Attachment 2. Comparison of the commonly prescribed antidiabetic treatments

KEY

Licences

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RED	Not recommended

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+	With
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Not rec.	Not recommended
CI	Contraindicated

***Use with insulin**	NICE NG28 states that where insulin is initiated, to continue to offer metformin with insulin for people without contraindications or intolerances. Review the continued need for other blood glucose lowering agents. See specific guidance on use of GLP-1s with insulin below (under GLP-1s)

(See Summaries of Product Characteristics, NG28, and main bulletin for full reference list.)

Where specified, 28 day cost is calculated based on maximum dose using Drug Tariff April 2021.

- Recommendations from the consensus report of the American Diabetic Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines; specific drugs that improve cardiovascular outcomes only stated. Refer to table 2 in bulletin.

DPP-4i – Dipeptidyl peptidase-4 inhibitor

GLP-1 - Glucagon like peptide-1 receptor agonists

SGLT2i – Sodium glucose cotransporter-2 inhibitor

SU - Sulphonylurea

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Drug	Lowest to maximum dose	28 day cost	Renal impairment, eGFR (mL/minute/1.73 m²)				Hepatic impairment	First Intensification (Dual therapy)					Second Intensification (Triple therapy)				Insulin based treatment *
			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments		Monotherapy	+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Metformin - Offer standard release metformin as initial drug treatment. Increase the dose gradually over several weeks to minimise the risk of gastro-intestinal side effects. GI side effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.																	
Metformin tablets	500 micrograms - 1mg (maximum 4mg per dose) with main meals - maximum 16mg daily.	£3.72 - £7.44	Reduce dose if less than 45mL/ minute/1.73m2. Starting dose is at most half the maximum dose.	Contra-indicated	Contra-indicated	Prescribe with caution for those at risk of sudden deterioration in kidney function and those at risk of eGFR falling below 45mL/minute /1.73m². Monitor annually or more frequently, e.g. 3 to 6 months in patients at increased risk.	Withdraw if tissue hypoxia likely.	Y		Y	Y	Y						Y
Metformin modified release M/R tablets (only if GI side effects on standard release metformin)	500mg - 2g once daily with evening meal	£2.00 - £6.40						Y		Y	Y	Y						Y

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			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Repaglinide - 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.																		
Repaglinide tablets	500 micrograms with main meals – maximum 16mg daily	£3.85 - £9.34	Not affected			Caution advised during titration, as insulin sensitivity is increased in renal impairment	No clinical studies. CI in severe hepatic disorder	Y	Y	N	N	N	N	N	N	N	N	N
Sulfonylureas - Consider if metformin not tolerated or contra-indicated, or if rapid response required because of hypoglycaemic symptoms. Educate patient about risk of hypoglycaemia. Avoid in pregnancy and breastfeeding.																		
Gliclazide tablets First line choice, shorter acting sulfonylurea	40mg - 320mg daily	£1.60 - £4.84 (consider cost of blood glucose testing strips)	Risk of hypoglycaemia. Use lowest dose that adequately controls blood glucose.	CI	CI	Principally metabolised in liver, can be used in renal impairment, but careful blood glucose monitoring is needed.	CI in severe hepatic impairment.	Y	Y									Y

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			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Glimepiride tablets	2mg – 6mg daily	£1.47 - £3.16	Risk of hypoglycaemia. Use lowest dose that adequately controls blood glucose.	CI	CI	Regular hepatic and haema-tological monitoring (especially leucocytes and thrombocytes) are required during treatment	CI in severe hepatic insufficiency	Y	Y									Y
Glipizide tablets	2.5mg – 15mg daily; maximum 20mg in divided doses	£1.67 - £13.36	Risk of hypoglycaemia. Use lowest dose that adequately controls blood glucose.	CI	CI		CI severe hepatic insufficiency	Y	Y									Y
Gliclazide MR tablets - only use if compliance with standard release is a problem	30mg - 120mg once daily with breakfast	£2.81 - £9.54	Risk of hypoglycaemia. Use lowest dose that adequately controls blood glucose.	CI	CI	Pharmaco-kinetics and/ or pharma-codynamics of glipizide may be affected in patients with impaired renal function.	CI in severe hepatic impairment	Y	Y									Y

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			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Tolbutamide tablets - please note high acquisition cost	500mg - 1.5g daily in divided doses or once daily with or after meals; maximum 2g daily	£6.90 - £27.60	Risk of hypoglycaemia. Use lowest dose that adequately controls blood glucose.	CI	CI		Caution in impaired hepatic function. CI in serious hepatic impairment	Y	y									Y
Pioglitazone tablets	15mg - 45mg once daily	£1.57 - £2.74	No dose adjustment necessary. Do not use in dialysed patients - no experience.				Not rec. Monitor liver function before and periodically during treatment. See SPC for further info.	Y	Y	Y		Y	N	Y		N	N	Y

Pioglitazone – consider as monotherapy if metformin (or repaglinide) is contraindicated or not tolerated. Do not offer or continue to offer if patient has heart failure or history of heart failure, hepatic impairment, diabetic ketoacidosis, current or a history of bladder cancer or uninvestigated macroscopic haematuria. In patients who fail to show an adequate response at 3-6 months, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained.

