss benefits of metformin so due consideration can be given to its cardiovascular-protective effects before any decision is made to reduce the dose Advise patient to discontinue temporarily if acutely unwell and at risk for severe dehydration	Determine renal function before treatment and at least annually (at least twice a year in patients with additional risk factors for renal impairment, or if deterioration suspected) Review metformin dose if eGFR <45 ml/min/1.73m^2 Stop metformin if eGFR <30 ml/min/1.73m^2
Gliclazide	Low	Start 40-80mg OD with food ↑ by 80mg according to response Usual MAX = 160mg BD	Increased appetite & weight gain therefore caution if patient overweight Hypoglycaemia, provide 'Safe driving tips' from Diabetes.org.uk website Gastro-intestinal disturbances	Contraindicated in ketoacidosis Avoid where possible in severe hepatic impairment Use with care in those with mild to moderate renal impairment, avoid where possible in severe renal impairment due to increased risk of hypoglycaemia. Avoid where possible in acute porphyria	Frequency of hypoglycaemia
Repaglinide	Low	500mcg TDS immediately before or up to 30 minutes before each main meal ↑by 1mg according to response every 1-2 weeks MAX = 4mg TDS	Gastro-intestinal side effects such as abdominal pain, diarrhoea, constipation, nausea, vomiting Hypoglycaemia (rarely), provide 'Safe driving tips' from Diabetes.org.uk website	Contraindicated in ketoacidosis Avoid where possible in severe hepatic impairment Use with caution in renal impairment	Frequency of hypoglycaemia
Sitagliptin	High	100mg OD Reduce dose to 50mg once daily if eGFR 30–50 mL/min/1.73m^2; reduce dose to 25 mg once daily if eGFR less than 30mL/min/1.73 m²	Gastro-intestinal side effects such as constipation and nausea Peripheral oedema Upper respiratory tract infection Nasopharyngitis Musculoskeletal pain Less commonly dry mouth, anorexia, headache, drowsiness, dizziness, hypoglycaemia, osteoarthritis	Contraindicated in ketoacidosis Inform patients about the symptoms of acute pancreatitis – persistent, severe abdominal pain (sometimes radiating to the back) – and to tell their doctor if they have such symptoms. Discontinue if acute pancreatitis is suspected. Dose of concomitant sulfonylurea or insulin may need to be reduced to prevent hypoglycaemia	**Only continue if the patient has had a reduction of at least 5.5 mmol/mol (0.5 %) in HbA1c within 6 months** Assessment of renal function is recommended prior to initiation and periodically thereafter.

	Month cost	Instructions for use	Side effect	Cautions and contraindications	Monitoring & stopping criteria
Pioglitazone	Low	Start 15mg OD ↑ to 30-45mg OD according to response; higher doses are at a greater risk of side effects (include fluid retention). Elderly start at 15mg OD & ↑ gradually	Oedema, bone fracture, ?bladder cancer (see 'Cautions and Contraindications' and 'Monitoring and stopping criteria') Weight gain Upper respiratory tract infection Musculoskeletal pain Headache Erectile dysfunction Hypoaesthesia Visual disturbances Anaemia	Contraindicated in ketoacidosis Contraindicated in cardiac failure or history of cardiac failure, uninvestigated macroscopic haematuria, previous or active bladder cancer Cautioned in post-menopausal women due to increased risk of fracture Avoid in acute porphyria Caution in those with increased risk of heart failure (use lower doses and specialist use only with insulin) Discontinue if jaundice occurs For further information, see pioglitazone datasheet http://ncl-jfc.org.uk/prescribing-guidelines.html	**Only continue if the patient has had a reduction of at least 5.5 mmol/mol (0.5 %) in HbA1c within 6 months** Signs of oedema – exclude heart failure and consider treatment with thiazide or withdrawing treatment. Liver function before treatment, and periodically thereafter For further information, see pioglitazone datasheet http://ncl-jfc.org.uk/prescribing-guidelines.html

