BNF Chapter 6.3 Diabetes mellitus and hypoglycaemia

Formulary prepared and based on BNF, Summary of Product Characteristics and information provided below unless otherwise stated.For full information on treatment side effects, cautions and contraindications, see electronic British National Formulary (www.bnf.org) or the relevant summary of product characteristics (www.medicines.org.uk).

NICE Clinical Guidelines

Type 1 diabetes in adults: diagnosis and management

NICE guidelines NG17

Diagnosis and management of type 1 diabetes in children, young people and adults

NICE guidelines CG15

Type 2 diabetes in adults: Management

NICE guideline NG28

NICE Technology Appraisals

NICE TA203 Liraglutide for the treatment of type 2 diabetes mellitus

NICE TA203

NICE TA248 Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes

NICE TA248

NICE TA288 Dapagliflozin in combination therapy for treating type 2 diabetes

NICE TA288

NICE TA315 Canagliflozin in combination therapy for treating type 2 diabetes

NICE TA315

NICE TA336 Empagliflozin in combination therapy for treating type 2 diabetes

NICE TA336

NICE TA 390 Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes

NICE TA390

Local Prescribing Information

GP Prescribing Information - GLP-1 Agonists for Type 2 Diabetes
http://nww.knowledgeanglia.nhs.uk/tag/glp1_agonists.pdf

Norfolk Diabetes Management Guidelines 2013 From the Norfolk Clinical Diabetes Networks
http://nww.knowledgeanglia.nhs.uk/diabetes/diabetes_guidelines/diabetes_guidelines.pdf

Drug Safety Update

Pioglitazone: risk of bladder cancer

https://www.gov.uk/drug-safety-update/pioglitazone-risk-of-bladder-cancer

Insulin combined with pioglitazone: risk of cardiac failure

https://www.gov.uk/drug-safety-update/insulin-combined-with-pioglitazone-risk-of-cardiac-failure

Exenatide (Byetta ▼): risk of severe pancreatitis and renal failure

https://www.gov.uk/drug-safety-update/exenatide-byetta-risk-of-severe-pancreatitis-and-renal-failure

Dipeptidylpeptidase-4 inhibitors ('gliptins'): risk of acute pancreatitis

https://www.gov.uk/drug-safety-update/dipeptidylpeptidase-4-inhibitors-risk-of-acute-pancreatitis

SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin): risk of diabetic ketoacidosis

https://www.gov.uk/drug-safety-update/sglt2-inhibitors-canagliflozin-dapagliflozin-empagliflozin-risk-of-diabetic-ketoacidosis

SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis

https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis

NEL CSU Key Message Guidance available for further information

Bulletin 22: Blood Glucose Test Strips
Bulletin 22

Blood Glucose Meters and Test Strip cost comparison

Bulletin 23: Lancets
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Lancets cost comparison

