Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes (T2D)

These guidelines are intended to support prescribers regarding the medicines aspects of the Type 2 Diabetes Algorithm, please refer to the BNF or Summary of Product Characteristics for further information on contraindications, precautions, adverse effects and interactions for any named medicine.

Treatment of Hyperglycaemia

- Only prescribe one agent from each class.
- Substituting agents is unlikely to improve glucose control – swapping metformin plus gliclazide for metformin plus pioglitazone is more likely to cause deterioration in glycaemic control in the short term.
- **The addition of a third agent to a combination of two oral hypoglycaemic medicines taken at maximally tolerated doses may only lower HbA1c by approximately 5.5mmol/mol*.**
- **For a person on dual therapy who is markedly hyperglycaemic, NICE guidance states to consider starting insulin therapy in preference to adding other medicines to control blood glucose unless there is strong justification not to.**

Glycaemic Target

- **An individualised target should be discussed and agreed with each patient and reviewed every 3-6 months. HbA1c should be measured at 3-6 monthly intervals until stable on unchanging therapy and 6 monthly thereafter.**
- Lifestyle should be reviewed before every treatment escalation.

NICE CKS (Diabetes – type 2, July 2016)

- Agree and set a target HbA1c value with the person.
    - For people treated with lifestyle measures alone or who are taking one antidiabetic medicine not associated with hypoglycaemia, the usual target HbA1c is 48 mmol/mol (6.5%). However, an individual's target may be set above this level.
    - For people taking two or more antidiabetic medicines (including insulin), or a single medicine associated with hypoglycaemia the usual target HbA1c is 53 mmol/mol (7.0%). However, an individual's target may be set above this level.
        - In certain circumstances it may be appropriate to maintain a lower target (for example 48 mmol/mol [6.5%]) in people taking two or more antidiabetic medicines. This should be decided on an individual basis.
- When setting a target HbA1c value, take into account:
    - The person's preference.
    - The balance of likely benefits and harms of treatment.
    - The risk of microvascular and macrovascular complications- consider age, duration of diabetes and current complication status.
    - The risk and consequences of hypoglycaemia- consider employment or driving issues.
    - Whether the person will benefit from self-monitoring.
    - The intensity of treatment.
- Avoid the use of highly intensive management strategies to achieve an HbA1c level less than 48 mmol/mol (6.5%).

***Reporting Units for HbA1c**

Glycated haemoglobin (HbA1c) is the recommended method of measuring long term control of blood glucose in people with both type 1 diabetes and T2D. Previously the results were reported as a percentage (%). This has changed to millimoles/mole (mmol/mol) where people with diabetes will receive their HbA1c measurement in mmol/mol **only**. See conversion table for more detail.

HbA1c conversion table		
HbA1c (new units)	**HbA1c (old units)**	**A 0.5% difference in HbA1c is equivalent to a difference of about 5.5mmol/mol, and a 1% difference is equivalent to a difference of about 11mmol/mol.** Note that these are rounded equivalents.
(mmol/mol)	%	
20	4.0	
31	5.0	
42	6.0	
48	6.5	
53	7.0	
59	7.5	
64	8.0	
75	9.0	
86	10.0	

Patient education

All people newly diagnosed with T2D (and/or their carer) should be offered referral to a structured education programme (e.g. DESMOND). Inform people and their carers that structured education is an integral part of diabetes care. If patients are unable or unwilling to attend the group education sessions they should be referred to a dietitian and early initiation of metformin should be considered.

Individulised Care

Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of each person, taking into account their preferences, comorbidities, risks from polypharmacy and their ability to benefit from long-term interventions because of reduced life expectancy. Reassess the person's needs and circumstances at each review and consider whether to stop any medicines that are not effective.

NICE National Institute for Health and Care Excellence

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA1c levels in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level.
- Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- 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 while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard–release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified–release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin and an SU
  - *metformin and an SGLT-2i*[b]
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone[a] and an SU
    - *metformin, pioglitazone[a] or an SU, and an SGLT-2i*[b]
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic[c] for adults with type 2 diabetes who:
- have a 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

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
  - an SGLT-2i[b] instead of a DPP-4i if an SU or pioglitazone[a] is not appropriate
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i, SGLT-2i or pioglitazone or 53 mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy[e] with:
  - a DPP-4i and pioglitazone[a]
  - a DPP-4i and an SU
  - pioglitazone[a] and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Insulin-based treatment
- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine[g] if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem or blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- *An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option*[b].

Abbreviations: DPP-4i Dipeptidyl peptidase-4 inhibitor, GLP-1 Glucagon-like peptide-1, SGLT-2i Sodium–glucose cotransporter 2 inhibitors, SU Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. See NICE technology appraisal guidance 288 & 418, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin, respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions, as options in triple therapy regimens and in combination with insulin. All three are also options as monotherapies in adults in whom metformin is contraindicated or not tolerated. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

BIGUANIDES - METFORMIN (Metformin is the only available biguanide) Decreases gluconeogenesis and increases peripheral utilisation of glucose.			
MEDICINE	**NOTES**	**FORMULARY CHOICE**	**PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS**
Metformin  **Price per month (May 19):** 1g twice daily £3.36	Metformin has a cardio protective effect. ***NICE guidance (NG28):*** *Offer standard-release metformin as the initial medicine treatment for adults with type 2 diabetes.* *Continue with metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.* **NICE guidance (PH38):** *Use clinical judgement on whether (and when) to offer standard-release metformin to support lifestyle change for people whose HbA1c or fasting plasma glucose blood test results have deteriorated if:* *this has happened despite their participation in an intensive lifestyle-change programme,* ***or** they are unable to participate in an intensive lifestyle-change programme.* Continue to offer advice on diet and physical activity along with support to achieve their lifestyle and weight-loss goals For patients unable to swallow tablets consider crushing the standard tablet. The oral powder was discontinued in April 2014. A liquid is on the market but is not cost-effective (£68 per month).	First choice	Gradually titrate the dose of metformin (i.e. increase to the maximum tolerated dose). This must be done over several weeks to minimise risk of gastrointestinal (GI) side effects. (NICE NG28) If adding metformin to gliclazide, it may be appropriate to decrease the gliclazide dose in order to titrate the metformin. HbA1c target for patients on metformin **plus** gliclazide should not be lower than 53mmol/ml. **RENAL IMPAIRMENT** (NICE NG28)**:** Review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73-m^2. • Stop the metformin if the eGFR is below 30 ml/minute/1.73-m^2. • Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73-m^2. Patients taking up to 2g daily of the standard-release metformin may start with the same daily dose of metformin modified release
Metformin MR  **Price per month (May 19):** 2g daily: £6.40	Consider a trial of extended-absorption metformin tablets where GI tolerability prevents continuation of metformin therapy. (NICE NG28)	Second choice (for patients with proven GI intolerance)	

