NICE National Institute for Health and Care Excellence

Blood-glucose-lowering therapy for type 2 diabetes

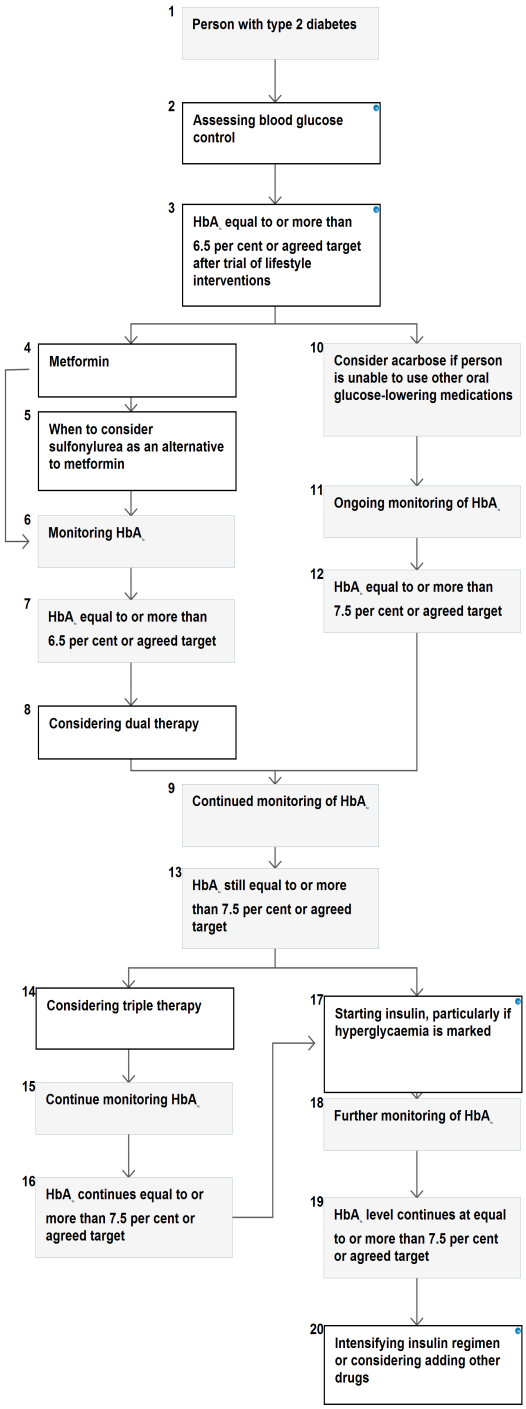
A NICE pathway brings together all NICE guidance, quality standards and materials to support implementation on a specific topic area. The pathways are interactive and designed to be used online. This pdf version gives you a single pathway diagram and uses numbering to link the boxes in the diagram to the associated recommendations.

To view the online version of this pathway visit:

http://pathways.nice.org.uk/pathways/diabetes

Pathway last updated: 10 September 2014

NICE *Pathways*



1 Person with type 2 diabetes

No additional information

2 Assessing blood glucose control

HbA_{1c}

Discuss individual HbA_{1c} target level, which may be above the general target of 6.5%.

Encourage maintaining target unless resulting side effects or efforts to achieve this impair quality of life.

Discuss how any reduction in HbA_{1c} towards agreed target benefits future health.

Offer therapy (lifestyle and medication) to help achieve and maintain HbA_{1c} target.

Measure using high-precision methods and report results in DCCT-aligned units.

If HbA_{1c} remains above target, but pre-meal self-monitoring levels remain well controlled (less than 7.0 mmol/litre), consider self-monitoring to detect postprandial hyperglycaemia (greater than 8.5 mmol/litre), and manage to below this level if detected.

Monitoring

Monitor 2–6 monthly (according to individual needs) until stable on unchanging therapy[1].

Monitor 6-monthly once blood glucose level and blood glucose-lowering therapy are stable.

Further investigation

Seek advice from a team with specialist expertise in diabetes or clinical biochemistry if there are unexplained discrepancies between HbA_{1c} and other glucose measurements.

Special circumstances

If HbA_{1c} result is invalid[2], estimate trends in blood glucose control using one of the following:

- fructosamine estimation

[1] Use measurements taken at intervals of < 3 months to indicate direction of change, rather than a new steady state.

[2] Disturbed erythrocyte turnover and abnormal haemoglobin type make HbA_{1c} results invalid.

- quality-controlled plasma glucose profiles
- total glycated haemoglobin estimation (if abnormal haemoglobins).

