Prescribing Clinical Network for
Surrey and Crawley, Horsham
and Mid-Sussex CCGs

Comparison of the commonly prescribed antidiabetic treatments

Comparison of the commonly prescribed antidiabetic treatments See Summary of Product Characteristics and NG28[1]

KEY

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NICE guidance

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***Use with insulin**	NICE NG28 states that where insulin is initiated, to continue to offer metformin with insulin for people without contra-indications 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	Doses (maximal or usual)	28 day cost at maximum dose/Drug Tariff June 2016	Renal impairment, eGFR (ml/min/1.73m²)				Hepatic impairment	Monotherapy	1st intensification (Dual therapy)					2nd intensification (Triple therapy)				Insulin based treatment *
			30-60 ^ (30-50 for DPP-4 inhibitors)	15-29	<15 or on dialysis	Comments			+Metformin	+SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT-2i	
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	2g daily in divided doses (twice to three times daily)	~£3.44	Reduce dose if less than 45ml/min	Stop	Stop	Prescribe with caution for those at risk of sudden deterioration in kidney function and those at risk of eGFR falling below 45ml/min/1.73m².	Discuss benefits of therapy with patient in mild to moderate liver impairment so informed decision can be made on whether to continue or stop metformin.	Y		Y	Y	Y						Y
Metformin modified release tablets (only if GI side effects on standard release metformin)	2g daily (or 1g twice daily)	~£8.52						Y		Y	Y	Y						Y

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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	Up to 16mg daily (maximum single dose 4mg)	£14.63 (at 16mg)	Not affected		Caution advised during titration		No clinical studies. C/I in severe hepatic disorder	Y	Y	N	N	N	N	N	N	N	N	N

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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 First line choice, shorter acting sulfonylurea	40mg - 320mg daily (split to twice daily for higher doses)	~£3.40	Caution	CI	CI	Can be used in renal impairment but careful monitoring of blood glucose essential.	C/I in severe hepatic impairment.	Y	Y									Y
Glimepiride	4mg daily	£0.99	Caution	CI	CI	Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) are required during treatment.	CI severe hepatic insufficiency	Y	Y									Y

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Sulfonylureas continued																		
Glipizide	Up to 15mg-20mg daily	~£9.44	Caution – cons-ervative doses	CI	CI		CI severe hepatic insufficiency	Y	Y									Y
Gliclazide MR DROP-List - only use if compliance with standard release is a problem	Up to 120mg daily	£9.54	Caution	CI	CI	Pharmacokinetics and/or pharmaco-dynamics of glipizide may be affected in patients with impaired renal function.	CI severe hepatic impairment	Y	Y									Y

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Glibenclamide Not recommended - higher risk of hypo-glycaemia	Up to 15mg daily	£2.55 (2.5mg - £6.95)	Caution	CI	CI		CI	Y	Y									Y
Tolbutamide Please note high acquisition cost	Up to 2g daily	£44.48	Caution - reduce doses Careful mon-itoring of the blood glucose levels required.	CI	CI		Caution in impaired hepatic function. CI in serious hepatic impairment	Y	y									Y

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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																		
Pioglitazone	Up to 45mg daily	~£30.46	No dose adjustment necessary. Do not use in dialysed patients - no experience.				Not rec. Monitor liver function before and periodically during treatment.	Y	Y	Y		Y	N	Y		N	N	Y