SULFONYLUREAS – GLICLAZIDE Augments insulin secretion and consequently is only effective when some residual pancreatic beta-call activity is present.			
MEDICINE	**NOTES**	**FORMULARY CHOICE**	**PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS**
Gliclazide  **Price per month (May 19):** 80mg daily-160mg twice daily £0.82 - £3.28	**Prescribe gliclazide when a sulfonylurea is indicated.** ***NICE guidance (NG28):*** *Consider a sulfonylurea as an option for first-line glucose-lowering therapy if:* • *the person is not overweight* • *the person does not tolerate metformin (or it is contraindicated)* ***or*** • *a rapid response to therapy is required because of hyperglycaemic symptoms.* *Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.*	First choice	Educate the person about the risk of hypoglycaemia, particularly if they have renal impairment. Increase dose every 4-6 weeks to achieve glycaemic target (do not exceed maximum dose). Check blood glucose (finger prick) before each titration to reduce risk of causing hypoglycaemia. HbA1c results of less than 48mmol/ml in patients on gliclazide should prompt a review of therapy due to a risk of symptomatic hypoglycaemia. If adding metformin to gliclazide, it may be appropriate to decrease the gliclazide dose in order to titrate the metformin. For patients on gliclazide **plus** metformin aim for HbA1c target of 53mmol/mol Gliclazide can cause weight gain (a few kilograms). **Advice for drivers:** For Group 1 drivers (car/motorcycle) it may be appropriate to monitor blood glucose regularly and at times relevant to driving to enable the detection of hypoglycaemia. Group 2 drivers (bus/lorry) on sulfonylureas are required by law to monitor glucose level at least twice daily and at times relevant to driving. For more information about driving with diabetes see the Government guidance for drivers with diabetes and advice for drivers on the Diabetes UK website. DVLA also has info- see guidance for professionals.
Gliclazide MR  **Price per month (May 19):** 30mg -120mg daily £2.81-£9.54	Use gliclazide MR (modified release) if compliance is poor.	Second choice (where there are concerns over compliance with standard release)	

GLIPTINS (also known as DPP-4 inhibitors) Inhibit dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion			
MEDICINE	**NOTES**	**FORMULARY CHOICE**	**PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS**
Alogliptin (Vipidia▼®) Amb3 **Price per month (May 19):** 6.25mg- 25mg daily £26.60	Low risk of hypoglycaemia and are weight neutral. **NICE guidance (NG28):** *Consider initial treatment with a DPP-4 inhibitor OR pioglitazone OR a sulfonylurea in patients in whom metformin is contraindicated or not tolerated.* *Can be used as part of dual or triple therapy if initial treatment does not control HbA1c to below the person's individually agreed target in the below combination:* • *metformin and a DPP-4 inhibitor* • *a DPP-4 inhibitor and pioglitazone* • *a DPP-4 inhibitor and a sulfonylurea* • *metformin, a DPP-4 inhibitor and a sulfonylurea* **Licensed in combination with:** other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. NB there is currently limited data regarding use of alogliptin when used as triple therapy with metformin and a sulphonylurea	First choice gliptin (cheapest Nov 16)	No long term safety data available for these agents. See sitagliptin entry for MHRA warning regarding **pancreatitis** (applies to all gliptins). **Renal impairment (CrCl, SPC):** • ≥50ml/min – no dose adjustment • 30-50ml/min – 12.5mg daily • <30ml/min – 6.25mg daily No dose adjustment is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function.
Sitagliptin (Januvia®) Amb3 **Price per month (May 19):** 25mg -100mg	Low risk of hypoglycaemia and are weight neutral. **As per NICE NG28 above** **Licensed combinations:** • Monotherapy when metformin is inappropriate due to contraindications or intolerance.	First choice gliptin	No long term safety data available for these agents. **Renal impairment (CrCl, SPC):** • ≥45ml/min – no dose adjustment • ≥30 - <45ml/min – 50mg daily • <30ml/min – 25mg daily

daily £33.26	• Dual therapy with metformin, sulfonylurea or pioglitazone. • Triple therapy with metformin & sulfonylurea or pioglitazone. • Insulin (with or without metformin)		No dose adjustment is necessary based on age. Limited safety data is available in patients ≥ 75 years of age and care should be exercised. **Applies to all gliptins:** Discuss the potential benefits and risks of treatment with a gliptin with the person to enable them to make an informed decision. Increased risk of **pancreatitis** associated with all gliptins. Patients should be informed of the characteristic symptoms of acute pancreatitis – persistent, severe abdominal pain (sometimes radiating to the back) – and encouraged to tell their healthcare provider if they have such symptoms. Link to MHRA warning
Linagliptin (Trajenta®▼) Amb3 **Price per month (May 19):** 5mg daily £33.26	Low risk of hypoglycaemia and are weight neutral. **Use as per NICE NG 28 above.** **Licensed combinations:** • As monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment • in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control	Second choice gliptin	No long term safety data available for these agents. See sitagliptin entry for MHRA warning regarding **pancreatitis** (applies to all gliptins). **Renal impairment (SPC):** Does not require dose reduction in renal impairment, No dose adjustment is necessary based on age. However, clinical experience in patients > 80 years of age is limited and caution should be exercised when treating this population.

