Wolverhampton
Diabetes Care

	Metformin
Indication	1st line agent should be prescribed from diagnosis in all patients suitable for tablet treatment if there are no contra-indications. 2nd line agent when sulphonylurea has been used first line.
Mechanism of action	Reduce hepatic glucose production and appetite. Weight neutral and little hypoglycaemia risk.
Extra-glycaemic effect	Reduces cardiovascular events in overweight and obese patients to a greater extent than predicted by its glucose lowering effects.
Dosing	Start up: Metformin 500mg with or after food. Increase gradually Target/Maximum: 850 mg BD/ TDS (based on tolerability)
Side effects	GI disturbance is common and may resolve with dose reduction. Tablets can be taken with or immediately after a meal to reduce GI side effects. Slow release Metformin preparation is an option in patients poorly tolerant of generic metformin, starting with 500mg with evening meal, and then slowly up titrating to 1g B.D.
Contra-indications	• Renal impairment - serum creatinine> 150 umol/l oreGFR<30 ml/hr (reduce dose when eGFR<45ml/hr) • Severe cardiac failure, severe liver disease, or significant alcohol dependency • Acute illness with haemodynamic compromise or hypoxic state • Use of iodinated contrast for radiological examinations (withdraw on the day and for 48 hours after the procedure; restart once normal renal function is documented)

	Sulphonylurea
Indication	1st line agent - Thin, symptomatic, hyperglycaemic patients - Metformin intolerant or contraindicated 2nd line agent in combination with metformin or other OHA Concomitant use with insulin is not recommended
Mechanism of action	Stimulate insulin release from the pancreas.
Side effects	Weight gain averaging 2-4 kg is a recognised consequence (may excessive in some patients). Re-assess dietary issues before prescribing Hypoglycaemia: recognition and management should be discussed at start-up
Commonly used agents	Short acting: Gliclazide Medium to long acting: (Glimepiride, Gliclazide MR) reduce pill burden and can improve compliance (but expensive) Wolverhampton Formulary: http://medicines.wolvespct.nhs.uk/formulary/bnf6.asp
Dosing	Gliclazide initially 40-80 mg O.D., with titration every 2-4 weeks to achieve glycaemic target or until maximum dose of 160mg B.D is reached. Glimepiride 1mg O.D. titrate up to 4mg O.D Diamicron MR 30 mg O.D., titrate up to 120 mg O.D.
Prandial glucose regulators	Nateglinide and repaglinide: licenced for use with metformin Infrequent indication: when there is a risk of, or need to avoid hypoglycaemia Rapidly absorbed and have a short half-life (~1hr) and therefore needs to be taken every meal time Tolbutamide is a Ultra short acting sulphonylurea and cheaper prandial regulator
Additional information	Gliclazide is metabolized predominantly by the liver and can be used in renal impairment Long acting sulphonylurea (Glibenclamide and Chlorpropamide) are rarely used and best avoided in older people and those with eGFR<60ml/min)

	Thiazolidinediones (Glitazones)
Caution	In the light of the increasing evidence of the increased risk of bladder cancer in patients taking pioglitazone • No new patients should be started on pioglitazone • Existing patients should be reviewed ▪ Patients with active bladder cancer or with a history of bladder cancer, and those with un-investigated haematuria, should not receive pioglitazone ▪ Patients should be reviewed every 3–6 month; pioglitazone should be stopped in patients who do not respond adequately to treatment e.g. reduction in glycosylated haemoglobin, HbA1c ▪ Elderly patients should be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone
Indication	Pioglitazone should only be prescribed in primary care for individuals where it the most effective clinical option and where the risks and benefits have been carefully considered by both patient and clinician. 2nd line agent: - in combination with Metformin or a sulphonylurea when either drug is contraindicated and/or patient intolerant 3rd line agent: - as an alternative to insulin only when there is fear of insulin or the use of insulin is not preferred Use with insulin should only occur in exceptional cases and under specialist supervision
Mechanism of action	Increases insulin sensitivity
Side effects	Weight gain averaging 3-4 kg, Fluid retention
Available option	Pioglitazone
Contraindication	Bladder cancer: increased risk in patients using pioglitazone. Contraindicated in patients with current bladder cancer, a history of bladder cancer, or un-investigated macroscopic Heart failure: contraindicated in patients with any degree of heart failure Increased fracture risk:recommended to be avoided in patients with high fracture risk