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Drug	Lowest to maximum dose	28 day cost	Renal impairment, eGFR (mL/minute/1.73 m²)				Hepatic impairment	Monotherapy	First Intensification (Dual therapy)					Second Intensification (Triple therapy)				Insulin based treatment *
			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Dipeptidyl peptidase-4 (DPP-4) inhibitors – Consider as monotherapy if metformin (or repaglinide) is contraindicated or not tolerated. May be preferable to pioglitazone if at risk or HF, fractures, hepatic impairment, bladder cancer or further weight gain would cause significant problems. Avoid in pregnancy and breastfeeding. Discontinue if patient experiences symptoms of acute pancreatitis. Flat pricing structure across all strengths - optimise dose. Colour coding based on information on other DPP-4 inhibitors contained in guidance.																		
Sitagliptin tablets (Januvia)	Up to 100mg once daily	£33.26	Reduce to 50mg once daily^	25mg once daily	25mg once daily. Treatment may be administered without regard to the timing of dialysis	Assessment of renal function is recom-mended prior to initiation and periodically thereafter	No dose adjustment in mild and moderate hepatic impairment. Not studied in severe hepatic impairment so care should be exercised in this group	Y	Y	Y	Y		N	Y	Y		N	Y
Vildagliptin tablets (Galvus)	50mg twice daily	£33.35	No dosage adjustment	50mg once daily	50mg once daily. Limited experience with dialysis	Monitor renal function regularly	Avoid with hepatic impairment including ALT OR AST >3 times upper normal	Y	Y	Y	Y		N	Y	N		N	Y

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			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Linagliptin tablets (Trajenta)	5mg once daily	£33.26	No dosage adjustment				No reduction but limited experience	Y	Y	N	N		N	Y	N		N	Y

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Drug	Lowest to maximum dose	28 day cost	Renal impairment, eGFR (mL/minute/1.73 m²)				Hepatic impairment	Monotherapy	First Intensification (Dual therapy)					Second Intensification (Triple therapy)				Insulin based treatment *
			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Saxagliptin tablets (Onglyza)	Up to 5mg once daily	£31.60	No dosage adjustment	No dosage adjustment	2.5mg once daily. Not rec. in patients with End Stage Renal Disease (ESRD) Requiring haemo dialysis	Assessment of renal function is recom-mended prior to initiation of treatment, and, in keeping with routine care, renal assessment should be done periodically thereafter	Use with caution in patients with moderate hepatic impairment. Not recom-mended in severe hepatic impairment.	Y	Y	Y	Y		N	Y	N		N	Y
Alogliptin tablets (Vipidia)	Up to 25mg once daily	£26.60	12.5mg once daily^	6.25mg once daily	6.25mg once daily		No dosage adjustment in mild to moderate hepatic impairment (Child-Pugh score of 5-9). Limited experience in severe hepatic impairment and so not recommended. (Child-Pugh score >9).	N	Y	Y	Y		N	Y	Y		N	Y

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			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	

Sodium – Sodium glucose cotransporter-2 inhibitor:

Monotherapy: Canaglifozin, dapaglifozin, empaglifozin and ertugliflozin when metformin is contraindicated or not tolerated and when diet/exercise alone do not provide adequate glycaemic control, only if a DPP-4i would otherwise be prescribed and a SU or pioglitazone is not appropriate. (NICE TA 390)

Dual therapy: Canaglifozin, dapaglifozin, empaglifozin and ertugliflozin to be added to metformin as an option in dual therapy. See NICE TA 288, 315, 336, 572.

Triple therapy: Canagliflozin, empagliflozin and dapagliflozin are recommended as part of triple therapy with metformin and a sulphonylurea or metformin and pioglitazone. See NICE TA 315, 336, 418. Ertugliflozin is recommended as part of a triple therapy regimen with metformin and a DPP-4i if uncontrolled with metformin and DPP-4i and a SU or pioglitazone is not appropriate (NICE TA 583).

Combination with Insulin: Canaglifozin, dapaglifozin and empaglifozin are recommended in combination with insulin with or without other antidiabetic drugs (NICE TA 288, 597, 315, 418).

Patients should be advised to report symptoms of volume depletion.

