### Pharmacological Glycaemic Control in Type 2 Diabetes

<table>
<thead>
<tr>
<th><strong>Aim(s) and Objective(s)</strong></th>
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<tr>
<td>This guideline aims to offer advice on the pharmacological management for those who require measures beyond diet and exercise to attain their optimal individual target for glucose control in Type 2 Diabetes. The aim of treatment is to control symptoms, prevent microvascular and macrovascular complications, whilst considering the risks and benefits of the major glucose lowering agents (oral/injectable) currently available.</td>
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<th><strong>Author(s)</strong></th>
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<td>Dr Susan Arnott, Lead Clinician, Diabetes MCN, NHS Lanarkshire</td>
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<tr>
<th><strong>User Group</strong></th>
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<td>Primary Care</td>
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<td>Secondary Care</td>
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<td>Out of Hours</td>
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<td>Diabetes Specialist staff</td>
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</table>

This guideline is not intended to serve as a protocol or standard of care. Ultimately a judgement must be made by the appropriate healthcare professional(s) responsible for a particular clinical procedure or treatment plan following discussion with the patient, covering the diagnostic and treatment options available. It is advised that any significant departure from the guideline should be documented in the patient’s medical record at the time the decision is taken.

This guideline should be considered in conjunction with others on lifestyle management in Type 2 Diabetes

### Guideline

**PATHOPHYSIOLOGY OF TYPE 2 DIABETES**

Type 2 Diabetes is characterised by complex pathophysiology (see Figure 1). Pharmacological management is likely to require a combination of agents with complementary modes of action.

**Aims of therapy**

Type 2 Diabetes is a progressive disease. HbA1c rises by 0.2-0.3% per year, irrespective of treatment. The management of hyperglycaemia is challenging. The immediate purpose of lowering blood glucose is to provide relief from symptoms (thirst, polyuria, nocturia, and blurred vision). Thereafter, the aim is to prevent microvascular complications: loss of vision (retinopathy), renal failure (nephropathy), foot ulceration (neuropathy) and macrovascular complications (myocardial infarction, stroke, peripheral arterial disease). The ideal aim is to preserve pancreatic β cell function, thus preventing the progression of diabetes.

People with diabetes are likely to need a combination of medications in order to optimise glycaemic control, reduce cardiovascular risk and manage complications.

A step wise approach to treatment is suggested with continuation of each level of treatment as long as this is tolerated, HbA1c target is achieved or falls >5-6mmol/mol (>0.5%) within the first 3 to 6 months of that treatment. **If it is unsuccessful, discontinue that treatment and try something else.**
Targets for glycaemic control
An HbA1c target of 53 mmol/mol (7.0%), in most people with Type 2 diabetes, is thought reasonable to reduce the risk of microvascular and macrovascular disease. A target of 48 mmol/mol (6.5%) may be appropriate at diagnosis as studies suggest a long term beneficial effect of more intensive glycaemic control in the early years after diagnosis (legacy effect). Targets should be agreed with each individual to balance benefit with harm, in particular from hypoglycaemia and weight gain.

PHARMACOLOGICAL THERAPEUTIC AGENTS IN TYPE 2 DIABETES

Metformin
Therapeutic option
1st line

Mechanism of action
First introduced in the late 1950s the biguanide Metformin decreases hepatic glucose production and may improve peripheral glucose disposal, thus decreasing insulin resistance. Activation of the energy-regulating enzyme AMP-kinase in liver and muscle is a principal mode of action although it has been shown to have multiple metabolic effects. It is excreted unchanged in the urine via tubular secretion. Its clinical efficacy requires the presence of insulin (endogenous β cell function) but the drug does not stimulate insulin release and typically causes a small decrease in basal insulin concentrations in hyperinsulinaemic patients. Its effects are independent of weight, age and duration of diabetes. It should be used with caution in renal disease (eGFR <30) and hepatic disease (transaminases >2.5 x upper limit of normal), respiratory disease or any other hypoxic condition (sp02 <90%), severe infection, alcohol abuse, history of acidosis or with intravenous contrast media. The only significant drug interaction is with cimetidine.