THIAZOLIDINEDIONES (also known as GLITAZONES) **(Pioglitazone is the only available thiazolidinedione)** Reduces peripheral insulin resistance, leading to a reduction of blood glucose concentration			
MEDICINE	**NOTES**	**FORMULARY CHOICE**	**PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS**
Pioglitazone (Actos®) Green **Price per month (Oct 16):** 15mg -45mg daily £1.45-£2.15	***NICE guidance (NG 28)*** *Consider initial treatment with a DPP-4 inhibitor OR pioglitazone OR a sulfonylurea in patients in whom metformin is contraindicated or not tolerated.* *Can be used as part of dual or triple therapy if initial treatment does not control HbA1c to below the person's individually agreed target in the following combinations:* • *Metformin and pioglitazone* • *Pioglitazone and a sulfonylurea* • *A DPP -4 inhibitor and pioglitazone* • *Metformin, pioglitazone and a sulfonylurea* **Licensed combinations:** • Dual therapy with metformin or sulfonylurea. • Triple therapy with metformin & sulfonylurea. • Insulin (if metformin not appropriate)	Pioglitazone is the only thiazolinedione available	Do **NOT** start or continue pioglitazone in people who: • have heart failure (NYHA class I-IV) • are at a higher risk of fracture • macula oedema • hepatic failure • a history of **bladder cancer** or in patients with uninvestigated macroscopic or microscopic haematuria. Risk of bladder cancer: MHRA safety update • Diabetic ketoacidosis MHRA guide on patient selection and risk minimisation. Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain, and oedema. Risk of cardiac failure when combined with insulin: MHRA safety update Pioglitazone can cause weight gain. Discuss the potential benefits and risks of treatment with pioglitazone with the person to enable them to make an informed decision. Pioglitazone may be preferable to a gliptin if: • the person has marked insulin insensitivity, or

			• a gliptin is contraindicated, or • the person has previously had a poor response to, or did not tolerate, a gliptin. **Renal impairment (SPC):** No dose adjustment is necessary in patients with impaired renal function (creatinine clearance> 4 ml/min). No dose adjustment is necessary for elderly patients. Start with the lowest available dose and increase gradually, particularly when used in combination with insulin.

GLP-1 (Glucagon-like peptide-1) AGONISTS (Increase insulin secretion, suppress glucagon secretion, and slow gastric emptying)			
MEDICINE	**NOTES**	**FORMULARY CHOICE**	**PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS**
Lixisenatide (Lyxumia®▼) Amb2 **Price per month (May 19):** 20 micrograms daily £57.93	**Once daily subcutaneous injection** • **Lixisenatide is currently the GLP-1 agonist with the lowest acquisition cost.** ***NICE guidance (NG28):*** **Dual / Triple therapy:** *Can be used in dual or triple therapy regimens when control of blood glucose remains or becomes inadequate (HbA1c ≥ 59mmol/mol or agreed individualised target). Patients should be on maximally tolerated doses of oral hypoglycaemic agents **and** have a BMI;* • *≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or* • *< 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.* **Licensed in combination with:** • Oral glucose-lowering medicinal products (but not recommended with sulfonylureas) and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control. (See exenatide for comments on use with basal insulin)	Prescriber to decide most appropriate GLP-1 agonist after discussion with patient. If all other patient factors are equal prescribe the GLP-1 agonist with the lowest acquisition cost	**DUAL THERAPY - continue lixisenatide <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol (1%) after 6 months.** **TRIPLE THERAPY - continue lixisenatide <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol (1%) and a 3% loss of initial bodyweight after 6 months.** **Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.** No long term safety data available. **Renal impairment (CrCl, SPC):** • 50-80ml/min – no dose adjustment • 30-50ml/min – use with caution • <30ml/min – not recommended No dose adjustment required based on age, but limited therapeutic experience in patients > 75yrs. See exenatide for information on hypoglycaemia and **pancreatitis risk** (applies to all GLP-1 agonists).
Exenatide (Byetta®▼) Amb2 **Price per month**	**Twice daily subcutaneous injection** ***NICE guidance (NG28):*** **Dual / Triple therapy:** *Can be used in dual or triple therapy regimens when control*	Prescriber to decide most appropriate GLP-1 agonist after	**DUAL THERAPY - continue exenatide <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol (1%) after 6 months.** **TRIPLE THERAPY - continue exenatide <u>only</u> if the**

(May 19): 5 or 10mcg daily £81.89	*of blood glucose remains or becomes inadequate (HbA1c ≥ 59mmol/mol or agreed individualised target). Patients should be on maximally tolerated doses of oral hypoglycaemic agents **and** have a BMI;* • *≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or* • *< 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.* **Licensed indications:** Dual therapy with metformin, a sulfonylurea or pioglitazone. Triple therapy with metformin & a sulfonylurea or metformin & pioglitazone. **In combination with insulin:** Exenatide is licensed for addition to adult patients currently receiving insulin +/- metformin and/or pioglitazone who have not achieved adequate glycaemic control with these agents. Use with insulin has been approved for use locally only when patients fulfill the following criteria: • BMI >35 and HbA1c > 75mmol/mol and currently using insulin.	discussion with patient. If all other patient factors are equal prescribe the GLP-1 agonist with the lowest acquisition cost	**person has a reduction in HbA1c of ≥11mmol/mol (1%) and a 3% loss of initial bodyweight after 6 months.** **Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.** No long term safety data available. **Renal impairment (CrCl, SPC):** • 50-80ml/min – no dose adjustment • 30-50ml/min – dose escalation from 5 mcg to 10 mcg should proceed conservatively • <30ml/min – not recommended Use with caution and dose escalation from 5 mcg to 10 mcg should proceed conservatively in patients >70 years. The clinical experience in patients >75 years is very limited. **Applies to ALL GLP-1 agonists:** • Discuss the potential benefits and risks of treatment with a GLP-1 agonist with the person to enable them to make an informed decision. • Routine monitoring of blood glucose levels is only required if the GLP-1 agonist is given in combination with another agent likely to cause hypoglycaemia e.g. sulfonylurea. • There have been reports of necrotising and haemorrhagic **pancreatitis** with GLP-1 agonists, some of which were fatal. If pancreatitis is suspected, treatment with the GLP-1 agonist should be suspended immediately; if pancreatitis is diagnosed, the GLP-1 agonist should be permanently discontinued. (MHRA warning)

