

Guideline for antihyperglycaemic therapy in adults with type 2 diabetes

Version Control

Version Number	Date	Amendments made
1	January 2018	
1.1	February 2018	Amended to reflect updated SPC advice for sitagliptin dosage adjustment in renal impairment.
1.2	April 2018	Amended to reference appendix B within the algorithm pages and to reflect updated SPC renal impairment advice for dulaglutide. Glimepiride added to appendix B
1.3	September 2018	Statement added regarding the use of combination GLP-1 mimetics and insulin. Statement relating to continuation of GLP-1 mimetics highlighted in bold red.
1.4	January 2019	Updated SPC advice relating to renal impairment in dapagliflozin included
1.5	November 2019	Cardiovascular section added to patient factors. Amendments made to preferred agents for GLP-1 mimetics and SGLT-2 agents.

Care after diagnosis and education

- An individualised approach to diabetes care should be adopted taking into account patient factors including frailty, susceptibility to hypoglycaemia, weight, cardiovascular risk and renal function.
- Upon diagnosis **ALL** patients should be offered structured education (DESMOND, X-PERT or locally approved courses) within 6-12 months of diagnosis.
- For those patients who are unable or unwilling to attend such courses further education should be offered including signposting to diabetes.org.uk and/or local interventions such as nutrition and dietetic services, local fitness classes/regimes, mental health services and Local Specialist Obesity Services (for patients with a BMI > 35 kg/m²).
- In order to achieve the best possible care competent patients should be encouraged to take responsibility for the management of their diabetes and receive comprehensive counselling prior to the initiation of any new medicine. A self management contract (see appendix B) may facilitate patients and prescribers to agree care goals and encourage patients to strive for the best possible outcomes from their treatments.

Initiating and optimising treatments

This guideline does not include all antihyperglycaemic medicines for the management of type 2 diabetes. Where appropriate prescribers may prescribe medicines not considered in this guideline (glinides and acarbose). Medicine preferences stated in the guideline are intended to guide prescribers initiating new treatments. Patients should be able to continue their existing treatments until they and their clinician consider it appropriate to stop.

1. When HbA1c rises above the patients agreed target, **lifestyle advice should be reinforced prior to initiating each new treatment.** (If a patient is symptomatically hyperglycaemic, clinicians should consider insulin or sulfonylurea rescue therapy and review treatment once blood glucose control is achieved).
2. Before adding/switching treatments, prescribers must be satisfied that:
 - the dose of current treatment has been suitably optimised **and**
 - the patient is using existing treatment regularly and correctly.
3. Prescribers should ensure that patients are **reviewed preferably within 3 months** of initiating a new treatment (or no later than 6 months after initiation). In accordance with the NICE quality standard statement 4, adults with type 2 diabetes whose HbA1c level is 58 mmol/mol (7.5%) or above after 6 months with single-drug treatment should be offered dual therapy, as this can delay the need for a second intensification of therapy or commencement of insulin therapy.
4. Where tolerated and not contraindicated, **metformin should be offered throughout the treatment pathway** (including following insulin initiation).
5. The benefits/risks of other blood glucose lowering therapies should be reviewed at least 6 monthly.

Cost effective prescribing

- Where more than one treatment is suitable based on patient factors, prescribers should prescribe the treatment with the lowest acquisition cost.
- Review patients on modified release preparations of metformin and gliclazide to ascertain whether they could be managed on immediate release preparations.
- Despite the lower acquisition cost of sulfonylureas, the actual cost of treating patients with sulfonylureas will be higher due to the need for blood glucose monitoring. Review patients taking glibenclamide and tolbutamide to establish whether patients could be switched to gliclazide/glimepiride.
- Only consider GLP-1 mimetics if dual therapy has failed to control HbA1c and only continue if HbA1c reduction of $\geq 1\%$ (11mmol/mol) and weight loss of $\geq 3\%$ at 6 months.
- Patients may be switched to an alternative drug in the same class on the grounds of efficacy and tolerability if the prescriber feels this is appropriate, however drugs of the same class should not be combined (e.g. 2 gliflozins or 2 gliptins).
- Clinicians should:
 - not use combinations of gliptins and GLP-1 mimetics (increased risk of pancreatic cancer for small benefit in treatment)
 - avoid dapagliflozin with pioglitazone (due to increased risk of bladder cancer)
 - consider titrating the dose of sulfonylureas down and discontinuing in patients who have started bolus insulin therapy or if hypoglycaemia occurs on basal insulin regimens.