Glycaemic control
Metformin can be expected to reduce HbA1c by an average of 10.60mmol/mol (1%)

Other effects
Metformin shows more benefit for total cholesterol than diet alone but little difference for HDL cholesterol, LDL cholesterol, triglycerides, or blood pressure. For overweight and obese patients Metformin has improved outcomes for any diabetes-related outcome, diabetes-related death and all cause mortality. Metformin also has a significantly reduced risk of myocardial infarction. While the data for clinically relevant outcomes with Metformin may be limited, they are stronger than for any other available oral agent for the treatment of Type 2 diabetes. Metformin is the only glucose-lowering agent NOT associated with harm in patients with Type 2 Diabetes and heart failure.

Adverse effects
- Gastro-intestinal side effects (diarrhoea) – these usually remit if the dose is reduced and re-titrated slowly. Only 5-15% cannot tolerate any dose at all
- Metallic taste
- Hypoglycaemia is rare but not unknown
- Weight neutral
- Possibly reduced absorption of Vitamin B12 in patients with a poor diet. Deficiency significant enough to cause megaloblastic anaemia is uncommon
- Lactic acidosis is a rare complication if there is reduced renal clearance of Metformin in renal impairment. Avoid if creatinine >150mmol/l (eGFR<30) – signs are non-specific but often include hyperventilation, malaise and abdominal discomfort
General information

- Metformin should be taken with or immediately after a meal
- It should be introduced at low dose, with gradual escalation to 1g twice daily at weekly intervals. Little benefit in glycaemic control occurs at doses beyond 1g twice daily at the expense of an increased incidence of gastrointestinal side effects
- In those who do not tolerate higher doses, dose reduction (not necessarily discontinuation) is appropriate
- Nausea, diarrhoea, and abdominal pain are the most common adverse effects. People should be informed that these side effects often improve after a few days of continued therapy, or with a small dose reduction
- A modified release preparation (Metformin MR) is also available, suitable for once daily dosing; some individuals otherwise intolerant of Metformin may find this more acceptable, or may in some cases, be able to take higher doses. If no difference is found in tolerability switch back to the maximum tolerated dose of regular Metformin
- Metformin should usually be discontinued during a severe illness (e.g. myocardial infarction, pneumonia, severe infection and/or dehydration) as it may aggravate tissue hypoxia and accumulate when renal function is impaired. In these circumstances, it may be appropriate to use other glucose-lowering therapies, including insulin, and admission to hospital may be appropriate
- As iodine-containing contrast media may cause acute deterioration of renal function, local arrangements should be in place for discontinuation of Metformin prior to radiological investigations using >100 ml of contrast or where serum creatinine is raised

Sulphonylureas (SUs)

Therapeutic option

1st line if Metformin not tolerated
2nd line in combination therapy with Metformin

Mechanism of action

First introduced in the 1960s, sulphonylureas increase endogenous release of insulin from pancreatic \( \beta \)-cells. The drugs available are classed according to their date of release: first generation SUs, now rarely used in the UK, and second generation (glipizide, gliclazide, glibenclamide glimepiride). They are metabolised by the liver but their metabolites and routes of excretion vary considerably. Since the hypoglycaemic effect of sulphonylureas is due mainly to increased insulin secretion it is dependent on adequate \( \beta \) cell function and is independent of age and body weight. They should be used with caution in hepatic or renal disease or porphyria.

Glycaemic control

Sulphonylureas can be expected to reduce HbA1c by on average 10.60mmol/mol (1%).

Other effects

No known effects on lipid profile or blood pressure

Adverse effects

- Mild hypoglycaemia - 20% of patients treated with a sulphonylurea report one or more mild episodes of hypoglycaemia a year
- Severe hypoglycaemia (defined as requiring third party help or medical intervention). One person with type 2 diabetes in every 100 treated with a sulphonylurea each year experience an episode of severe hypoglycaemia, compared with one in every 2,000 treated with
Metformin and one in every 10 treated with insulin. This is especially common in the elderly. It occurs as the drugs can initiate insulin release when glucose concentrations are below the normal threshold for glucose stimulating insulin release (around 5 mmol/l).