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			30-60 ^ (30-50 for DPP-4 inhibitors)	15-29	<15 or on dialysis	Comments			+Metformin	+SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT-2i	
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. **Note** – alogliptin not specifically included in NG28. Colour coding based on information on other DPP-4 inhibitors contained in guidance.																		
Sitagliptin tablets	Up to 100mg daily	£33.26	Reduce to 50mg ^	25mg	25mg Treatment may be administered without regard to the timing of dialysis	Assessment of renal function is recommended prior to initiation and periodically thereafter.	Has not been studied in patients with severe hepatic impairment. Exercise care	Y	Y	Y	Y		N	Y	N		N	Y
Vildagliptin tablets	50mg twice daily	£33.35	No dosage adj-ustment	50mg daily	50mg 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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Dipeptidyl peptidase-4 (DPP-4) inhibitors continued																		
Linagliptin tablets ▼	5mg daily	£33.26	No dosage adjustment				No reduction but limited experience	Y	Y	Y	Y		N	Y	N		N	Y
Saxagliptin tablets	Up to 5mg daily	£31.60	No dosage adjustment	No dosage adjustment	2.5mg Not rec. in patients with End Stage Renal Disease (ESRD) Requiring hae-modialysis	Assessment of renal function is recommended 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 recommended in severe hepatic impairment.	Y	Y	Y	Y		N	Y	N		N	Y

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Alogliptin▼	Up to 25mg daily	£26.60	12.5mg^	6.25 mg	6.25mg		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).	Y	Y	Y	Y		N	Y*	N		N	Y

***Note - Safety and efficacy not fully established**

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Sodium –glucose co-transporter 2 (SGLT-2) inhibitor

Consider adding to metformin as an option in dual therapy. See NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended by NICE TAGs as options as dual therapy (with metformin); and in combination with insulin. At the time of publication, only canaglifozin and empagliflozin are recommended as options in triple therapy regimens. Dapagliflozin is not recommended in triple therapy unless part of a clinical trial. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288.

NICE TA 390: Canagliflozin, dapagliflozin and empagliflozin as monotherapies are recommended as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

- A dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and
- A sulfonylurea or pioglitazone is not appropriate.

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 SGLT-2 inhibitors. If DKA is suspected or diagnosed in treatment with a SGLT-2 inhibitor it should be discontinued.

Due to the mechanism of action, the efficacy of SGLT-2 inhibitors are dependent on renal function. Monitoring of renal function is recommended for all three SGLT-2s – see the SPCs for information on the required monitoring.: Monitor renal function prior to initiation and at least yearly thereafter.

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Sodium-glucose co-transporter 2 (SGLT-2) inhibitor continued																		
Dapagliflozin tablets ▼	5-10mg daily	£36.59	Not rec.	Not rec.	Not rec.	If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m2, dapagliflozin treatment should be discontinued For renal function approaching moderate renal impairment, at least 2 to 4 times per year.	Initial dose 5mg in severe impairment, increased according to response.	Y	Y	Y	N	Y		Y	N	Y		Y

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Sodium-glucose co-transporter 2 (SGLT-2) inhibitor continued																		
Canagliflozin ▼	100-300mg	£36.59	Not rec.	Not rec.	Not rec.	[a]Canagliflozin treatment should be discontinued If renal function falls persistently below eGFR 45 mL/ min/1.73m². For renal function approaching moderate renal impairment, at least 2 to 4 times per year.	Not recommended in severe hepatic impairment.	Y	Y	Y	Y	N		Y	Y	N		Y

N.B. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m² canagliflozin should be adjusted to or maintained at 100mg once daily[a]

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Sodium-glucose co-transporter 2 (SGLT-2) inhibitor continued																		
Empagliflozin ▼	10-25mg	£36.59	Not rec.*	Not rec.	Not rec.	[b]Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m²·.	Not recommended in severe hepatic impairment.	Y	Y	Y	Y	N		Y	Y	N		Y

*N.B. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min /1.73m² the dose of empagliflozin should be adjusted to or maintained at 10mg once daily[b].

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Glucagon-like peptide-1 (GLP-1) mimetics

Add as part of triple therapy ONLY if BMI is ≥ 35kg/m^2 in people of European descent (adjust for ethnic groups) and there are specific psychological or medical problems associated with high body weight, or BMI<35kg/m2 and insulin is unacceptable because of occupational implications or weight loss would benefit other co-morbidities.

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).

Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.

Note – dulaglutide and albiglutide not specifically included in NG28. Colour coding based on information on other GLP-1s contained in guidance and SPCs.