Monotherapy

If confirmed HbA1c \geq 48mmol/mol (6.5%) following lifestyle interventions.

If the patient is symptomatically hyperglycaemic, consider insulin or a sulfonylurea first line

Metformin

HYPOGLYCAEMIA RISK	Low
WEIGHT	Neutral/loss
ANNUAL COST	Standard release < £50, Modified release < £200
CARDIOVASCULAR EFFECTS	Associated cardiovascular benefit
USE IN CKD STAGES 3-5 (GFR < 60 ML/MIN)	Stages 4-5 avoid, stage 3 dose reduction may be considered
USE IN FRAIL/ELDERLY PATIENTS	Suitable, care in patients with dehydration at risk of age-related anorexia

Reinforce advice on lifestyle and adherence to drug treatment whenever a new treatment is initiated. Aim to review treatment and HbA1c preferably after 3 months (max 6 months)

First intensification

Metformin +

The ordering of agents in the table does not represent prescribing preference

If HbA1c rises to 58 mmol/mol (7.5%) despite optimisation of metformin treatment

* Sulfonylurea	1st Line	Gliclazide
	2nd Line	Glimepiride
* Gliptin	1st Line	Alogliptin (not monotherapy)
	2nd Line	Sitagliptin or Linagliptin (in renal impairment)
* Gliflozin	1st Line	Canagliflozin/ Dapagliflozin /Empagliflozin
	2nd Line	Ertugliflozin

	Sulfonylurea	Pioglitazone	Gliptin	Gliflozin	Insulin (basal)
HYPOGLYCAEMIA RISK	Moderate	Low	Low	Low	High
WEIGHT	Gain	Gain	Neutral	Loss (consider if BMI > 30)	Gain
ANNUAL COST	< £50	< £50	< £400	< £450	£120- £700
CARDIOVASCULAR EFFECTS	Associated with increased risk of cardiovascular events	Can cause fluid retention which may exacerbate or precipitate heart failure	Neutral for overall CV safety measures although slightly increased rates of hospitalisation for heart failure for saxagliptin (cannot be excluded as a class effect)	Associated cardiovascular benefit particularly in patients with established atherosclerotic cardiovascular disease, chronic kidney disease or at risk of heart failure	Associated with increased risk of cardiovascular events
USE IN CKD STAGES 3-5 (GFR < 60 ML/MIN) #	Stage 5 avoid, stage 4 use lowest effective dose, stage 3 no dose adjustment necessary	Suitable for all stages (not licensed in dialysis)	No dose adjustment necessary for linagliptin, dose reductions required for other DDP-4 inhibitors	Do not initiate, if GFR persistently falls below 60mL/min dose should be adjusted	Suitable for all stages, blood glucose monitoring should be intensified and dose adjusted on an individual basis
USE IN FRAIL/ELDERLY PATIENTS	Less suitable in frail patients due to increased risk of hypoglycaemia, if used dose should start low and be increased carefully	Avoid in elderly patients likely to have history of fractures, bladder cancer, cardiac failure	Relatively safe. No dose adjustments necessary based on age (unless due to renal function)	Risk of volume depletion and hypotension higher in frail/elderly patients and those taking ACE-inhibitors/ diuretics	Long acting insulin preferred in frail patients where there is a higher risk of hypoglycaemia, or assistance with administration necessary

Use in CKD stages 3-5 section of the table is intended to provide a summary only. For detailed advice please consult appendix A.