Bulletin 24: Pen Needles
Bulletin 24

Needles for pre-filled and reusable Pen Injectors cost comparison

Formulary Key			
1st line formulary choice	Encouraged		
Alternative formulary choice	On Formulary		
2nd line formulary choice	2nd Line		
Shared Care (TAG Amber)	Shared Care Agreement		
Short acting Insulins			
Soluble Insulin			
Adults with Type-1 Diabetes on multiple insulin injection regimens with meal-time insulin			
Actrapid® 100 units/mL	10mL vial		
Insuman® Rapid 100 units/mL	3mL cartridge*	*Compatible pens for 3mL cartridges = ClikSTAR®, Autopen® 24	
Humulin S® 100 units/mL	10mL vial 3mL cartridge*	*Compatible pens for 3mL cartridges = HumaPen®, Autopen® Classic	
Rapid-Acting Insulin Analogues			
Adults with Type-1 Diabetes on multiple insulin injection regimens with meal-time insulin when: **• Nocturnal or late inter-prandial hypoglycaemia is a problem** **• Wish to avoid need to snack, while maintaining equivalent blood glucose control** **• Individual lifestyle factors such as irregular eating patterns makes a rapid-acting insulin analogue desirable**			
Apidra® (Insulin Glulisine) 100 units/mL	10mL vial 3mL cartridge* 3mL Solostar® (prefilled device)	*Compatible pens for 3mL cartridges = ClikSTAR®, Autopen® 24	
Humalog® (Insulin Lispro) 100 units/mL	10mL vial 3mL cartridge* 3mL Kwikpen® (prefilled device)	*Compatible pens for 3mL cartridges = HumaPen®, Autopen® Classic	
NovoRapid (Insulin Aspart) 100 units/mL	10mL vial 3 mL Penfill® cartridge* 3mL Flexpen® (prefilled device) 3mL FlexTouch® (prefilled device)	*Compatible pens for 3mL Penfill® - Novopen® devices	
Humalog® (Insulin Lispro) 200 units/mL	3ml KwikPen (prefilled device)		TAG Green: Prescribable on request of Diabetes Specialist for adults who require greater than 20units of fast acting insulin and more than 200 units of insulin per day, with poor glycaemic control i.e. HbA1c of greater than 75mmol/mol.
Intermediate and Long Acting Insulins			
See local insulin pathway for patients with Type 2 diabetes			
Isophane Insulin (NPH)			
First-line for adults with type-2 diabetes requiring insulin. **First-line for adults with type-1 diabetes for basal/nocturnal insulin supply**			
Insuman Basal (100 units/mL)	5mL vial 3mL cartridge* 3mL Solostar® (prefilled device)	*Compatible pens for 3mL cartridges = ClikSTAR®, Autopen® 24	Key Message Bulletin on the use of insulin in Type 2 Diabetes is available at Knowledge Anglia
Humulin I (100 units/mL)	10mL vial 3mL cartridge* 3mL Kwikpen® (prefilled device)	*Compatible pens for 3mL cartridges = HumaPen®, Autopen® Classic	
Long Acting Insulin Analogues			
Second-Line for adults with Type-2 Diabetes requiring insulin. **Second-line for adults with Type-1 Diabetes for basal/nocturnal insulin supply.**			
Preferred choice			
Abasaglar® (Insulin Glargine) 100 units/mL Diabetes mellitus type 1 and type 2: insulin glargine biosimilar (Abasaglar) NICE advice [ESNM64]	3mL cartridge* 3mL KwikPen® (prefilled device)	*Compatible pens for 3mL cartridges = Autopen® Classic	**Type 2 diabetes consider only if:**[1,2] • the person needs help with injecting insulin (e.g. from a district nurse) and a long-acting insulin analogue would reduce injections from twice to once daily, or • the person suffers from recurrent hypoglycaemic episodes. **Type 1 diabetes (adults) consider if:**[3] • nocturnal hypoglycaemia is a problem on isophane (NPH) insulin • morning hyperglycaemia on isophane (NPH) insulin results in difficult day-time blood glucose control • rapid-acting insulin analogues are used for meal-time blood glucose control.
Second line choice			
Levemir® (Insulin Detemir) 100 units/mL	3 mL Penfill® cartridge* 3mL Flexpen® (prefilled device) 3mL InnoLet® (prefilled device)	*Compatible pens for 3mL Penfill® - Novopen® devices InnoLet® devices are useful for persons with visual acuity and/or dexterity problems	**Type 2 diabetes consider only if:**[1] • the person needs help with injecting insulin (e.g. from a district nurse) and a long-acting insulin analogue would reduce injections from twice to once daily, or • the person suffers from recurrent hypoglycaemic episodes. **Type 1 diabetes (adults) consider if:**[4] • the person is unable to achieve good glycaemic control with established insulins.