Caution with thiazide or loop diuretic use. Rare cases of diabetic ketoacidosis (DKA) including life-threatening cases (affecting up to 1 in 1000 patients) have been reported in clinical trials and in post marketing experience in patients treated with SGLT2 inhibitors. If DKA is suspected or diagnosed in treatment with a SGLT2 inhibitor it should be discontinued.

Counsel patients on the potential risk for DKA.

Due to the mechanism of action, the efficacy of SGLT2 inhibitors are dependent on renal function. Monitoring of renal function is recommended for all SGLT2 inhibitors – see the SPCs for information on the required monitoring. Monitor renal function prior to initiation and at least yearly thereafter.

Be aware of ADA/EASD guidance to treat patients with HF or CKD (with/without established artherosclerotic cardiovascular disease).[2]

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Drug	Lowest to maximum dose	28 day cost	Renal impairment, eGFR (mL/minute/1.73 m²)				Hepatic impairment	Monotherapy	First Intensification (Dual therapy)					Second Intensification (Triple therapy)				Insulin based treatment *
			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Dapagliflozin tablets (Forxiga)	10mg once daily	£36.59	Not rec.	Not rec.	Not rec.	Only initiate if eGFR >60mls/min. If renal function falls persistently below eGFR 45mL/minute /1.73m², dapagliflozin treatment should be discontinued. For renal function approaching moderate impairment (eGFR <60ml/min/1.73m²), check eGFR at least 2 to 4 times per year.	Initial dose 5mg once daily in severe impairment, increased according to response.	Y	Y HF or CKD predominates or ASCVD predominates*	Y	Y	Y		Y	Y	Y		Y

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Canagliflozin tablets (Invokana)	100mg - 300mg once daily before breakfast.	£36.59	Intiate with 100mg once daily if eGFR >30ml/min/1.73m²	Do not initiate. Only continue if already taking.	Not rec. – unlikely to be effective	For renal function approaching moderate renal impairment (eGFR 60ml/ min/1.73m²), check eGFR at least 2 to 4 times per year.	Not recommended in severe hepatic impairment. No dose adjustment required in mild to moderate hepatic impairment.	Y	Y HF or CKD predominates or ASCVD predominates*	y	Y	N		y	Y	N		Y

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			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Empagliflozin tablets (Jardiance)	10-25mg once daily	£36.59	Not rec. In patients tolerating empagliflozin whose eGFR falls persistently below 60 mL/minute/1.73 m² the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 mL/minute/1.73 m²	Not rec.	Not rec. unlikely to be effective.		Not recommended in severe hepatic impairment. No dose adjustment required in mild to moderate hepatic impairment	Y	Y HF or CKD predominates or ASCVD predominates*	Y	Y	N		y	Y	N		Y

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			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments		Monotherapy	+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Ertugliflozin tablets (Steglatro)▼	5mg - 15mg once daily in the morning	£29.40	Not rec. Discontinue when eGFR or CrCl is persistently less than 45 mL/ minute/1.73 m²	Not rec.	Not rec.		Not recommended in severe hepatic impairment. No dose adjustment required in mild to moderate hepatic impairment	Y	Y	Y	Y	N		Y	Y	Y		Y

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			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
GLP-1s - add as part of triple therapy only if adult with type 2 diabetes who has a body mass index (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.[NICE NG28] Avoid in pregnancy and breastfeeding. Discontinue if pancreatitis suspected. Discontinue if reduction in HbA1c is less than 1% (11 mmol/mol) and there is less than 3% weight loss after 6 months (only HbA1c reduction required for dual therapy).[1] Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team Colour coding based on information on other GLP-1s contained in guidance and SPCs. Be aware of ADA/EASD guidance to treat patients with established artherosclerotic cardiovascular disease and patients with high risk.[2]																	
Exenatide (Byetta) injection	5 micrograms twice daily for 1 month then 10 micrograms twice daily	£81.89	Dose increase to proceed conservatively in moderate renal impairment (eGFR 30-50mL/ minute/1.73m².)	Not rec.	Not rec.		No dosage adjustment	N	Y ASCVD predominates or high risk1 or HF or CKD predominates*	Y	Y	N	N	Y	Y	N	N	Y - basal

Attachment 2. Comparison of the commonly prescribed antidiabetic treatments

KEY

Licences

Monotherapy, dual therapy or triple therapy [**Y** includes if stated under drug interactions or pharmacodynamics, **N** or **blank** if not specifically stated in licence)]

NICE guidance

GREEN	"Offer criteria" stated by NICE guidance
AMBER	"Consider" criteria stated by NICE
RED	Not recommended

GREY	N/A
+	With
-	Without

Not rec.	Not recommended
CI	Contraindicated

***Use with insulin**	NICE NG28 states that where insulin is initiated, to continue to offer metformin with insulin for people without contraindications or intolerances. Review the continued need for other blood glucose lowering agents. See specific guidance on use of GLP-1s with insulin below (under GLP-1s)