Self-monitoring

Self-monitoring of plasma glucose should be available:

- to those on insulin treatment
- to those on oral glucose-lowering medications to provide information on hypoglycaemia
- to assess changes in glucose control resulting from medications and lifestyle change
- to monitor changes during intercurrent illness
- to ensure safety during activities, including driving.

Discuss the purpose of self-monitoring and how to interpret and act on the results.

Offer to a person newly diagnosed only as an integral part of self-management education.

Monitoring

Assess at least annually, and in a structured way:

- self-monitoring skills
- the quality and frequency of testing
- how the results are used
- the impact on quality of life
- the continued benefit
- the equipment used.

Discuss urine glucose monitoring if plasma monitoring is found to be unacceptable.

Quality standards

The following quality statement is relevant to this part of the pathway.

4. Glycaemic control

3 HbA_{1c} equal to or more than 6.5 per cent or agreed target after trial of lifestyle interventions

The diabetes quality standard contains quality statements about glycaemic control and medication for people with diabetes.

Quality standards

The following quality statements are relevant to this part of the pathway.

4. Glycaemic control

5. Medication

4 Metformin

Step up metformin over several weeks to minimise risk of gastrointestinal (GI) side effects.

Consider trial of extended-absorption metformin if GI tolerability prevents the person continuing with metformin.

Review metformin dose if serum creatinine > 130 micromol/litre or estimated glomerular filtration rate (eGFR) < 45 ml/minute/1.73 m^2.

Stop metformin if serum creatinine > 150 micromol/litre or the eGFR < 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 to < 45 ml/minute/1.73 m^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.

5 When to consider sulfonylurea as an alternative to metformin

Consider sulfonylurea here if:

- not overweight (tailor the assessment of body-weight-associated risk according to ethnic group, see the diet pathway for more information)
- metformin is not tolerated or is contraindicated, or
- a rapid therapeutic response is required because of hyperglycaemic symptoms.

Offer once-daily sulfonylurea if adherence is a problem.

Prescribe a sulfonylurea with a low acquisition cost (not glibenclamide) when an insulin secretagogue is indicated.

Educate the person about the risk of hypoglycaemia, particularly if he or she has renal impairment.

6 Monitoring HbA1c

No additional information

7 HbA1c equal to or more than 6.5 per cent or agreed target

No additional information

8 Considering dual therapy

Sulfonylurea

Offer once-daily sulfonylurea if adherence is a problem.

Prescribe a sulfonylurea with a low acquisition cost (not glibenclamide) when an insulin secretagogue is indicated.

Educate the person about the risk of hypoglycaemia, particularly if he or she has renal impairment.

DPP-4 inhibitors (sitagliptin, vildagliptin)

Consider substituting a DPP-4 inhibitor (sitagliptin, vildagliptin) for sulfonylurea if there is significant risk of hypoglycaemia (or its consequences) or a sulfonylurea is contraindicated or not tolerated.

Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) to sulfonylurea if metformin is contraindicated or not tolerated.

Continue DPP-4 inhibitor therapy only if there is a reduction of ≥ 0.5 percentage points in HbA_{1c} in 6 months.

Discuss the benefits and risks of a DPP-4 inhibitor with the person, bearing in mind that a DPP-4 inhibitor might be preferable to a thiazolidinedione if:

- further weight gain would cause significant problems, or
- a thiazolidinedione is contraindicated, or
- the person had a poor response to or did not tolerate a thiazolidinedione in the past.

Thiazolidinedione (pioglitazone)

Consider substituting a thiazolidinedione (pioglitazone) for sulfonylurea if there is significant risk of hypoglycaemia (or its consequences) or a sulfonylurea is contraindicated or not tolerated.

Consider adding a thiazolidinedione (pioglitazone) to sulfonylurea if metformin is contraindicated or not tolerated.

Continue thiazolidinedione therapy only if there is a reduction of ≥ 0.5 percentage points in HbA_{1c} in 6 months.

Do not start or continue a thiazolidinedione if the person has heart failure or is at higher risk of fracture.

When selecting a thiazolidinedione, take into account the most up-to-date advice from regulatory authorities, cost, safety and prescribing issues.

Discuss the benefits and risks of a thiazolidinedione with the person, bearing in mind that a thiazolidinedione might be preferable to a DPP-4 inhibitor if:

- the person has marked insulin insensitivity, or
- a DPP-4 inhibitor is contraindicated, or
- the person had a poor response to or did not tolerate a DPP-4 inhibitor in the past.