Exenatide prolonged release (Bydureon®▼)  **Price per month (May 19):** 2mg weekly: £73.36	**Once weekly subcutaneous injection** **NICE NG28** **Dual / Triple therapy:** *Can be used in dual or triple therapy regimens when control of blood glucose remains or becomes inadequate (HbA1c ≥ 59mmol/mol or agreed individualised target). Patients should be on maximally tolerated doses of oral hypoglycaemic agents **and** have a BMI;* • *≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or* *< 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities* **Licensed in combination with:** other glucose-lowering medicinal products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control.	Prescriber to decide most appropriate GLP-1 agonist after discussion with patient. If all other patient factors are equal prescribe the GLP-1 agonist with the lowest acquisition cost	**DUAL THERAPY - continue exenatide MR <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol (1%) after 6 months.** **TRIPLE THERAPY - continue exenatide MR <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol (1%) and a 3% loss of initial bodyweight after 6 months.** **Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.** No long term safety data available. **Renal impairment (CrCl, SPC):** • 50-80ml/min – no dose adjustment • <50ml/min – not recommended No dose adjustment required based on age, but limited therapeutic experience in patients > 75yrs. See exenatide for information on hypoglycaemia risk and warning about **pancreatitis risk** (applies to all GLP-1 agonists).
Dulaglutide (Trulicity▼)  **Price per month (May 19):** **0.75mg once weekly: £73.25** **1.5mg once weekly: £73.25**	**Once weekly subcutaneous injection** **NICE NG28** **Dual / Triple therapy:** *Can be used in dual or triple therapy regimens when control of blood glucose remains or becomes inadequate (HbA1c ≥ 59mmol/mol or agreed individualised target). Patients should be on maximally tolerated doses of oral hypoglycaemic agents **and** have a BMI;* • *≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and*	Prescriber to decide most appropriate GLP-1 agonist after discussion with patient. If all other patient factors are equal	**DUAL THERAPY - continue dulaglutide <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol^2 (1%) after 6 months.** **TRIPLE THERAPY - continue dulaglutide <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol^2 (1%) and a 3% loss of initial bodyweight after 6 months.** **Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing**

	specific psychological or medical problems associated with high body weight, or *< 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities* **Licensed in combination with:** Oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control. (See exenatide for comments on use with basal insulin)	prescribe the GLP-1 agonist with the lowest acquisition cost	**support from a consultant-led multidisciplinary team.** No long term safety data available. **Renal impairment (CrCl, SPC):** • 30-90ml/min - no dose adjustment • <30ml/min – not recommended No dose adjustment required based on age, but limited therapeutic experience in patients > 75yrs, in these patients start at 0.75mg weekly See exenatide for information on hypoglycaemia risk and warning about **pancreatitis risk** (applies to all GLP-1 agonists).
Liraglutide (Victoza®) Amb2 **Price per month (May 19):** 1.2mg daily £78.48	**Once daily subcutaneous injection** **NICE NG28** **Dual / Triple therapy:** *Can be used in dual or triple therapy regimens when control of blood glucose remains or becomes inadequate (HbA1c ≥ 59mmol/mol or agreed individualised target). Patients should be on maximally tolerated doses of oral hypoglycaemic agents **and** have a BMI;* • *≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or* • *< 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities* **Licensed in combination with:** Other medicinal products for the treatment of diabetes. (See exenatide for comments on use with basal insulin)	Prescriber to decide most appropriate GLP-1 agonist after discussion with patient. If all other patient factors are equal prescribe the GLP-1 agonist with the lowest acquisition cost	**DUAL THERAPY - continue liraglutide <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol^2 (1%) after 6 months.** **TRIPLE THERAPY - continue liraglutide <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol^2 (1%) and a 3% loss of initial bodyweight after 6 months.** **Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.** No long term safety data available. **Renal impairment (CrCl, SPC):** • Not recommended in End Stage Renal Disease No dose adjustment required based on age, but limited therapeutic experience in patients > 75yrs. See exenatide for information on hypoglycaemia risk and warning about **pancreatitis risk** (applies to all GLP-1 agonists).

Semaglutide (Ozempic®▼) Amb2 **Price per month (May 19):** 0.5mg weekly £73.25 1mg weekly £73.25	**Once weekly subcutaneous injection** **NICE NG28** **Dual / Triple therapy:** *Can be used in dual or triple therapy regimens when control of blood glucose remains or becomes inadequate (HbA1c ≥ 59mmol/mol or agreed individualised target). Patients should be on maximally tolerated doses of oral hypoglycaemic agents **and** have a BMI;* • *≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or* • *< 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities* **Licensed in combination with:** Other medicinal products for the treatment of diabetes	Prescriber to decide most appropriate GLP-1 agonist after discussion with patient. If all other patient factors are equal prescribe the GLP-1 agonist with the lowest acquisition cost	**DUAL THERAPY - continue semaglutide <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol^2 (1%) after 6 months.** **TRIPLE THERAPY - continue semaglutide <u>only</u> if the person has a reduction in HbA1c of ≥11mmol/mol^2 (1%) and a 3% loss of initial bodyweight after 6 months.** **Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.** No long term safety data available. **Renal impairment (CrCl, SPC):** • Not recommended in End Stage Renal Disease No dose adjustment required based on age, but limited therapeutic experience in patients > 75yrs. See exenatide for information on hypoglycaemia risk and warning about **pancreatitis risk** (applies to all GLP-1 agonists).

SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITOR Reversibly inhibits sodium-glucose co-transporter-2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.			
MEDICINE	**NOTES**	**FORMULARY CHOICE**	**PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS**
Dapagliflozin (Forxiga®▼)  **Price per 28 days (May 19):** 10mg* daily £36.59 *5mg available for patients with hepatic dysfunction-see pg. 22	**NICE TA288:** ***Dual therapy: Met + dapagliflozin:*** *Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:* • *a sulfonylurea is contraindicated or not tolerated or* • *the person is at significant risk of hypoglycaemia or its consequences.* ***Dapagliflozin + insulin:*** *Dapagliflozin in combination with insulin with or without other antidiabetic medicines is recommended as an option for treating type 2 diabetes.* ***Triple therapy: Met + gliclazide + dapagliflozin*** *Dapagliflozin is recommended for triple therapy when used in combination* ***with metformin and gliclazide. As per NICE TA 418*** **NICE TA390:** ***Monotherapy*** *Dapagliflozin is recommended as an option if metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:* • *a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and* • *a sulfonylurea or pioglitazone is not appropriate.* **Licensed in combination with:**	Prescriber to decide most appropriate SGLT2 inhibitor after discussion with patient. If all other patient factors are equal prescribe the SGLT2 inhibitor with the lowest acquisition cost.	No long term safety data available. Licensed for initiation in adults between 18 and 75 years only. **Renal impairment (eGFR or CrCl SPC):** • >60ml/min – no dose adjustment • <60ml/min – do not initiate dapagliflozin. • <45ml/min – discontinue dapagliflozin if CrCl is persistently below 45ml/min Due to its mechanism of action, patients taking dapagliflozin are at **increased risk of urinary tract infection** and **will test positive for glucose in their urine.** Increases diuresis associated with a modest decrease in blood pressure (more pronounced in patients with very high blood glucose concentrations). Not recommended for patients receiving loop diuretics or who are volume depleted e.g. due to acute illness (such as gastrointestinal illness). While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Canagliflozin may increase the risk of lower-limb amputation (mainly toes) in patients with type 2

	Other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.		diabetes. The risk may be a class effect. Carefully monitor patients who have risk factors for amputation and consider stopping SGLT2 inhibitor if patients develop foot complications. See MHRA warning for more information. Rare cases of Diabetic Ketoacidosis (DKA) have been reported in patients taking SGLT-2 inhibitors. Presentation can be atypical with only a moderate rise in blood glucose levels, below 14mmol/L. If DKA is suspected or diagnosed treatment with dapagliflozin should be discontinued. See MHRA warning for more information.
Canagliflozin (Invokana®▼) Amb3 **Price per 28 days (May 19):** 100mg or 300 mg daily £39.20	**NICE TA315:** ***Dual therapy: Met + Canagliflozin*** *Canagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:* • *a sulfonylurea is contraindicated or not tolerated or* • *the person is at significant risk of hypoglycaemia or its consequences.* ***Triple therapy: Met + (Glic or Pio) + Canagliflozin*** *Canagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:* • *metformin and a sulfonylurea or* • *metformin and a thiazolidinedione.* ***Canagliflozin + insulin:*** Canagliflozin in combination with insulin with or without other antidiabetic medicines is recommended as an option for treating type 2 diabetes. **NICE TA390:** ***Monotherapy*** *Canagliflozin is recommended as an option if metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:* • *a dipeptidyl peptidase-4 (DPP-4) inhibitor would*	Prescriber to decide most appropriate SGLT2 inhibitor after discussion with patient. If all other patient factors are equal prescribe the SGLT2 inhibitor with the lowest acquisition cost.	No long term safety data available. Licensed for adults aged over 18 years only. For patients over 65 years renal function and risk of volume depletion should be taken into account. **Renal impairment (eGFR or CrCl, SPC):** • 60-89ml/min – no dose adjustment. • <60ml/min – do not initiate canagliflozin. Max dose 100mg daily if eGFR or CrCl persistently falls below 60ml/min whilst on canagliflozin. • <45ml/min- discontinue if eGFR or CrCl is persistently below 45ml/min whilst on canagliflozin Due to its mechanism of action, patients taking canagliflozin are at **increased risk of urinary tract infection** and **will test positive for glucose in their urine.** Canagliflozin may increase the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. The risk may be a class effect. Carefully monitor patients who have risk factors for amputation and consider stopping SGLT2 inhibitor if patients

	otherwise be prescribed and • *a sulfonylurea or pioglitazone is not appropriate.* **Licensed in combination with:** Other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.		develop foot complications. See MHRA warning for more information. Rare cases of Diabetic Ketoacidosis (DKA) have been reported in patients taking SGLT-2 inhibitors. Presentation can be atypical with only a moderate rise in blood glucose levels, below 14mmol/L. If DKA is suspected or diagnosed treatment with Canagliflozin should be discontinued. See MHRA warning for more information.
Empagliflozin (Jardiance®▼) Amb3 **Price per 28 days (May 19):** 10mg or 25mg daily £36.59	**NICE TA336:** ***Dual therapy: Metformin + Empagliflozin*** *Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:* • *a sulfonylurea is contraindicated or not tolerated or* • *the person is at significant risk of hypoglycaemia or its consequences.* ***Triple therapy:*** *Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:* • *metformin and a sulfonylurea or* • *metformin and a thiazolidinedione.* ***Empagliflozin + insulin:*** *Empagliflozin in combination with insulin with or without other antidiabetic medicines is recommended as an option for treating type 2 diabetes.* **NICE TA390:** ***Monotherapy*** *Empagliflozin is recommended as an option if metformin is*	Prescriber to decide most appropriate SGLT2 inhibitor after discussion with patient. If all other patient factors are equal prescribe the SGLT2 inhibitor with the lowest acquisition cost.	No long term safety data available. No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be taken into account. In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience. **Renal impairment (eGFR or CrCl, SPC):** • 60-89ml/min – no dose adjustment. • <60ml/min – do not initiate empagliflozin. Max dose 10mg daily if eGFR or CrCl persistently falls below 60ml/min whilst on empagliflozin. • <45 ml/min- discontinue empagliflozin if eGFR or CrCl persistently falls below 45ml/min whilst on empagliflozin Due to its mechanism of action, patients taking empagliflozin are at increased risk of urinary tract infection and will test positive for glucose in their urine. Empagliflozin may increase the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. The risk may be a class effect. Carefully monitor patients who have risk factors for amputation and consider stopping SGLT2 inhibitor if patients

	contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if: • *a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and* • *a sulfonylurea or pioglitazone is not appropriate.* **Licensed in combination with:** Other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.		develop foot complications. See MHRA warning for more information. Rare cases of Diabetic Ketoacidosis (DKA) have been reported in patients taking SGLT-2 inhibitors. Presentation can be atypical with only a moderate rise in blood glucose levels, below 14mmol/L. If DKA is suspected or diagnosed treatment with Empagliflozin should be discontinued. See MHRA warning for more information.
Ertugliflozin (Steglatro®▼)  **Price per 28 days (May 19):** 5mg or 15mg daily £29.40	**NICE TA 572** **Monotherapy or dual therapy: Metformin + Ertugliflozin** *Ertugliflozin as monotherapy is recommended as an option for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemia control, only if:* • *A dipeptidyl peptidase 4 (DPP-4) inhibitor would otherwise be prescribed and* • *A sulfonylurea or pioglitazone is not appropriate* *Ertugliflozin in a dual-therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:* • *A sulfonylurea is contraindicated or not tolerated or* • *The person is at significant risk of hypoglycaemia or its consequences* **NICE TA 583** **Triple therapy: Metformin + DPP-4 + Ertugliflozin** *Ertugliflozin with metformin and dipeptidyl peptidatase-4 (DPP-4) inhibitor is recommended as an option for treating type 2 diabetes in adults when diet and exercise alone do not provide adequate glycaemic control, only if:* • *The disease is uncontrolled with metformin and a DPP-4 inhibitor, and* • *A sulfonylurea or pioglitazone is not appropriate.*	Prescriber to decide most appropriate SGLT2 inhibitor after discussion with patient. If all other patient factors are equal prescribe the SGLT2 inhibitor with the lowest acquisition cost.	No long term safety data available. Licensed for initiation in patients > 18 years. There is limited experience in patients > 75 years. **Renal impairment (eGFR or CrCl, SPC):** • 60-89ml/min – no dose adjustment. • <60ml/min – do not initiate ertugliflozin • <45ml/min- discontinue if eGFR or CrCl is persistently below 45ml/min Due to its mechanism of action, patients taking ertugliflozin are at **increased risk of urinary tract infection** and **will test positive for glucose in their urine.** Ertugliflozin may increase the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. The risk may be a class effect. Carefully monitor patients who have risk factors for amputation and consider stopping SGLT2 inhibitor if patients develop foot complications. See MHRA warning for more information. Rare cases of Diabetic Ketoacidosis (DKA) have been reported in patients taking SGLT-2 inhibitors. Presentation can be atypical with only a moderate rise

	Licensed in combination with: Other medicinal products for the treatment of diabetes		in blood glucose levels, below 14mmol/L. If DKA is suspected or diagnosed treatment with ertugliflozin should be discontinued. See MHRA warning for more information.

OTHER ANTIDIABETIC AGENTS			
MEDICINE	**NOTES**	**FORMULARY CHOICE**	**PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS**
Acarbose (Glucobay®)  Inhibits intestinal alpha glucosidases (delays digestion and absorption of starch and sucrose) **Price per 28 days (May 19):** 50mg- 200mg three times daily £11.51- £38.06	Useful in the occasional overweight patient. ***No longer recommended in NICE guidance on treating type 2 diabetes*** **Licensed indication:** Acarbose tablets are recommended for the treatment of T2D in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.		Usage limited by gastrointestinal intolerance.

Insulin Therapy in T2D

Insulin treatment

- If other measures do not keep HbA1c to <59 mmol/mol (or other agreed target), discuss benefits and risk of insulin treatment.
- **Initiate with a structured programme including patient education and management plan.** Insulin therapy should be initiated from a choice of a number of insulin types and regimens by a practitioner with the appropriate knowledge, competencies and experience to choose the most appropriate starting regimen tailored to each patient.
- Begin with human NPH insulin (Isophane insulin e.g. Insulatard®, Humulin I®, Insuman® Basal) taken at bedtime or twice daily according to need.
- **There is no evidence of a clinical benefit of analogue insulins over human insulins in T2D.**
- Consider starting both NPH and short-acting insulin, particularly where HbA1c >75mmol/mol administered either separately or as a pre-mixed (biphasic) human insulin preparation. Consider pre-**mixed (biphasic) preparations that include rapid acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if:**
    - A person prefers injecting insulin immediately before a meal, or
    - Hypoglycaemia is a problem, or
    - Blood glucose levels rise markedly after meals
- Insulin analogues rather than NPH insulin preparations should only be considered when:
    - The person needs assistance from a carer or healthcare professional to inject insulin, and the use of insulin detemir or insulin glargine would reduce the frequency of injections from twice daily to once daily, or
    - The person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or
    - People cannot use the device needed to inject NPH but could administer their own insulin safely and accurately if switched to a long acting analogue, or
    - The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering medicines.
- Recurrent symptomatic hypoglycaemia should prompt a re-examination of the current insulin regimen, injection sites, a search for other co-morbidities (such as liver or renal disease) and a review of the agreed HbA1c target. If tight control is still required, then consider a trial of analogue insulin.
- **Where insulin glargine is considered appropriate, new patients should be initiated on a Glargine Biosimilar** (see formulary for recommended brand). **This should be prescribed by brand.**
- Note that insulin degludec and insulin glargine 300 units/ ml (Toujeo®) may only be initiated for defined patient groups (see formulary for more detail).
- Monitor a person using a basal insulin regimen (NPH or a long-acting insulin analogue [insulin glargine/detemir]) for the need for mealtime insulin (or a pre-mixed insulin preparation). If blood glucose control remains inadequate (not to agreed target levels without problematic hypoglycaemia), move to a more intensive, twice/three times daily biphasic insulin or mealtime plus basal insulin regimen (basal bolus).
- Human insulins (such as Humulin S®, Actrapid®, Insuman Rapid®, Isophane insulin, biphasic isophane insulin) should be considered as first line therapy before moving to analogue or analogue mixtures. Insulin analogues should only be considered if one of the criteria described above is met.