Toujeo® (Insulin Glargine) High-strength insulin glargine **300 units/ml** NICE Advice [ESNM62] NICE Advice [ESNM65]	1.5mL SoloStar® pen (prefilled device)		Toujeo is not bioequivalent to Lantus: they are not interchangeable without dose adjustment. TAG Green: Prescribable on request of Diabetes Specialist for adults who require greater than 200 units of insulin per day, with poor glycaemic control i.e. HbA1c of greater than 75mmol/mol.
Biphasic (Pre-mixed insulin)			
Isophane (NPH) + Soluble Insulin			
First-line – Type-2 diabetes (where pre-mixed insulin indicated) **First-line – Type-1 diabetes in adults where twice daily insulin regimens are indicated, including:** • those who find adherence to lunch-time insulin injections difficult • those with learning difficulties and may require assistance			
Insuman® Comb 15 (15% soluble, 85% isophane)	100units/mL 3mL cartridge*	*Compatible pens for 3mL cartridges = ClikSTAR®, Autopen® 24	
Insuman® Comb 25 (25% soluble, 75% isophane)	100units/mL 3mL cartridge* 3mL Solostar® (prefilled device)	*Compatible pens for 3mL cartridges = ClikSTAR®, Autopen® 24	
Insuman® Comb 50 (50% soluble, 50% isophane)	100units/mL 3mL cartridge*	*Compatible pens for 3mL cartridges = ClikSTAR®, Autopen® 24	
Humulin M3® (30% soluble, 70% isophane) 100 units/mL	3mL cartridge* 3mL Kwikpen® (prefilled device)	Compatible pens for 3mL cartridges = HumaPen®, Autopen® Classic	
Insulin analogues			
Second-line – Type 2 diabetes (where pre-mixed insulin indicated). Consider when: • Immediate injection before a meal is preferred, or • Hypoglycaemia is a problem, or • Blood glucose levels rise markedly after meals **Second-line – Type 1 diabetes in adults** where twice daily insulin regimens indicated and nocturnal hypoglycaemia is a problem.			
Preferred choice			
Humalog® Mix25 (25% insulin lispro, 75% insulin lispro protamine) 100 units/mL	10mL vial 3mL cartridge* 3mL Kwikpen® (prefilled device)	*Compatible pens for 3mL cartridges = HumaPen®, Autopen® Classic	
Humalog® Mix50 (50% insulin lispro, 50% insulin lispro protamine) 100 units/mL	3mL cartridge* 3mL Kwikpen® (prefilled device)	*Compatible pens for 3mL cartridges = HumaPen®, Autopen® Classic	
Second line choice			
Novomix® 30 (30% insulin aspart, 70% insulin aspart protamine) 100 units/mL	3 mL Penfill® cartridge* 3mL Flexpen® (prefilled device)	*Compatible pens for 3mL Penfill® - Novopen® devices	
Antidiabetic drugs			
Metformin			
First-line for all persons with type 2 diabetes requiring blood glucose lowering treatment (unless contraindicated)			
Metformin tablets 500mg, 850mg First Line	Step up dose over several weeks to minimise GI side-effects. Dose: 500mg OD for one week (tea-time), then 500mg BD for one week (breakfast and tea-time), then increase by 500mg increments as required (usual max 2g daily).	Review metformin dose if serum creatinine > 130 micromol/l or eGFR < 45ml/min/1.73m2 Stop metformin if serum creatinine > 150 micromol/l or eGFR < 30ml/min/1.73m2	
Second line choice			
Metformin MR tablets 500mg, 750mg, 1g	Consider if GI side effects prevent person from continuing with normal release metformin rather than prescribing an alternative drug.	Review metformin dose if serum creatinine > 130 micromol/l or eGFR < 45ml/min/1.73m2 Stop metformin if serum creatinine > 150 micromol/l or eGFR < 30ml/min/1.73m2	
Sulphonylureas			
First-line add-on therapy where HbA1c remains above target despite optimal dosing with metformin.			
Option for Second-line monotherapy for persons with type 2 diabetes where metformin is contraindicated or not tolerated.			
Gliclazide tablets 80mg	Tablets are half-scored to enable 40mg dosing. 40mg tablets - expensive choice		
Thiazolidinediones			
Option for Second-line add-on therapy **• Consider adding to metformin if there is a significant risk of hypoglycaemia (or its consequences e.g. those who rely on driving for their income).** **• Consider addition to sulphonylurea where metformin is contraindicated or not tolerated.** **• Option for triple therapy (with metformin and sulphonylurea) where the use of insulin is unacceptable.**			