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RED	Not recommended	**-**	Without		

***Use with insulin**	NICE NG28 states that where insulin is initiated, to continue to offer metformin with insulin for people without contra-indications 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	Doses (maximal or usual)	28 day cost at maximum dose/Drug Tariff June 2016	Renal impairment, eGFR (ml/min/1.73m²)				Hepatic impairment	Monotherapy	1st intensification (Dual therapy)					2nd intensification (Triple therapy)				Insulin based treatment *
			30-60 ^ (30-50 for DPP-4 inhibitors)	15-29	<15 or on dialysis	Comments			+Metformin	+SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT-2i	
Glucagon-like peptide-1 (GLP-1) mimetics																		
Exenatide (Byetta) injection	5 micro-grams twice daily for 1 month then 10 micro-grams twice daily	£63.69	Dose increase to proceed con-servatively in moderate renal impa-irment eGFR 30-50ml/min/1.73m²	Not rec.	Not rec.		No dosage adjustment	N	Y	Y	Y	N	N	Y	Y	N	N	Y - basal

KEY

Licences

Monotherapy, dual therapy or triple therapy [**Y** including 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	**GREY**	N/A	**Not rec.**	Not recommended
AMBER	"Consider" criteria stated by NICE	**+**	With	**CI**	Contra-indicated
RED	Not recommended	**-**	Without		

***Use with insulin**	NICE NG28 states that where insulin is initiated, to continue to offer metformin with insulin for people without contra-indications 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	Doses (maximal or usual)	28 day cost at maximum dose/Drug Tariff June 2016	Renal impairment, eGFR (ml/min/1.73m²)				Hepatic impairment	Monotherapy	1st intensification (Dual therapy)					2nd intensification (Triple therapy)				Insulin based treatment *
			30-60 ^ (30-50 for DPP-4 inhibitors)	15-29	<15 or on dialysis	Comments			+Metformin	+SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT-2i	
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 1.2mg injection	1.2mg -1.8mg daily	£73.24 – £109.87	No dose adju-stment required.	Not rec.	Not rec.		Not rec. – limited experience	N	Y	Y	Y	N	N	Y	Y	N	N	Y - basal
Lixisenatide injection ▼	10 micr-ograms once daily for 14 days then 20 micr-ograms daily	£54.14	Caution-limited experience	Not rec.	Not rec.		No dosage adjustment	N	Y	Y	Y	N	N	Y	Y	N	N	Y - basal

KEY

Licences: Monotherapy, dual therapy or triple therapy [**Y** including 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	**GREY**	N/A	**Not rec.**	Not recommended
AMBER	"Consider" criteria stated by NICE	**+**	With	**CI**	Contra-indicated
RED	Not recommended	**-**	Without		

***Use with insulin**	NICE NG28 states that where insulin is initiated, to continue to offer metformin with insulin for people without contra-indications 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	Doses (maximal or usual)	28 day cost at maximum dose/Drug Tariff June 2016	Renal impairment, eGFR (ml/min/1.73m^2)				Hepatic impairment	Monotherapy	1st intensification (Dual therapy)					2nd intensification (Triple therapy)				Insulin based treatment *
			30-60 ^ (30-50 for DPP-4 inhibitors)	15-29	<15 or on dialysis	Comments			+Metformin	+SU	+Pioglitazone	+DPP-4i	+SGLT-2i	Metformin + SU	Metformin + pioglitazone	Metformin + DPP-4i	Metformin + SGLT-2i	
Dulaglutide	0.75mg – 1.5mg once weekly	£73.25	No dosage adj-ustment required	Not rec.	Not rec.		No dosage adjustment	N	Y	Y	Y	N	N	Y	Y	N	N	Y - basal
Albiglutide injection ▼	30-50mg once weekly	£71	No dosage adj-ustment	Not rec.	Not rec.		No dosage adjustment – limited experience	N	Y	Y	Y	N	N	Y	Y	N	N	Y - basal