Second intensification

Metformin +

If HbA1c rises to 58 mmol/mol (7.5%) despite optimisation of therapy at first intensification

*Preferred drugs included in this guideline are based on cost, safety, inclusion on hospital formularies and current local impact data. Specialists may wish to prescribe alternative agents where they are clinically appropriate

Sulfonylurea +	Pioglitazone +	Gliptin +	Gliflozin +
Pioglitazone	Sulfonylurea	Sulfonylurea	Sulfonylurea
OR	OR	OR	OR
Gliptin	Gliptin	Pioglitazone	Pioglitazone
OR	OR	OR	OR
Gliflozin	Gliflozin	Gliflozin	Gliptin
		OR	OR
		Insulin (basal)	Insulin (basal)

N.B. The triple therapies to be used at second intensification are based on the licensed indications contained in the products SPCs and ADA Standards of care 2017. Some recommendations may vary from NG28 (Type 2 diabetes in adults: management). There are variations in the licensing of drugs in each of the DDP-4 inhibitor and SGLT-2 inhibitor classes of medicines. Please consult individual SPCs for licensed combinations.

Injection therapy

If treatment optimisation and still above target HbA1c. Continue to offer metformin and review other blood glucose lowering therapies

Insulin based therapy

See insulin algorithm (page 5)
Additional annual cost for bolus insulin £200-400

OR

GLP-1 mimetic If: -BMI > 35kg/m² and specific psychological or medical problems associated with obesity
OR BMI < 35kg/m² and insulin would have significant occupational implications

OR weight loss would benefit other obesity-related comorbidities.

Only continue if 6 month HbA1c reduction of 11 mmol/mol [1.0%] and weight loss \geq 3%.

Annual cost £700-1400, low risk of hypo, weight loss, avoid in CKD stage 5, and associated cardiovascular benefit for liraglutide, semaglutide and dulaglutide.

1st Line *	Weekly Dulaglutide/ Semaglutide
2nd Line	Liraglutide (if daily administration preferred)

GLP-1 mimetic in combination with insulin only on advice of specialist with ongoing support from a consultant-led multidisciplinary team

For patients in whom metformin is contraindicated or not tolerated

Monotherapy

The ordering of agents in the table does not represent prescribing preference

If confirmed HbA1c ≥ 48mmol/mol (6.5%) following lifestyle interventions.

If the patient is symptomatically hyperglycaemic, consider insulin or a sulfonylurea first line

	Sulfonylurea	Pioglitazone	Gliptin	Gliflozin	Insulin (basal)
HYPOGLYCAEMIA RISK	Moderate	Low	Low	Low	High
WEIGHT	Gain	Gain	Neutral	Loss (consider if BMI > 30)	Gain
ANNUAL COST	< £50	< £50	< £400	< £450	£120- £700
CARDIOVASCULAR EFFECTS	Associated with increased risk of cardiovascular events	Can cause fluid retention which may exacerbate or precipitate heart failure	Neutral for overall CV safety measures although slightly increased rates of hospitalisation for heart failure for saxagliptin (cannot be excluded as a class effect)	Associated cardiovascular benefit particularly in patients with established atherosclerotic cardiovascular disease, chronic kidney disease or at risk of heart failure	Associated with increased risk of cardiovascular events
USE IN CKD STAGES 3-5 (GFR < 60 ML/MIN) #	Stage 5 avoid, stage 4 use lowest effective dose, stage 3 no dose adjustment necessary	Suitable for all stages (not licensed in dialysis)	No dose adjustment necessary for linagliptin, dose reductions required for other DDP-4 inhibitors	Do not initiate, if GFR persistently falls below 60mL/min dose should be adjusted	Suitable for all stages, blood glucose monitoring should be intensified and dose adjusted on an individual basis
USE IN FRAIL/ELDERLY PATIENTS	Less suitable in frail patients due to increased risk of hypoglycaemia, if used dose should start low and be increased carefully	Avoid in elderly patients likely to have history of fractures, bladder cancer, cardiac failure	Relatively safe. No dose adjustments necessary based on age (unless due to renal function)	Risk of volume depletion and hypotension higher in frail/elderly patients and those taking ACE-inhibitors/ diuretics	Long acting insulin preferred in frail patients where there is a higher risk of hypoglycaemia, or assistance with administration necessary

Use in CKD stages 3-5 section of the table is intended to provide a summary only. For detailed advice please consult appendix A.