Pioglitazone tablets 15mg, 30mg, 45mg	Continue pioglitazone therapy only if there is a reduction of ≥ 0.5 percentage points (5.5mmol/L) in HbA1c in 6 months. LFT monitoring required.		**DO NOT start or continue therapy in persons with heart failure.** **Incidence of heart failure increased when glitazones combined with insulin – careful monitoring required.** **Use with caution in those with increased risk of fractures (especially post menopausal women).** **Contra-indicated in active or previous bladder cancer.** **AVOID in hepatic impairment.**
DPP- 4 Inhibitors (Gliptins)			
Option for Second-line add-on therapy **• Consider adding to metformin if there is a significant risk of hypoglycaemia (or its consequences e.g. those who rely on driving for their income).** **• Consider addition to sulphonylurea where metformin is contraindicated or not tolerated**			
Option for triple therapy with metformin and sulphonylurea where the use of insulin is unacceptable.			
Option for use with insulin with or without metformin when stable dose of insulin has not provided adequate glycaemic control.			
Alogliptin tablets 25mg, 12.5mg, 6.25mg (Vipidia) ▼	Once daily	**Dose reduction required for renal impairment: 12.5mg for moderate renal impairment, 6.25mg for severe or end stage renal impairment**	Stop gliptin therapy if a reduction of ≥ 0.5 percentage points (5.5mmol/L) in HbA1c is not acheived after 6 months. A gliptin may be preferable to pioglitazone if: • Further weight gain would cause significant problems, or • Pioglitazone is contraindicated, or • The person had a poor response to or did not tolerate pioglitazone in the past.
Linagliptin tablets 5mg (Trajenta) ▼	Once daily	No dose reduction required in renal or hepatic impairment.	
Combination gliptin products: Suitable for patients on stable regimes with separate tablets where the reduction in number of tablets is beneficial for compliance.			
SGLT-2 Inhibitors			
Option for use in **• Dual therapy regimens** in combination with metformin only if a sulfonylurea is contraindicated or not tolerated, or there is significant risk of hypoglycaemia. **• Combination with insulin** with or without other antidiabetic drugs **Canagliflozin and Empagliflozin** may be used in **triple therapy regimens** in combination with metformin and a sulfonylurea or metformin and a thiazolidinedione.			
Serious, life-threatening, and fatal cases of DKA have been reported in patients taking an SGLT2 inhibitor. In several cases, presentation of DKA was atypical with only moderately elevated blood glucose levels (eg <14mmol/L). This could delay diagnosis and treatment. Patients should be informed of the signs and symptoms of DKA (eg rapid weight loss, feeling sick or being sick, stomach pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat). Patients presenting with these signs and symptoms should be tested for raised ketones. **MHRA Drug Safety Update: SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis**			
Dapagliflozin 5mg, 10mg Tablets (Forxiga) ▼ **NICE TA288**	10 mg once daily. Initial dose 5mg in severe hepatic impairment. Elderly over 75 years - initiation not recommended	Avoid if eGFR less than 60mL/min/1.73m^2 as ineffective.	**TAG Green - GP prescribable at the request of a Specialist or Consultant.**
Canagliflozin 100mg, 300mg Tablets (Invokana) ▼ **NICE TA315**	100 mg once daily preferably before breakfast; if necessary and if tolerated, increase to 300 mg once daily	Avoid initiation if eGFR less than 60 mL/minute/1.73 m^2 as ineffective. Reduce dose to 100 mg once daily if eGFR falls persistently below 60 mL/minute/1.73m^2 and existing canagliflozin treatment tolerated; stop if eGFR less than 45 mL/minute/1.73m^2	**Increased risk of urinary tract and genital infections. Possible increased risk of breast and bladder cancer.** **Do not use in combination with pioglitazone.**
Empagliflozin 10mg, 25mg Tablets (Jardiance) ▼ **NICE TA336**	10 mg once daily, increasing to 25mg max. dose if necessary and tolerated.	Avoid initiation if eGFR less than 60 mL/minute/1.73 m2 as ineffective. In patientswhose eGFR falls below 60 ml/min/1.73 m^2, adjust or maintain dose at 10 mg once daily. stop if eGFR less than 45 mL/minute/1.73m^2	The TAG committee recommended a Prescriber's Rating of 6 for Emapgliflozin (May 2015): *Nothing New - The product may be a new substance but is superfluous because it does not add to the clinical possibilities offered by previous products available. (In most cases these are "me-too" products).* Clinical recommendations from the Therapeutics Advisory Group (TAG) and Commissioners' Decisions

Injectable non-Insulin Antidiabetic Drugs (GLP-1 Agonist)

See local guidance on prescribing GLP-Agonists[7]

Option for Third-line add-on therapy in addition to metformin and a sulphonylurea or metformin and a thiazolidinedione or earlier as dual therapy if contraindications to these drugs or not tolerated in patients with:

• a BMI ≥ 35 kg/m2 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
• a BMI < 35 kg/m2, and therapy with insulin would have significant occupational implications
• or weight loss would benefit other significant obesity-related comorbidities.