	Month cost	Instructions for use	Side effect	Cautions and contraindications	Monitoring & stopping criteria
All SGLT2-i ('flozin')	High	**Advice for treating patients with SGLT2-i:** • Advise increased fluid intake (at least 500 mL/day) to compensate for increased urinary fluid losses, to avoid dehydration and acute kidney injury (AKI) • If HbA1c <64 mmol/mol reduce dose of SU by 50% and insulin by 20% to reduce risk of hypoglycaemia on commencing SGLT2-i. • Advise patient of symptoms of genital candida infection and to commence topical clotrimazole 1% if these develop • Advise patient of the risk of dehydration and possible AKI if not able to drink or diarrhoea / vomiting • Inform them of the very small and uncertain risk of lower limb amputation (primarily of the toe). Advice patients to: o stay well hydrated o carry out routine preventive foot care o seek medical advice promptly if they develop skin ulceration, discolouration, or new pain or tenderness • Inform them of the very small risk of diabetic ketoacidosis (DKA) and of the signs and symptoms of DKA. Advise them to seek immediate medical advice if they develop any of these: o *rapid weight loss* o *feeling sick or being sick* o *stomach pain* o *fast and deep breathing* o *sleepiness* o *a sweet smell to the breath* o *a sweet or metallic taste in the mouth* o *a different odour to urine or sweat* • Discuss the risk factors for DKA with patients o a low beta cell function reserve (e.g. patients with T2DM who have low C-peptide levels, latent autoimmune diabetes in adults [LADA], or a history of pancreatitis) o conditions leading to restricted food intake or severe dehydration o sudden reduction in insulin o increased insulin requirements due to acute illness o surgery o alcohol abuse • Interrupt treatment with the SGLT2-i in patients who: o are hospitalised for major surgery (discontinue 48 hours before elective surgery due to prolonged action) o have acute serious illnesses o are volume depleted (poor oral intake, diarrhoea, vomiting) o have prolonged periods of fasting treatment may be restarted once the patient's condition has stabilised. Patients who are able to eat should substitute meals for carbohydrate rich drinks if possible (e.g. Lucozade and fruit juice).	Gastro-intestinal side effects such as constipation, nausea and thirst Urinary Tract infection Vulvovaginal candidiasis Dizziness postural, syncope Dyslipidaemia Polyuria Serious and potentially life-threatening cases of diabetic ketoacidosis (DKA) have been reported. Many cases occurred during the first 2 months of treatment. Most were associated with off-label use in T1DM. Patients should be told to report signs of DKA including nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, fatigue or sleepiness. Treatment should be discontinued immediately if DKA is suspected or diagnosed. Bone fractures (particularly in older patients with a prior history/risk of cardiovascular disease) Lower limb amputation (primarily of the toe) in high cardiovascular risk patients	Patients already prescribed insulin should have the SGLT2-i initiated by the Diabetes Specialist Team due to the higher risk of DKA (patients on insulin will require Ketostix or capillary ketone testing blood strips) Do not use in patients in which type 1 DM is possible (e.g. younger slim patients) or in patients with a history of pancreatitis (which may lead to insulin-deficiency) Do not use in patients with urine ketones (> +) or in ketoacidosis In patients with significant symptoms of decompensated diabetes (weight loss, polyuria, polydipsia, nocturia) consider the possibility of an insulin deficient state (e.g. Early type 1 diabetes, latent autoimmune diabetes, ketosis-prone type 2 diabetes/Flatbush diabetes/type 1.5 diabetes). Avoid SGLT2-i in such patients as may worsen risk of dehydration and, in rare cases, precipitate DKA See MHRA alert on DKA. Renal impairment: see individual monographs below Liver impairment: see individual monographs Heart failure: see individual monographs Avoid in women with recurrent vulvovaginal candidiasis Caution in patients in whom a drop in blood pressure could pose risk Caution in patients with conditions that may predispose to acute kidney injury (AKI). Including hypovolaemia, CKD, CHF, concurrent diuretics, ACEi, ARB and NSAID. See FDA alert on AKI. Caution in patients who have risk factors for amputation (e.g. previous amputations, existing peripheral vascular disease, or neuropathy). In such patients, monitor more closely. See MHRA alert on amputations. Follow 'Advise for treating patients with SGLT2-i' Contact Diabetes Specialist Team for advice if required	**Only continue if the patient has had a reduction of at least 5.5 mmol/mol (0.5 %) in HbA1c within 6 months** Determine renal function before treatment, 3 months after starting treatment and at least annually (due to volume depletion, small mean ↓eGFR may be observed within the first 6 weeks of treatment). Withhold therapy in patients who are acute volume depleted (e.g. poor oral intake, diarrhoea or vomiting) or prolonged periods of fasting, including prior to major surgery. **If patient experiences symptoms of severe illness suggestive of DKA (see *italics* under 'Advise for treating patients with SGLT2-i'):** • discontinue treatment with the SGLT2-i immediately if DKA is suspected or diagnosed. Check capillary blood glucose, advise increased carbohydrate intake if normal or low. • refer to A&E to be screened for DKA (capillary ketones ± venous blood gas) do not restart treatment with any SGLT2-i in patients who experienced DKA during use, unless another cause for DKA was identified and resolved **If patient experiences significant lower limb complication (skin ulcer, osteomyelitis, or gangrene):** • discontinue SGLT2-i at least until the condition has resolved, and continue to monitor the patient closely