Reinforce advice on lifestyle and adherence to drug treatment whenever a new treatment is initiated. Aim to review treatment and HbA1c preferably after 3 months (max 6 months)

First intensification

If HbA1c rises to 58 mmol/mol (7.5%) despite optimisation of monotherapy

*Preferred drugs included in this guideline are based on cost, safety, inclusion on hospital formularies and current local epact data. Specialists may wish to prescribe alternative agents where they are clinically appropriate

* Sulfonylurea	1st Line	Gliclazide
	2nd Line	Glimepiride
* Gliptin	1st Line	Alogliptin (not monotherapy)
	2nd Line	Sitagliptin or Linagliptin (in renal impairment)
* Gliflozin	1st Line	Canagliflozin/ Dapagliflozin /Empagliflozin
	2nd Line	Ertugliflozin

Sulfonylurea	Pioglitazone	Gliptin	Gliflozin
+	+	+	+
Pioglitazone	Sulfonylurea	Sulfonylurea	Sulfonylurea
OR	OR	OR	OR
Gliptin	Gliptin	Pioglitazone	Pioglitazone
OR	OR	OR	OR
Gliflozin	Gliflozin	Gliflozin	Gliptin
		OR	OR
		Insulin (basal)	Insulin (basal)

N.B. The dual therapy options at first intensification are based on the licensed indications contained in the products SPCs. Some recommendations may vary from NG28 (Type 2 diabetes in adults: management). There are variations in the licensing of some drugs. Please consult individual SPCs for licensed combinations.

Second intensification

If HbA1c rises to 58 mmol/mol (7.5%) despite optimisation of therapy at first intensification

Insulin based therapy
See insulin algorithm (page 5)
Additional annual cost for bolus insulin £200-400

OR

GLP-1 mimetic If: -BMI > 35kg/m² and specific psychological or medical problems associated with obesity
OR BMI < 35kg/m² and insulin would have significant occupational implications
OR weight loss would benefit other obesity-related comorbidities.
Only continue if 6 month HbA1c reduction of 11 mmol/mol [1.0%] and weight loss ≥ 3%.
 Annual cost £700-1400, low risk of hypo, weight loss, avoid in **CKD stage 5**, and associated cardiovascular benefit for liraglutide, semaglutide and dulaglutide.

1st Line	* Weekly Dulaglutide/ Semaglutide
2nd Line	Liraglutide (if daily administration preferred)

GLP-1 mimetic in combination with insulin only on advice of specialist with ongoing support from a consultant-led multidisciplinary team

Insulin-based treatment in type 2 diabetes

Insulin therapy should be commenced by a healthcare professional who is appropriately trained and experienced in the initiation of insulin.

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

GLP-1 mimetic in combination with insulin only on advice of specialist with ongoing support from a consultant-led multidisciplinary team

Preferred basal treatment

Offer NPH (isophane) insulin once or twice daily

Monitor patients who are on a basal insulin (and pre-mixed insulin) for the need for short-acting insulin before meals

Preferred biphasic treatment

Offer pre-mixed (biphasic) human insulin if HbA1c > 75mmol/mol (9.0%)*

* If preferred patients may be started on separate NPH and short acting insulin

Preferred bolus insulin treatment

Offer a choice of rapid-acting insulin analogues

2nd line alternative basal treatments

Consider insulin glargine/detemir if:

- Patient needs assistance to inject insulin or
- lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or
- Patient would otherwise need twice-daily NPH insulin + oral antihyperglycaemic agents

Specialists may exceptionally consider initiating insulin degludec if:

- Patient is experiencing poor glycaemic control or recurrent hypoglycaemic episodes with their existing long-acting insulin analogue or
- Patient is unable to take basal insulin at the same time each day

Specialists may consider high strength formulations (Toujeo or Tresiba 200) if:

Patient experiencing symptomatic nocturnal hypoglycaemia whilst being treated with a first line long-acting insulin analogue

2nd line alternative biphasic treatment

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

- Patient prefers injecting before a meal or
- Blood glucose levels rise markedly after meals or
- Hypoglycaemia is a problem

2nd line alternative bolus insulin treatment

Consider Fiasp (insulin aspart) exceptionally if patient not managed on existing bolus insulin and:

- The prescriber believes a faster onset of action would be beneficial to the patient or
- A patient requires "tight" control of blood glucose levels or
- A patient has rapid post meal increases in blood glucose levels

Preferred insulins included in this guideline are based on cost, safety, inclusion on hospital formularies and current local eact data. Specialists may wish to prescribe alternative agents where they are clinically appropriate