Drug	Lowest to maximum dose	28 day cost	Renal impairment, eGFR (mL/minute/1.73 m²)				Hepatic impairment	Monotherapy	First Intensification (Dual therapy)					Second Intensification (Triple therapy)				Insulin based treatment *
			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Exenatide (Bydureon) injection	2 milligrams ONCE WEEKLY	£73.36	Not rec.	Not rec.	Not rec.		No dosage adjustment	N	Y	Y	Y	N	N	Y	Y	N	N	N
Liraglutide injection (Victoza)	0.6mg once daily for at least a one week, increased to 1.2mg for at least a week and then increased if necessary to 1.8mg once daily	£78.48 – £117.72	No dose adjustment required.	Not rec.	Not rec.		Not rec. – limited experience	N	Y	Y	y	N	N	Y	Y	N	N	Y-basal
Lixisenatide injection (Lyxumia) ▼	10 micrograms once daily for 14 days then 20 micrograms once daily	£57.93 (20 micro-grams daily)	Use with caution if eGFR 30–50 mL/minute/1.73m².	Avoid if eGFR less than 30 mL/minute /1.73m²—no information available.	Not rec.		No dosage adjustment	N	Y	Y	Y	N	N	Y	Y	N	N	Y-basal

Attachment 2. Comparison of the commonly prescribed antidiabetic treatments

KEY

Licences

Monotherapy, dual therapy or triple therapy [**Y** includes if stated under drug interactions or pharmacodynamics, **N** or **blank** if not specifically stated in licence)]

NICE guidance

GREEN	"Offer criteria" stated by NICE guidance
AMBER	"Consider" criteria stated by NICE
RED	Not recommended

GREY	N/A
+	With
-	Without

Not rec.	Not recommended
CI	Contraindicated

***Use with insulin**	NICE NG28 states that where insulin is initiated, to continue to offer metformin with insulin for people without contraindications or intolerances. Review the continued need for other blood glucose lowering agents. See specific guidance on use of GLP-1s with insulin below (under GLP-1s)

Drug	Lowest to maximum dose	28 day cost	Renal impairment, eGFR (mL/minute/1.73 m²)				Hepatic impairment	Monotherapy	First Intensification (Dual therapy)					Second Intensification (Triple therapy)				Insulin based treatment *
			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments			+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Dulaglutide injection (Trulicity)	Monotherapy: 0.75mg once weekly. Add on therapy: 1.5mg - 4.5mg once weekly (potentially vulnerable populations 0.75mg once weekly).	£73.25	No dosage adjustment required	No dosage adjustment required	Not rec., very limited experience		No dosage adjustment	Y	Y ASCVD predominates or high risk[1] or HF or CKD predominates*	Y	Y	N	N	Y	Y	N	N	Y-basal
Semaglutide injection (Ozempic)	250 microgram – 1mg ONCE WEEKLY	£73.25	No dosage adjustment required	No dosage adjustment required	Limited experience in severe impairment, advise caution. Limited experience in ESRD – not recommended		No dosage adjustment. Limited experience with severe hepatic impairment-caution needed.	Y	Y	Y	Y	N	N	Y	Y	N	N	Y – basal

This document is for use within the NHS and is not for commercial or marketing purposes

Attachment 2. Comparison of the commonly prescribed antidiabetic treatments

KEY

Licences

Monotherapy, dual therapy or triple therapy [**Y** includes if stated under drug interactions or pharmacodynamics, **N** or **blank** if not specifically stated in licence)]

NICE guidance

GREEN	"Offer criteria" stated by NICE guidance
AMBER	"Consider" criteria stated by NICE
RED	Not recommended

GREY	N/A
+	With
-	Without

Not rec.	Not recommended
CI	Contraindicated

***Use with insulin**	NICE NG28 states that where insulin is initiated, to continue to offer metformin with insulin for people without contraindications or intolerances. Review the continued need for other blood glucose lowering agents. See specific guidance on use of GLP-1s with insulin below (under GLP-1s)

Drug	Lowest to maximum dose	28 day cost	Renal impairment, eGFR (mL/minute/1.73 m²)				Hepatic impairment	First Intensification (Dual therapy)					Second Intensification (Triple therapy)				Insulin based treatment *
			30-60 (30-50 for DPP-4i^ inhibitors)	15-29	<15 or on dialysis	Comments		Monotherapy	+ Metformin	+ SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT2i	
Semaglutide tablets (Rybelsus) ▼	3mg once daily for one month increasing to 7-14mg at monthly intervals if required.	£73.25	No dosage adjustment required	No dosage adjustment required	Not recommended in end stage renal disease		No dosage adjustment for mild, moderate or severe hepatic impairment. Limited experience with severe hepatic impairment.	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y-basal