	Month cost	Instructions for use	Side effect	Cautions and contraindications	Monitoring & stopping criteria
Canagliflozin	High	Start 100mg OD if GFR >60 mL/min/1.73m^2 If required may increase to 300 mg after 3 months if GFR still >60 mL/min/1.73m^2; higher dose is at a greater risk of adverse reactions related to volume depletion in the first 3 months See '**Advice for treating patients with SGLT2-i**', as per 'All SGLT2-i'	See 'All SGLT2-i'	Maximum dose of 100mg if eGFR 45-60 mL/min/1.73m^2 (may be less effective and higher risk of AE). Contraindicated if eGFR <45 mL/min/1.73m^2 as ineffective. Contraindicated with severe hepatic impairment (not studied) Experience in heart failure NYHA III is limited, no experience in clinical studies in NYHA IV. Otherwise, as per 'All SGLT2-i'	See 'All SGLT2-i'
Dapagliflozin	High	10mg OD if GFR >60 mL/min/1.73m^2 Severe hepatic impairment: Start 5mg OD and increase to 10mg OD if tolerated Not licensed in combination with pioglitazone See '**Advice for treating patients with SGLT2-i**', as per 'All SGLT2-i'	See 'All SGLT2-i' (bone fracture and lower limb amputation have not been reported for dapagliflozin however these adverse outcomes may be a SGLT2-i class effect)	Contraindicated if eGFR <60mL/min/1.73m^2 as ineffective and higher risk of AE Caution with severe hepatic impairment (increased exposure) Experience in heart failure NYHA I-II is limited, no experience in clinical studies in NYHA III-IV. Otherwise, as per 'All SGLT2-i'	See 'All SGLT2-i'
Empagliflozin	High	10mg OD if GFR >60 mL/min/1.73m^2 Do not routinely increase to 25mg dose as is not associated with a meaningful improvement in HbA1c, BP or cardiovascular outcomes. See '**Advice for treating patients with SGLT2-i**', as per 'All SGLT2-i'	See 'All SGLT2-i' (bone fracture and lower limb amputation have not been reported for empagliflozin however these adverse outcomes may be a SGLT2-i class effect)	Maximum dose of 10mg if eGFR 45-60 mL/min/1.73m^2 (may be less effective and higher risk of AE). Contraindicated if eGFR <45 mL/min/1.73m^2 as ineffective. Contraindicated with severe hepatic impairment (not studied) Experience in heart failure NYHA I-II is limited, no experience in clinical studies in NYHA III-IV. Otherwise, as per 'All SGLT2-i'	See 'All SGLT2-i'
Liraglutide	High	1.2mg OD (subcutaneous injection)	Refer to GP fact sheet	Refer to GP fact sheet	Refer to GP fact sheet
Dulaglutide	High	1.5mg OW (subcutaneous injection)	Refer to GP fact sheet	Refer to GP fact sheet	Refer to GP fact sheet

Renal/hepatic impairment – initiating treatment

	Renal function						Hepatic function	
	CKD stage 1 >90mL/min	**CKD stage 2** 60-90mL/min	**CKD stage 3a** 45-59mL/min	**CKD stage 3b** 30-44mL/min	**CKD stage 4** 15-29mL/min	**CKD stage 5** <15mL/min	**Mild/Moderate**	**Severe**
Metformin	✓	✓	✓	✓ (review regularly)	✗	✗	Specialist initiation only	✗
Gliclazide	✓	✓	✓	✓	✓ (use lowest effective dose)	✗	✓	✗
Repaglinide	✓	✓	✓	✓	✓ (use lowest effective dose)	✓ (use lowest effective dose)	✓ (clinical experience is lacking)	✗
Sitaglitpin	**100mg**	**100mg**	**50mg**	**50mg**	**25mg**	**25mg**	✓	✗
Pioglitazone	✓	✓	✓	✓	✓	✓ (monitor carefully with dialysis)	✗	✗
Empagliflozin	✓	✓	✗	✗	✗	✗	✓	✗
Dapagliflozin	✓	✓	✗	✗	✗	✗	✓	✓ (start at 5mg, increase to 10mg if tolerated)
Canagliflozin	✓	✓	✗	✗	✗	✗	✓	✗
Liraglutide	✓	✓	✓	✓	✗	✗	✗	✗
Dulaglutide	✓	✓	✓	✓	✗	✗	✓	✓
Insulin	✓	✓	✓	✓	✓ (requirement may be reduced)	✓	✓	✓ (requirement may be reduced)

Patient decision aid for HbA1c target

Make a mark on the lines to show how you feel about these statements. The more you agree with the statement on the left, the further to the left you should put the mark. The more you agree with the statement on the right, the further to the right you should put the mark. You and your healthcare professional can use this to help decide the best target HbA1c level for you.

Thinking about things like driving, having severe hypos would not be a problem for me*	Thinking about things like driving, having severe hypos would be a big problem for me*
I'm not bothered about the possibility of getting other side effects	Getting other side effects would be a big problem for me
I'm happy to take more medicines if I need to	I don't want to take any more medicines
I don't have any health problems apart from my diabetes	I have lots of health problems
Thinking about my age and my health overall, I'm hoping to see longer-term benefits	Thinking about my age and my health overall, shorter-term benefits are more important to me

*Hypos might also be a problem for you for other reasons, such as if you operate machinery, if you are at risk of falling, or if you find it difficult to recognise the warning symptoms of a hypo

Full NICE decision aid is available at https://www.nice.org.uk/guidance/ng28/resources/patient-decision-aid-2187281197

Patient decision aid for choice of therapy

Issue	**How important is this to me?**			
	Very important	Important	Unimportant	Very unimportant
Getting to a lower target blood glucose (HbA1c) level				
How many tablets I would have to take and how often				
The possibility of getting hypos				
The possibility of gaining weight				
The possibility of other side effects				
Other concerns or questions I want to discuss with my health care professional:				

Full NICE decision aid is available at https://www.nice.org.uk/guidance/ng28/resources/patient-decision-aid-2187281197