- Monitor a person using pre-mixed insulin once or twice daily for the need for a further pre-prandial injection or for an eventual change to a mealtime plus basal insulin regimen, based on human or analogue insulins, if blood glucose control remains inadequate.

Oral agent combination therapy with insulin

- When starting basal insulin therapy:
    - Continue with metformin for people without contraindications or intolerance. Review the need for other blood glucose lowering therapies
- When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):
    - Continue with metformin
    - Consider combining an SGLT2 inhibitor with insulin therapy if:
        - An SGLT2 inhibitor has previously had a marked glucose lowering effect, or
        - Blood glucose control is inadequate with high dose insulin.

Use of GLP1 analogues in combination with insulin

- Exenatide, lixisenatide, dulaglutide and liraglutide are licensed for addition to patients currently receiving insulin.
- Use of GLP1 analogues with insulin has been approved for use locally only when patients fulfill the following criteria; morbidly obese (BMI >35) **and** HbA1c >75mmol/mol **and** currently using insulin.
- This regimen must be initiated by a specialist.
- **Continue the GLP1 in combination with insulin only if the person has a reduction in HbA1c of ≥11mmol/mol and a 3% loss of initial bodyweight in 6 months**.

Intensifying the insulin regimen

- Monitor those using basal insulin regimens for the need for short acting insulin before meals or pre-mixed insulin.
- Monitor those using premixed insulin once or twice daily for need for further injections of short acting insulin before meals or change to mealtime plus basal regimen.

Insulin delivery devices

- Offer education to a person who requires insulin on using an injection device (usually a pen injector and cartridge or a disposable pen) to ensure that that they and/or their carer find it easy to use.
- Appropriate local arrangements should be in place for the disposal of sharps.
- Only insulin detemir (Levemir®) and Insulatard® can be used with the Innolet® device.
- If a person has a manual or visual disability and requires insulin, offer a device or adaptation that:
    - takes into account his or her individual needs
    - he or she can use successfully.

	Worsening renal function (GFR range in ml/min)						Hepatic Impairment	
MEDICINE	**CKD stage1 (GFR>90)**	**2 (90-60)**	**3a (59-45)**	**3b (44-30)**	**4 (29-15)**	**5 (< 15 or RRT)**	**Mild / Moderate**	**Severe**
Acarbose	✓	✓	✓	✓	✖ **(GFR <25ml/min)**		✓	✖ Contraindicated
Metformin / Metformin MR	✓	✓	✓	✓ (review regularly)	✖		Risks/benefits should be discussed in mild to moderate dysfunction	✖ Contraindicated
Gliclazide / Gliclazide MR	✓	✓	✓	✓	✓ (Use lowest effective dose)	✖	✓	✖ Contraindicated
Sitagliptin	**100mg**		**50mg** (GFR<50ml/min)		**25mg**		✓	✖ Not studied in severe hepatic impairment
Alogliptin	✓	✓	✓ (Decrease to 12.5mg if CrCl <50ml/min		✓ (Decrease to 6.25mg if CrCl <30ml/min		✓	✖ Not studied in severe hepatic impairment
Linagliptin	✓	✓	✓	✓	✓	✓	✓ No dose adjustment required, but clinical experience is lacking in hepatic impairment	
Pioglitazone	✓	✓	✓	✓	✓	✓ (not if dialysis)	✖ Contraindicated	✖ Contraindicated
Lixisenatide	✓	✓	✓ (Caution if GFR <50ml/min)		✖		✓	✓
Exenatide	✓	✓	✓	✓ (conservative dose escalation)	✖		✓	✓
Exenatide MR	✓	✓	✓ (not if GFR<50ml/min)	✖			✓	✓
Liraglutide	✓	✓	✓	✓	✓	✖	✓	✖ Not recommended
Dulaglutide	✓	✓	✓	✓	✖		✓	✓
Semaglutide	✓	✓	✓	✓	✓	✖	✓	✓
Dapagliflozin	✓	✓	✖ **(Do not initiate if GFR < 60ml/min. Discontinue if GFR persistently falls below 45ml/min**				✓	✓ Start at 5mg, increase to 10mg if well tolerated
Canagliflozin	✓	✓	✖ (Do not initiate if GFR <60ml/min, max dose 100mg od if GFR persistently falls below 60ml/min after initiation). Discontinue if GFR persistently falls below 45ml/min				✓	✖ Not recommended

Empagliflozin	✓	✓	× (Do not initiate if GFR <60ml/min, max dose 10mg od if GFR persistently falls below 60ml/min after initiation). Discontinue if GFR persistently falls below 45ml/min		✓	× Not recommended
Ertugliflozin	✓	✓	**× (Do not initiate if GFR < 60ml/min. Discontinue if GFR persistently falls below 45ml/min**		✓	× Not recommended
Insulin	✓	✓	✓	✓	✓ Requirements may be reduced in severe renal impairment – monitor and adjust dose accordingly	✓ Requirements may be altered in hepatic impairment – monitor and adjust dose accordingly

N.B. In patients at extremes of weight (BMI <18.5 kg/m^2 or >30 kg/m^2) or age (>70yr), calculate renal function using Cockcroft and Gault equation (see calculator available here). **Source of data is NICE guidance and manufacturers' recommendations. The Renal Drug Database** (password required) **may recommend lower thresholds for dose reductions.**