Lixisenatide 50micrograms/ml (Lyxumia) ▼	10micrograms dose pre-filled pen (14 doses) **ONCE DAILY administration**	Use with caution if eGFR <30-50ml/min/1.73m^2 Avoid if eGFR <30ml/min/1.73m^2	Treatment with a GLP-1 Agonist should only be continued if a beneficial response occurs and is maintained: NICE recommend continuing only if a reduction in HbA1c of at least 1 percentage point [11 mmol/mol] and a weight loss of at least 3% of initial body weight is acheived at 6 months. If this is achieved, patients should be reviewed at 12 months and a weight loss of 5% compared with baseline should be achieved[8,9]. If these targets are not reached the use of GLP-1 agonist should be reconsidered.
Exenatide injection 250micrograms/mL (Byetta) ▼	5micrograms/dose, 10micrograms/dose pre-filled pen (60 doses) **TWICE DAILY administration**	Use with caution if eGFR <30-50ml/min/1.73m^2 Avoid if eGFR <30ml/min/1.73m ^{2} May be used in conbination with insulin as per shared care agreement[7].	
Exenatide MR (Bydureon) ▼ **NICE TA248**	2 mg powder and solvent in pre-filled pen **ONCE WEEKLY administration**	Avoid if eGFR <50ml/min/1.73m^2	
Liraglutide 6mg/mL (Victoza) ▼ **NICE TA203**	3mL pre-filled pen 0.6mg once daily, increased after at least 1 week to 1.2 mg once daily, max. 1.8 mg once daily **ONCE DAILY administration**	Avoid if eGFR <60ml/min/1.73m^2	**Liraglutide 1.8 mg daily is not recommended.**

Co - use of GLP-1 agonists with insulin (SPECIALIST INITIATION ONLY)

Blood Glucose Testing Strips

Monitoring should be available to the following groups of patients[1];
• to those on insulin treatment
• to those on oral glucose lowering medications (i.e. sulphonylureas) to provide information on hypoglycaemia
• to assess changes in glucose control resulting from medications and lifestyle changes
• to monitor changes during inter-current illness
• to ensure safety during activities, including driving
Patients should understand the benefits of monitoring and understand how to interpret the results.

Use low cost choice blood glucose and ketone test strips < £10.00/50. Refer to: **Cost comparison** and **Key message Bulletin document** available on Knowledge Anglia	SPECIFIC METERS MAY BE REQUIRED FOR SOME PATIENTS e.g. • Type 1 Diabetes: may test for ketones or use carbohydrate counting meters. • Children: need to consider safety/convenience/continued engagement with testing. • Pregnant: may need to test for ketones • Dexterity problems: some meters / lancing devices etc may be more appropriate • Visual impairment: care needed but appropriate cost effective choices are available.

Hypodermic Equipment

Needles for Pre-filled and Re-usable Pen Injectors

For adults there is no clinical reason for recommending needles longer than 8mm. 4, 5 and 6mm needles are suitable for all people regardless of BMI; they may not require a lifted skin fold and can be given at 90 degrees to the skin

Use low cost choice of Insulin Pen Needles < £6.00/100. Refer to:

Key Message Bulletin and cost comparison document available on Knowledge Anglia

Lancets

Use low cost choice of Lancets < £3.00/100. Refer to:

Key Message Bulletin and cost comparison document available on Knowledge Anglia

1. NICE CG87 May 2009
http://publications.nice.org.uk/type-2-diabetes-cg87/guidance#glucose-control-insulin-therapy

2. SMC Advice published 7 April 2008
http://www.scottishmedicines.org.uk/SMC_Advice/Advice/456_08_insulin_glargine/insulin_glargine__Lantus_Solostar_

3. NICE CG15 November 2005
http://publications.nice.org.uk/type-1-diabetes-cg15/guidance#blood-glucose-control-and-insulin-therapy

4. SMC advice published 14 May 2012
http://www.scottishmedicines.org.uk/SMC_Advice/Advice/780_12_insulin_detemir_Levemir_ABBREVIATED/insulin_detemir_Levemir_ABBREVIATED

5. NICE TA288 Dapagliflozin in combination therapy for treating type 2 diabetes http://www.nice.org.uk/guidance/TA288/chapter/1-guidance

6. NICE TA315 Canagliflozin in combination therapy for treating type 2 diabetes http://www.nice.org.uk/guidance/TA315/chapter/1-guidance

7. GP Prescribing Information - GLP-1 Agonists for Type 2 Diabetes http://nww.knowledgeanglia.nhs.uk/tag/glp1_agonists.pdf

8. NICE TA203 Liraglutide for the treatment of type 2 diabetes mellitus
http://publications.nice.org.uk/liraglutide-for-the-treatment-of-type-2-diabetes-mellitus-ta203

9. NICE TA248 Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes http://publications.nice.org.uk/exenatide-prolonged-release-suspension-for-injection-in-combination-with-oral-antidiabetic-therapy-ta248