- Alcohol can potentiate their hypoglycaemic effect
- Weight gain of around 1-4kg, stabilising after first 6 months of therapy

**General information**

- These agents should ideally be taken 30 minutes before food. Start at low dose once daily, titrating up, depending on response, after 4 weeks. Maximal response can occur at low dose
- The main risk is hypoglycaemia. The warning signs of hypoglycaemia should be outlined to all people taking these agents. These include tremor, sweating, shaking, irritability, and later lack of concentration or confusion. This risk is further increased in older age groups, and in those with renal impairment and/or liver disease. Glibenclamide is particularly prone to causing hypoglycaemia and should not be used in the elderly. Gliclazide is available in a modified release (MR) preparation. This permits once daily dosing even when higher doses are required. This should only be considered to complement strategies in improving concordance and compliance with therapy by reducing the ‘tablet burden’. Prescribers should be aware that gliclazide MR 30 mg is therapeutically equivalent to standard gliclazide 80 mg (maximum dose therefore 120 mg once daily rather than 160 mg twice daily)
- People taking sulphonylureas should also be advised of their propensity to cause weight gain and therefore the need, if possible, to avoid calorie excess

**Pioglitazone**

**Therapeutic option**

2nd or 3rd line

Combination therapy (with metformin, sulphonylurea)

Can be added to insulin

**Mechanism of action**

Available since 2000, Pioglitazone is a Thiazolidinedione. It increases whole-body insulin sensitivity by activating nuclear receptors and promoting esterification and storage of circulating free fatty acids in subcutaneous adipose tissue, improving glucose uptake in adipose tissue, liver and skeletal muscle. It is extensively metabolised by the liver and excreted in bile. It is almost completely bound to plasma proteins but its concentration is generally low and they have not been reported to interfere with other protein bound drugs. It requires the presence of insulin for its metabolic effects. It should be used with caution in anaemia and impaired liver function and avoided in heart failure. It can take 3 months for it to demonstrate its full effect. Not all patients respond to its mode of action as it is highly dependant on adequate insulin concentrations being present.

**Glycaemic control**

Pioglitazone can be expected to reduce HbA₁c by between 6.99 and 13.77 mmol/mol (0.64 and 1.26%).

**Other effects**

- Studies have reported a reduction of all cause mortality with pioglitazone
- No LFT monitoring required
- Increases HDL, reduces triglycerides
- No known effect on blood pressure
Adverse effects

- Avoid in Heart Failure
- Oedema
- Weight gain – 1-4kg, stabilising over 6-12 months with the distribution of fat being altered – visceral deposits may be reduced while subcutaneous deposits increased
- Anaemia (a reduction in haemoglobin of up to 1g/dl may occur during therapy)
- Not associated with hypoglycaemia
- Fragility fractures in postmenopausal women
- Avoid if eGFR <30
- Contraindicated in those with a past history of renal carcinoma or risk factors for renal carcinoma (monitor for haematuria)

General information

- Pioglitazone is suitable for once daily dosing, in the morning
- Start at 15-30mg, increasing to 45mg after 3 months, according to response
- Discontinuation is appropriate should oedema occur
- People taking Pioglitazone should also be advised of the likelihood of weight gain and increased risk of fracture, although these are not necessarily reasons for discontinuation

Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitors)

Therapeutic option

2nd and 3rd line
Combination therapy (with metformin, sulphonylurea)

Mechanism of action

Dipeptidyl peptidase-4 inhibitors are oral agents which inhibit activity of the enzyme DPP-4 and hence prolong the actions of endogenous Glucagon Like Peptide 1 (GLP-1). There are four DPP-4 inhibitors currently available: saxagliptin, sitagliptin, linagliptin and vildagliptin. They require the presence of glucose in the gut to stimulate the incretin effect. This increases pancreatic insulin secretion and suppresses glucagon secretion, signalling liver to reduce glucose production.

Glycaemic control

DPP4-inhibitors can be expected to reduce HbA1c by 6.56-7.65mmol/mol (0.6-0.7%).

Other effects

The long term effects of these drugs on microvascular complications, cardiovascular disease and mortality are not yet known.