MHRA advice on risk of bladder cancer with pioglitazone

The Medicines and Healthcare products Regulatory Agency has issued new advice on risk of bladder cancer with the anti-diabetic drug pioglitazone. Please refer to the MHRA advice when prescribing pioglitazone.

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.

People currently receiving treatment initiated within the NHS with canagliflozin that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

These recommendations are from Canagliflozin in combination therapy for treating type 2 diabetes (NICE technology appraisal guidance 315).

NICE has written information for the public explaining the guidance on canagliflozin.

Dapagliflozin

Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described above for DPP-4 inhibitors.

People currently receiving dapagliflozin in a dual therapy regimen that is not recommended for them should be able to continue treatment until they and their clinician consider it appropriate to stop.

These recommendations are from Dapagliflozin in combination therapy for treating type 2 diabetes (NICE technology appraisal guidance 288).

NICE has written information for the public explaining the guidance on dapagliflozin.

Liraglutide

Liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulphonylurea) is recommended as an option for the treatment of people with type 2 diabetes, only if:

- the person is intolerant of either metformin **or** a sulphonylurea, or treatment with metformin or a sulphonylurea is contraindicated, **and**
- the person is intolerant of thiazolidinediones **and** DPP-4 inhibitors, or treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.

Treatment with liraglutide 1.2 mg daily in a dual therapy regimen should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} at 6 months).

Liraglutide 1.8 mg daily is not recommended for the treatment of people with type 2 diabetes.

People with type 2 diabetes currently receiving liraglutide who do not meet the criteria specified, or who are receiving liraglutide 1.8 mg, should have the option to continue their treatment until they and their clinicians consider it appropriate to stop.

These recommendations are from Liraglutide for the treatment of type 2 diabetes mellitus (NICE technology appraisal guidance 203).

NICE has written information for the public explaining the guidance on liraglutide.

Prolonged-release exenatide

Prolonged-release exenatide in dual therapy regimens (that is, in combination with metformin or a sulphonylurea) is recommended as a treatment option for people with type 2 diabetes, as described above for liraglutide; that is, only if:

- the person is intolerant of either metformin **or** a sulphonylurea, or a treatment with metformin **or** a sulphonylurea is contraindicated, **and**
- the person is intolerant of thiazolidinediones and DPP-4 inhibitors, **or** a treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.

Treatment with prolonged-release exenatide in a dual therapy regimen should only be continued as described above for liraglutide; that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} [11 mmol/mol] at 6 months).

These recommendations are from Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes (NICE technology appraisal guidance 248).

NICE has written information for the public explaining the guidance on exenatide.

Rapid-acting insulin secretagogue

Consider a rapid-acting insulin secretagogue for people with erratic lifestyles.

Resources

The following implementation tools are relevant to this part of the pathway.

Canagliflozin in combination therapy for treating type 2 diabetes: costing report

Canagliflozin in combination therapy for treating type 2 diabetes: costing template

GLP-1 agonists for the treatment of type 2 diabetes: clinical audit tool

Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes: costing statement

Dapagliflozin in combination therapy for treating type 2 diabetes: costing template

Liraglutide for the treatment of type 2 diabetes mellitus: costing template

9 Continued monitoring of HbA1c

No additional information

10 Consider acarbose if person is unable to use other oral glucose-lowering medications

No additional information

11 Ongoing monitoring of HbA1c

No additional information

12 HbA1c equal to or more than 7.5 per cent or agreed target

No additional information

13 HbA1c still equal to or more than 7.5 per cent or agreed target

No additional information

14 Considering triple therapy

Sitagliptin or pioglitazone

Consider adding sitagliptin or pioglitazone instead of insulin if insulin is unacceptable (because of employment, social, recreational or other personal issues, or obesity).

Continue DPP-4 inhibitor therapy only if there is a reduction of ≥ 0.5 percentage points in HbA_{1c} in 6 months.

Discuss the benefits and risks of a DPP-4 inhibitor with the person, bearing in mind that a DPP-4 inhibitor might be preferable to a thiazolidinedione if:

- further weight gain would cause significant problems, or
- a thiazolidinedione is contraindicated, or
- the person had a poor response to or did not tolerate a thiazolidinedione in the past.

Continue thiazolidinedione therapy only if there is a reduction of ≥ 0.5 percentage points in HbA_{1c} in 6 months.

Do not start or continue a thiazolidinedione if the person has heart failure or is at higher risk of fracture.

When selecting a thiazolidinedione, take into account the most up-to-date advice from regulatory authorities, cost, safety and prescribing issues.