	Gliptins/DPP-4 inhibitors
Indication	2nd line agent in combination with metformin instead of a sulphonylurea - where there is a significant risk of hypoglycaemia, or - where weight gain is an issue, or - the person does not tolerate sulfonylurea or is contraindicated 2nd line agent in combination with suplphonylurea instead of metformin - wherethe person does not tolerate metformin, or - metformin is contraindicated 3rd Line agent: - in combination with metformin and a sulfonylurea, if insulin is unacceptable because of lifestyle or other personal issues, or because the patient is obese Use with insulin should only be considered in selected cases
Mechanism of Action	Prevents breaks down GLP-1 that promotes pancreatic insulin secretion in a glucose-regulated manner
Side effects & caution	Nausea, nasophayngitis, headaches, dizziness, constipation Pancreatitis reported but rareIncreased risk of hypoglycaemia in combination with sulphonylurea Contraindication: pregnancy & lactation
Available options	Sitagliptin, Vildagliptin, Linagliptin, Saxagliptin Wolverhampton Formulary: http://medicines.wolvespct.nhs.uk/formulary/bnf6.asp
Renal impairment	Dose reduction except Linagliptin which has a low rate of renal excretion
Continuation of therapy	Only if there is a reduction of 0.5 percentage points in HbA1c in 6 months

		Added to				Monitoring
	As mono--therapy	Metformin (M)	Sulphonyl--urea (SU)	TZD	M+SU	
Sitagliptin	Yes	Yes	Yes	Yes	Yes	No
Vildagliptin	Yes	Yes	Yes	Yes	No	LFTs – 3 monthly (1 yr)
Saxagliptin	No	Yes	Yes	Yes	No	No
Linagliptin	Yes	Yes	No	No	Yes	No

	GLP-1 agonist
Indication	As 3rd line therapy in individuals on maximum tolerated doses of Metformin and Sulphonylurea/other oral agents AND A body mass index (BMI) ≥35 Kg/m2 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 body mass index(BMI)< 35.0 kg/m2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities
Mechanism of action	GLP-1 mimetic promotes pancreatic insulin secretion in a glucose-regulated manner and inhibits glucagon. Improves satiety and reduces appetite. Promotes weight loss and improvement in metabolic parameters
Side effects & caution	Nausea- common and settles over time Vomiting- can be severe in around 4% of patients Pancreatitis is rare (warn patient of risk at start up) Avoid if previous pancreatitis and/or associated risk factors Increased risk of hypoglycaemia in combination with sulphonylurea Contraindication: pregnancy & lactation
Available options	Exenatide BID (Byetta) ,Liraglutide OD (Victoza), Exenatide once weekly (Bydureon)
Renal impairment	Liraglutide is not licensed for use in moderate renal impairment (eGFR< 50ml/min); Exenatide can be used in moderate renal impairment but not severe renal impairment (eGFR< 30ml/min). In moderate renal impairment dose escalation from Exenatide 5 to 10 mcg should be undertaken cautiously
Continuation of therapy	Continue if reduction HbA1c of ≥1.0 percentage point and ≥ 3% of initial body weight in 6 months (NICE recommendation)
Additional information	The combination of insulin and a GLP-1 Receptor Agonist is currently unlicensed and should be under specialist supervision. It offers an attractive therapeutic option for obese patients with type 2 diabetes where incremental insulin results in spiralling weight gain

Hypoglycaemic agents in Renal Impairment				
	Mild (eGFR 60-90)	**Moderate (eGFR 30-59)**	**Severe (eGFR 15-29)**	**End stage/RRT (eGFR<15)**
Metformin	Yes	Yes (half maximal doses at eGFR 30-45)	No	No
Sulfonylurea (SOU)	Yes	Yes Caution with long acting SOU in elderly	Avoid long acting SOU Tolbutamide or Gliclazide preferred with close monitoring	No
Pioglitazone	Yes	Yes	Yes	No
Sitagliptin	Yes	Yes Reduce 50mg OD	Yes Reduce 25mg OD	Yes Reduce 25mg OD
Vildagliptin	Yes	Yes Reduce 50mg OD	Yes Reduce 50mg OD	Yes Reduce 50mg OD
Linagliptin	Yes	Yes No dose change	Yes No dose change	Yes No dose change
Saxagliptin	Yes	Yes Reduce 2.5mg OD	Yes Reduce to 2.5mg OD	No
Exenatide	Yes	Yes, escalation from 5 to 10 mcg proceed conservatively	No	No
Liraglutide	Yes	No	No	No
Exenatide weekly (Bydureon)	Yes	No	No	No