Adverse effects

- Well tolerated
- No severe hypoglycaemia
- Weight neutral

General information

- Suitable for once daily dosing, in the morning (Saxagliptin, Sitagliptin, Linagliptin) or twice daily dosing with meals (Vildagliptin)
- Generally well tolerated
- Questions remain about the possibility that they may predispose either to more frequent
(usually minor) infections, or acute pancreatitis

- People prescribed these agents should be encouraged to report potentially serious symptoms, particularly severe abdominal pain, and, where in doubt, DPP-4 inhibitors should be discontinued pending prompt further assessment
- Saxagliptin should be used with caution if eGFR <30, Sitagliptin and Vildagliptin if eGFR <50, Linagliptin can be used if eGFR <30

Note: a number of oral agents are available in combination with each other in fixed doses. Using these preparations to decrease ‘tablet burden’ may be convenient, and may be associated with increased concordance with therapy. This has also been shown to be cost effective.

**SGLT2 Inhibitor (Dapagliflozin)**

**Therapeutic option**

2\(^{nd}\) line in combination with Metformin only
4\(^{th}\) line in combination with Insulin

**Mechanism of action**

Inhibits the sodium-glucose cotransporter2 (SGLT2) inhibitor at the proximal convoluted tubule of the nephron in the kidney. In healthy individuals the kidney filters approximately 180g of glucose each day with virtually all of this being reabsorbed into the circulation such that urine remains essentially free of glucose. Dapagliflozin reduces glucose reabsorption at the proximal tubule, increasing urinary glucose excretion and calorie loss. It has an insulin independent mode of action

**Glycaemic control**

It can be expected to reduce HbA1c by 6mmol/mol (0.5%)

**Other effects**

The long term effects of these drugs on microvascular complications, cardiovascular disease and mortality are not yet known.

**Adverse effects**

- Genital infection
- Urinary tract infection
- Constipation
- Back pain

**General information**

- Available since 2012
- Niche patient group – over 18 only
- Once daily dosing
- Available in 5mg or 10mg strength – usual dose is 10mg daily
- Avoid in renal and hepatic impairment
- Can lead to weight loss
- Not associated with hypoglycaemia
Glucagon Like Peptide-1 Agonists (GLP 1 Agonists)

Therapeutic option
3rd line
Combination therapy (with Metformin, sulphonylurea)
Where insulin is unacceptable to the patient
Consider referral to the Diabetes Specialist Team

Mechanism of action
Glucagon Like Peptide (GLP)-1 is one of the key ‘incretin’ hormones - a group of rapidly metabolised peptides secreted from the gut in response to food which amplify secretion of insulin from pancreatic β-cells and inhibit inappropriate glucagon secretion. They also slow gastric emptying, resulting in slower absorption of glucose following meals, and reduce appetite. GLP-1 agonists mimic endogenous GLP-1 activity but are resistant to breakdown by the DPP-4 enzyme, resulting in more prolonged action. They increase insulin secretion in response to glucose in the gut hence require some residual pancreatic function. It may not be suitable for those with diabetes duration >10 years, these individuals being poorly represented in published studies.

Three GLP-1 agonists are currently available: exenatide, which requires twice daily subcutaneous injection and has a half-life of four hours, liraglutide and lixisenatide, which require once daily subcutaneous injection and have a half-life of 11-13 hours.

Glycaemic control
Exenatide and Lixisenatide can be expected to reduce HbA1c by 7.65 to 13.22 mmol/mol (0.7%-1.2%). Liraglutide (1.2-1.8 mg once daily) can be expected to reduce HbA1c by 10.93 to 12.02 mmol/mol (0.8-1%)

Other effects
The long term effects of these drugs on microvascular complications, cardiovascular disease and mortality are not yet known.

Adverse effects
- GLP-1 agonists are generally well tolerated; the most frequent adverse events are gastrointestinal, especially mild to moderate nausea
- Severe hypoglycaemia is rare and has only been reported when sulphonylureas are co-prescribed
- There is insufficient evidence to determine whether GLP-1 agonists increase background rates of acute pancreatitis
- GLP-1 agonist treatment may result in weight loss of around -1.6 to -3.1 kg based on studies at 24-52 weeks
- Use is restricted to those with a BMI > 30kg/m2
- Use with caution if eGFR<50

General information
- Start at the lowest dose, titrate after 1 month of therapy
- Administered via a pen device subcutaneously in the abdominal wall or thigh, like insulin
- In keeping with the appetite-suppressant effect of these agents the most common adverse effects are nausea, vomiting and diarrhoea
**Insulin**