Discuss the benefits and risks of a thiazolidinedione with the person, bearing in mind that a thiazolidinedione might be preferable to a DPP-4 inhibitor if:

- the person has marked insulin insensitivity, or
- a DPP-4 inhibitor is contraindicated, or
- the person had a poor response to or did not tolerate a DPP-4 inhibitor in the past.

MHRA advice on risk of bladder cancer with pioglitazone

The Medicines and Healthcare products Regulatory Agency has issued new advice on risk of bladder cancer with the anti-diabetic drug pioglitazone. Please refer to the MHRA advice when prescribing pioglitazone.

Exenatide

Twice-daily exenatide

Consider adding exenatide to metformin and a sulfonylurea if:

- BMI ≥ 35 kg/m^2 in people of European descent[1] and there are problems associated with high weight, or
- BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.

Continue exenatide only if the person has a reduction in HbA_{1c} of ≥ 1.0 percentage point and ≥ 3% of initial body weight in 6 months.

Discuss the benefits of exenatide to allow the person to make an informed decision.

Prolonged-release exenatide

Prolonged-release exenatide in triple therapy regimens (that is, in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes as described above for twice-daily exenatide; that is, when control of blood glucose remains or becomes inadequate (HbA_{1c} = 7.5% [59 mmol/mol] or other higher level agreed with the individual), and the person has:

- a BMI = 35 kg/m^2 in those of European family origin (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight **or**

[1] With adjustment for other ethnic groups.

- a BMI < 35 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

Treatment with prolonged-release exenatide in a triple therapy regimen should only be continued as described above for twice-daily exenatide; that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} [11 mmol/mol] and a weight loss of at least 3% of initial body weight at 6 months).

These recommendations are from Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes (NICE technology appraisal guidance 248).

NICE has written information for the public explaining the guidance on exenatide.

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.

This recommendation is from Canagliflozin in combination therapy for treating type 2 diabetes (NICE technology appraisal guidance 315).

NICE has written information for the public explaining the guidance on canagliflozin.

Liraglutide

Liraglutide 1.2 mg daily in triple therapy regimens (in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as an option for the treatment of people with type 2 diabetes, only when control of blood glucose remains or becomes inadequate ({HbA_{1c} ≥ 7.5%}, or other higher level agreed with the individual), and the person has:

- a body mass index (BMI) ≥ 35 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
- a BMI < 35 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

Treatment with liraglutide 1.2 mg daily in a triple therapy regimen should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months).

Liraglutide 1.8 mg daily is not recommended for the treatment of people with type 2 diabetes.

People with type 2 diabetes currently receiving liraglutide who do not meet the criteria specified, or who are receiving liraglutide 1.8 mg, should have the option to continue their treatment until they and their clinicians consider it appropriate to stop.

These recommendations are from Liraglutide for the treatment of type 2 diabetes mellitus (NICE technology appraisal guidance 203).

NICE has written information for the public explaining the guidance on liraglutide.

Dapagliflozin

Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended within its marketing authorisation for treating type 2 diabetes, except as part of a clinical trial.

People currently receiving dapagliflozin in a triple therapy regimen that is not recommended for them should be able to continue treatment until they and their clinician consider it appropriate to stop.

These recommendations are from Dapagliflozin in combination therapy for treating type 2 diabetes (NICE technology appraisal guidance 288).

NICE has written information for the public explaining the guidance on dapagliflozin.

Resources

The following implementation tools are relevant to this part of the pathway.

Canagliflozin in combination therapy for treating type 2 diabetes: costing report

Canagliflozin in combination therapy for treating type 2 diabetes: costing template

GLP-1 agonists for the treatment of type 2 diabetes: clinical audit tool

Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes: costing statement

Liraglutide for the treatment of type 2 diabetes mellitus: costing template

Dapagliflozin in combination therapy for treating type 2 diabetes: costing template

15 Continue monitoring HbA1c

No additional information

16 HbA1c continues equal to or more than 7.5 per cent or agreed target

No additional information

17 Starting insulin, particularly if hyperglycaemia is marked

If other measures do not keep HbA_{1c} to < 7.5% (or other agreed target), discuss benefits and risks of insulin treatment.

Initiate with a structured programme. For more information see the patient education section of this pathway.

Continue with metformin and sulfonylurea (and acarbose, if used), but only continue other drugs that are licensed for use with insulin. Review the use of sulfonylurea if hypoglycaemia occurs.

Begin with human NPH insulin taken at bedtime or twice daily according to need.