Type 2 diabetes mellitus treatments – Dual therapy combination table

Alphabetical > / Grouped by class v	Alogliptin	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin	Exenatide	Exenatide MR	Glicazide	Gliclazide MR	Insulin	Linagliptin	Liraglutide	Dulaglutide	Lixisenatide	Metformin	Metformin MR	Pioglitazone	Sitagliptin
Metformin	Y	Y	Y	Y	Y	NICE	NICE	Y	Y	Y	Y	NICE	NICE	NICE			Y	Y
Metformin MR	Y	Y	Y	Y	Y	NICE	NICE	Y	Y	Y	Y	NICE	NICE	NICE			Y	Y
Glicazide	Y	NICE	NICE	NICE	NICE	NICE	NICE			Y	Y	NICE	NICE	NICE	Y	Y	Y	Y
Gliclazide MR	Y	NICE	NICE	NICE	NICE	NICE	NICE			Y	Y	NICE	NICE	NICE	Y	Y	Y	Y
Alogliptin		NICE	NICE	NICE	NICE	NICE	NICE	Y	Y	Y		NICE	NICE	NICE	Y	Y	Y	
Linagliptin		NICE	NICE	NICE	NICE	NICE	NICE	Y	Y	Y		NICE	NICE	NICE	Y	Y	Y	
Sitagliptin		NICE	NICE	NICE	NICE	NICE	NICE	Y	Y	Y		NICE	NICE	NICE	Y	Y	Y	
Pioglitazone	Y	NICE	NICE	NICE	NICE	NICE	NICE	Y	Y	Y	Y	NICE	NICE	NICE	Y	Y		Y
Exenatide	NICE	NICE	NICE	NICE	NICE			NICE	NICE	Y	NICE				NICE	NICE	NICE	NICE
Exenatide MR	NICE	NICE	NICE	NICE	NICE			NICE	NICE	Y	NICE				NICE	NICE	NICE	NICE
Lixisenatide	NICE	NICE	NICE	NICE	NICE			NICE	NICE	Y	NICE				NICE	NICE	NICE	NICE
Liraglutide	NICE	NICE	NICE	NICE	NICE			NICE	NICE	Y	NICE				NICE	NICE	NICE	NICE
Dulaglutide	NICE	NICE	NICE	NICE	NICE			NICE	NICE	Y	NICE				NICE	NICE	NICE	NICE
Canagliflozin	NICE				NICE	NICE	NICE	NICE	NICE	Y	NICE	NICE	NICE	NICE	Y	Y	NICE	NICE
Dapagliflozin	NICE				NICE	NICE	NICE	NICE	NICE	Y	NICE	NICE	NICE	NICE	Y	Y	NICE	NICE
Empagliflozin	NICE				NICE	NICE	NICE	NICE	NICE	Y	NICE	NICE	NICE	NICE	Y	Y	NICE	NICE
Ertugliflozin	NICE	NICE	NICE	NICE		NICE	NICE	NICE	NICE	Y	NICE	NICE	NICE	NICE	Y	Y	NICE	NICE
Insulin	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y	Y	Y	Y	Y	Y

Key:

L	Not Licensed	NICE	Not recommended by NICE	Y	Combination licensed and can be used as per guideline		Combination not recommended	Y*	Licensed, but limited data

Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes. APC approved March 2017 (Updated May 17 with NICE update, Feb 18 with minor licensing changes, Sept 18, Jan 19 with formulary changes, May 19 to include new medications and licensing updates, July 2019 with NICE TA, September 2019 with update to sitagliptin renal dosing)

Type 2 diabetes mellitus treatments –Triple therapy combination table (see page 24 for key)

Grouped by class> / Grouped by class v	Met + Gliclazide	Met + Piogltazone	Met + alogliptin	Met + linagliptin	Met + sitagliptin	Met + canagliflozin	Met + dapagliflozin	Met + empagliflozin	Met + Exenatide	Met + Exenatide MR	Met + liraglutide	Met + lixisenatide	Met + insulin	Gliclazide + sitagliptin	Gliclazide+ linagliptin	Gliclazide + pioglitazone	Gliclazide+ exenatide	Gliclazide+ exenatide MR	Gliclazide+ lixisenatide	Gliclazide + liraglutide	Gliclazide + insulin
Metformin														Y	Y	Y	Y	Y	Y	Y	Y
Metformin MR														Y	Y	Y	Y	Y	Y	Y	Y
Glicazide		Y	Y*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y								
Gliclazide MR		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y								
Alogliptin	Y*	NICE				NICE	NICE	NICE	NICE	NICE	NICE	NICE	Y			NICE	NICE	NICE	NICE	NICE	Y
Linagliptin	Y	NICE				NICE	NICE	NICE	NICE	NICE	NICE	NICE	Y			NICE	NICE	NICE	NICE	NICE	Y
Sitagliptin	Y	NICE				NICE	NICE	NICE	NICE	NICE	NICE	NICE	Y			NICE	NICE	NICE	NICE	NICE	L
Pioglitazone	Y		NICE	NICE	NICE	Y	NICE	Y	NICE	NICE	NICE	NICE	L	NICE	NICE		NICE	NICE	NICE	NICE	L
Exenatide	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE					Y	NICE	NICE	NICE					L
Exenatide MR	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE					Y	NICE	NICE	NICE					Y
Lixisenatide	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE					Y	NICE	NICE	NICE					Y
Liraglutide	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE					Y	NICE	NICE	NICE					Y
Dulaglutide	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE					Y	NICE	NICE	NICE					Y
Semaglutide	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE					Y	NICE	NICE	NICE					Y
Canagliflozin	Y	Y	NICE	NICE	NICE				NICE	NICE	NICE	NICE	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE	Y
Dapagliflozin	Y	Y	NICE	NICE	NICE				NICE	NICE	NICE	NICE	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE	Y
Empagliflozin	Y	Y	NICE	NICE	NICE				NICE	NICE	NICE	NICE	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE	Y
Ertugliflozin	Y	Y	NICE	NICE	NICE				NICE	NICE	NICE	NICE	Y	NICE	NICE	NICE	NICE	NICE	NICE	NICE	Y
Insulin	Y	L	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		L	Y	L	L	Y	Y	Y	

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