	1st Line	2nd Line	3rd Line
Isophane insulin formulations	Humulin I KwikPen	Insulatard Penfill	
Long-acting insulin analogues formulations	Abasaglar KwikPen	Levemir FlexPen	Tresiba FlexTouch 100 (Specialist initiation)
High strength long-acting formulations (Specialist initiation)	Toujeo SoloStar	Tresiba FlexTouch 200	
Biphasic human insulin formulations	Humulin M3 KwikPen	Insuman Comb 25 SoloStar	
Biphasic short-acting analogue formulations	NovoMix 30 FlexPen	Humalog Mix KwikPen	
Bolus insulin formulations	Apidra SoloStar	Humalog KwikPen	Novorapid FlexPen or Fiasp FlexTouch

Patients currently receiving insulin products other than those recommended in this guideline should still continue their treatment unless their clinician considers it appropriate to stop. The insulin table does not imply therapeutic equivalence of drugs or doses.

Appendix A

Impact of renal function on antihyperglycaemic treatment

	CKD stage 1 and 2 GFR \geq 60 mL/min	CKD stage 3a GFR 45- 59 mL/min	CKD stage 3b GFR 30- 44 mL/min	CKD stage 4 GFR 15-29 mL/min	CKD stage 5 GFR < 15 mL/min or
Metformin		Reduce dose (starting dose \leq 1/2 maximum dose)		Not recommended at GFR < 25mL/min	
Glimepiride					Change over to insulin is indicated
Gliclazide				Use lowest effective dose	
Sitagliptin			Reduce dose to 50mg if GFR < 45 mL/min	Reduce dose to 25mg if GFR < 30mL/min	
Alogliptin		Reduce dose to 12.5mg if GFR < 50 mL/min		Reduce dose to 6.25mg if GFR < 30mL/min	
Linagliptin					
Saxagliptin		Reduce dose to 2.5mg for moderate to severe renal impairment			
Vildagliptin		Reduce dose to 50mg once daily if GFR < 50 mL/min			
Pioglitazone	Not licensed for dialysis patients				
Empagliflozin		Do not initiate if GFR < 60 mL/min, if GFR falls below 60 mL/min reduce dose to 10mg	Discontinue if GFR persistently < 45 mL/min		
Canagliflozin		Do not initiate if GFR < 60 mL/min, if GFR falls below 60 mL/min reduce dose to 100mg	Discontinue if GFR persistently < 45 mL/min		
Dapagliflozin		Do not initiate if GFR < 60 mL/min	Discontinue if GFR persistently < 45 mL/min		
Ertugliflozin		Do not initiate if GFR < 60 mL/min	Discontinue if GFR persistently < 45 mL/min		
Liraglutide					
Exenatide MR		Not recommended if GFR <50 mL/min			
Exenatide		Use 10 mcg dose conservatively if GFR 30-50 mL/min			
Lixisenatide					
Dulaglutide					
Semaglutide					Not recommended for use in end-stage renal
Insulin	Requirements may reduce in severe renal disease, monitor and adjust dose accordingly				

No dose adjustment	
Dose adjustment necessary	
Not recommended	

Appendix B - Self-management patient plan (word version of this document available at <http://www.lancsmmg.nhs.uk/prescribing-guidance/information-leaflets/>).



Type 2 Diabetes Self-Management Plan

Effective diabetes care can only be achieved through working closely with your diabetes healthcare team. Taking responsibility for your diabetes will enable you to manage your diabetes more effectively and reduce your risk of complications in the future. At around the time you are diagnosed, your doctor or nurse should provide you with information about type 2 diabetes. You should be offered a course to help you improve your understanding of type 2 diabetes and how to manage it in your everyday life.