Alternatively, consider a once-daily long-acting insulin analogue (insulin detemir, insulin glargine) if:

- the person needs help with injecting insulin and a long-acting insulin analogue would reduce injections from twice to once daily, or
- the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or
- the person would otherwise need twice-daily basal insulin injections plus oral glucose-lowering drugs, or
- the person cannot use the device to inject NPH insulin.

Consider twice-daily biphasic human insulin (pre-mixed) (particularly if HbA_{1c} ≥ 9.0%). A once-daily regimen may be an option.

Consider pre-mixed preparations of insulin analogues (including short-acting insulin analogues) rather than pre-mixed human insulin preparations if:

- immediate injection before a meal is preferred, or
- hypoglycaemia is a problem, or
- blood glucose levels rise markedly after meals.

Consider switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin if the person:

- does not reach target HbA_{1c} because of hypoglycaemia, or
- has significant hypoglycaemia with NPH insulin irrespective of HbA_{1c} level, or
- cannot use the delivery device for NPH insulin but could administer a long-acting insulin analogue, or
- needs help to inject insulin and could reduce the number of injections with a long-acting analogue.

Insulin pump therapy (CSII)

CSII therapy is not recommended for the treatment of people with type 2 diabetes mellitus.

This recommendation is from Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (NICE technology appraisal guidance 151).

Insulin delivery devices

Offer education to a person who requires insulin about using an injection device (usually a pen injector and cartridge or a disposable pen) that they and/or their carer find easy to use.

If a person has a manual or visual disability and requires insulin, offer an appropriate device or adaptation that can be used successfully.

Appropriate local arrangements should be in place for the disposal of sharps.

Quality standards

The following quality statement is relevant to this part of the pathway.

6. Insulin therapy

18 Further monitoring of HbA1c

No additional information

19 HbA1c level continues at equal to or more than 7.5 per cent or agreed target

No additional information

20 Intensifying insulin regimen or considering adding other drugs

Increase insulin dose and intensify regimen over time.

Monitor those using basal insulin regimens (NPH or a long-acting analogue [insulin detemir, insulin glargine]) for need for short-acting insulin before meals or pre-mixed insulin.

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

Pioglitazone with insulin

Consider pioglitazone with insulin if:

- a thiazolidenedione has previously had a marked glucose-lowering effect, or
- blood glucose control is inadequate with high-dose insulin.

Continue thiazolidinedione therapy only if there is a reduction of ≥ 0.5 percentage points in HbA_{1c} in 6 months.

Do not start or continue a thiazolidinedione if the person has heart failure or is at higher risk of fracture.

When selecting a thiazolidinedione, take into account the most up-to-date advice from regulatory authorities, cost, safety and prescribing issues.

Discuss the benefits and risks of a thiazolidinedione with the person.

MHRA advice on risk of bladder cancer with pioglitazone

The Medicines and Healthcare products Regulatory Agency has issued new advice on risk of bladder cancer with the anti-diabetic drug pioglitazone. Please refer to the MHRA advice when prescribing pioglitazone.

Canagliflozin with insulin

Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

This recommendation is from Canagliflozin in combination therapy for treating type 2 diabetes (NICE technology appraisal guidance 315).

NICE has written information for the public explaining the guidance on canagliflozin.

Dapagliflozin with insulin

Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

This recommendation is from Dapagliflozin in combination therapy for treating type 2 diabetes (NICE technology appraisal guidance 288).

NICE has written information for the public explaining the guidance on dapagliflozin.

Quality standards

The following quality statement is relevant to this part of the pathway.

6. Insulin therapy

Resources

The following implementation tool is relevant to this part of the pathway.

Canagliflozin in combination therapy for treating type 2 diabetes: costing report

Canagliflozin in combination therapy for treating type 2 diabetes: costing template

Dapagliflozin in combination therapy for treating type 2 diabetes: costing template

Sources

Type 2 diabetes - newer agents (partial update of CG66). NICE clinical guideline 87 (2009)

Canagliflozin in combination therapy for treating type 2 diabetes. NICE technology appraisal guidance 315 (2014)

Dapagliflozin in combination therapy for treating type 2 diabetes. NICE technology appraisal guidance 288 (2013)

Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. NICE technology appraisal guidance 248 (2012)

Liraglutide for the treatment of type 2 diabetes mellitus. NICE technology appraisal guidance 203 (2010)

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. NICE technology appraisal guidance 151 (2008)

Your responsibility

The guidance in this pathway represents the view of NICE, which was arrived at after careful consideration of the evidence available. Those working in the NHS, local authorities, the wider public, voluntary and community sectors and the private sector should take it into account when carrying out their professional, managerial or voluntary duties. Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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