Patient commitment

To get the most from my treatment for my diabetes, I agree to:

- Aim to keep my HbA_{1c} below as agreed with my diabetes healthcare team
- Exercise at least 5 days of the week
 - You should try to do 150 minutes of moderate intensity exercise (walking fast or hiking, pushing a lawn mower, cycling on level ground)
 - OR
 - try to do 75 minutes of vigorous activity (jogging, team sports, swimming, cycling fast or on hilly terrain)
 - OR
 - a mixture of moderate and vigorous activity where 1 minute of vigorous activity gives the same health benefits as 2 minutes of moderate exercise
- Try to eat a lower sugar and lower fat diet to help control my blood sugar and cholesterol
 - Total energy intake is less than energy expenditure where high sugar/saturated fat foods are eaten occasionally and in small portions
 - Choose foods lower in fat, salt and sugar including 5 daily portions of fruit and vegetables, wholegrains or higher fibre starchy carbohydrates, beans, pulses and oily fish twice weekly.
- I will try to obtain my ideal body weight/target body weight of..... and maintain my weight loss.
- Stop smoking
- Attend an eye examination at least yearly following my initial eye screening examination

- Check my feet every day to look for signs of redness, pain, build-up of hard skin or changes in the shape of my feet and attend a quality foot check by an appropriately trained person at least once per year
- Take my medication regularly and as directed by my diabetes healthcare team and report any issues or side effects with my medication to the diabetes healthcare team.
- If requested by my diabetes care team, I will test my blood sugar at the frequencies agreed and:
 - Know my target range
 - Contact my GP/nurse if my readings are consistently outside my target range

Patient agreement

I have discussed the above information with a member of the diabetes healthcare team and I understand that I need to follow the commitments above to improve control of my diabetes and minimise the risk of long term complications.

Patient name:

Patient signature:

Clinician name:

Clinician signature:

Date:

Appendix B continued – GLP-1 patient plan(word version of this document available at <http://www.lancsmmg.nhs.uk/prescribing-guidance/information-leaflets/>).



Glucagon-Like-Peptide-1 (GLP-1) mimetic treatment

To help you lose weight and control your blood glucose levels, your diabetes health care team have started you on a glucagon-like-peptide-1 mimetic (GLP-1) medicine called liraglutide (Victoza) / Exenatide (Byetta or Bydureon) / Dulaglutide (Trulicity) / Lixisenatide (Lyxumia) / Semaglutide (Ozempic). You will need to follow a low sugar and low-fat diet and undertake regular exercise in combination with these medicines.

The GLP-1 medicines only benefit some patients therefore the National Institute for Health and Care Excellence (NICE) advise that these treatments should only be continued in those patients who have had a 11mmol/mol or 1% reduction in their HbA1c (the blood test that measures your average blood glucose level over 2-3 months) and a reduction in weight of 3% following 6 months of treatment.

Over the next 6 months your diabetes health care team will monitor your HbA1c and weight to assess if you are a patient who benefits from GLP-1 treatment. If after 6 months your HbA1c and weight have not reduced by the above levels, your GLP-1 treatment will be stopped.

If you are a patient who has had the above reduction in HbA1c and weight, treatment will continue beyond 6 months and your diabetes health care team will review your treatment every 6 months to ensure that you are still benefiting from your treatment.

Your most recent HbA1c is: mmol/mol
After 6 months, your target HbA1c is: mmol/mol
Your current weight is: Kg
After 6 months, your target weight Kg

Patient agreement

I have discussed the above information with a member of the diabetes health care team and understand that treatment with a GLP-1 mimetic will only continue after 6 months if my HbA1c and weight measurement at 6 months demonstrates a beneficial effect as outlined above.

Patient name:

Patient signature:

Clinician name:

Clinician signature:

Date:

References

1. National Institute for Health and Care Excellence (2015) Type 2 diabetes in adults: management NICE guideline (NG28)
2. National Institute for Health and Care Excellence (2015) Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes NICE guideline (NG5)
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5. Mallery LH et al. Evidence-informed Guidelines for Treating Frail Older Adults with Type 2 Diabetes: From the Diabetes Care Program of Nova Scotia (DCPNS) and the Palliative and Therapeutic Harmonization (PATH) Program. Journal for Post-Acute and Long-Term Care Medicine(JAMDA), vol. 14, issue 11, 801-808, 2013.
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7. Ashley C and Currie A. The Renal Drug Handbook Third edition, 2009.
8. Scottish Intercollegiate Guidelines Network (2017) Pharmacological management of glycaemic control in people with type 2 diabetes (SIGN 154).
9. Davies MJ et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia vol. 61, issue 12, 2461-2498, 2018.

The Summary of Product Characteristics for all medicines included in the guideline have been consulted when including product specific information.