**Endogenous insulin abnormalities in Type 2 diabetes**

- Absent or blunted first phase insulin response to glucose
- Decreased overall insulin secretion
- Decreased sensitivity of the insulin response to glucose
- Both basal and postprandial glucose levels fail to trigger normal insulin secretion resulting in postprandial and fasting hyperglycaemia

**Therapeutic option**

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<thead>
<tr>
<th>3rd Line</th>
<th>Combination therapy</th>
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<tbody>
<tr>
<td>Requires a comprehensive support package</td>
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<tr>
<td>Consider referral to the Diabetes Specialist Team</td>
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</table>

**Insulin initiation** (see Figure 3)

Once daily bedtime NPH insulin (Humulin I®, Insulatard®, Insuman Basal®) should be used when adding insulin to oral hypoglycaemic therapy. This is as effective in reducing HbA1c as basal insulin analogue therapy (Lantus®, Levemir®). Basal insulin analogues (Lantus®, Levemir®) should be considered if there are concerns regarding hypoglycaemia risk as it is associated with fewer episodes of mild hypoglycaemia. There is no difference for severe hypoglycaemia.

Weight gain is slightly less with long acting insulin analogues than with NPH insulin when added to an oral hypoglycaemic agent (1 kg).

**Continuing oral agents when initiating basal insulin**

A systematic review showed that when starting insulin therapy, continuing Metformin therapy is associated with lower HbA1c (by up to 6.6 mmol/mol (0.6%)) and less weight gain (by up to 3.7 kg) without an increase in the risk of hypoglycaemia. Continuing sulphonylurea therapy when starting once daily insulin is associated with a greater HbA1c reduction (3.3 mmol/mol (0.3%)) than insulin monotherapy alone but can result in a higher risk of hypoglycaemia. Continuing Metformin, or sulphonylurea or both, in combination results in lower insulin requirements by around 46% compared with insulin alone.

Oral Metformin and sulphonylurea therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control.

When commencing insulin therapy, daily basal insulin should be initiated and the dose titrated against morning (fasting) glucose. The dose of insulin required to improve glycaemic control may be considerable depending on the degree of insulin resistance.
PRACTICAL GUIDE TO COMMENCING INSULIN IN TYPE 2 DIABETES

Consider insulin therapy for people with Type 2 diabetes if the HbA1c is persistently above their individual target on maximum tolerated oral/injectable hypoglycaemic therapy.

Assessment

1. Document the pre insulin HbA1c
2. Review the person’s knowledge of their diabetes
3. Explain that insulin treatment is recommended and why
4. Ensure the patient’s informed consent and motivation for treatment
5. Review diet and lifestyle, consider goal setting in relation to weight and physical activity
6. Refer to diabetes specialist dietician if not already attending for further assessment, advice and education
7. Review activity in relation to self monitoring of blood glucose – consider equipment (quality control, consumables), technique, frequency and problem solving for high or low readings
8. Educate about insulin delivery device, insulin storage, injection technique and sharps disposal
9. Educate about hypoglycaemia and how to treat should this occur
10. Discuss insulin therapy during intercurrent illness
11. Consider referral to the Diabetes Specialist Team if the Primary Care Team does not have the expertise or adequate time to support the initiation of treatment

Insulin Initiation (see Figure 3)

1. Insulin initiation should be planned for a time when support is available to the individual
2. Continue Metformin and sulphonylurea
3. Stop Pioglitazone, DPP-4 inhibitor, SGLT2 inhibitor or GLP 1 analogue (unless consultant diabetologist recommends they be continued with insulin) the day before the insulin start date
4. Start with once daily injection of NPH insulin at bedtime (Humulin I®, Insulatard®, Insuman Basal®)
5. Consider using once daily injection of basal insulin analogue (Lantus®, Levemir®) if concerned about hypoglycaemia and/or if patient will require ongoing community health care professional involvement for injection
6. Use 8mm needles (if pain or discomfort following injection – no benefit has been demonstrated in using 4mm, 5mm or 6mm needles over 8mm needles in terms of efficacy or tolerability and both are less cost effective) – a new needle should be used for each injection and disposed of using a needle clipping device.
7. Starting dose: 8-16 units daily depending on confidence (of avoiding hypoglycaemia) and the weight of the patient
8. Advise person to check their fasting blood glucose daily
9. Aim for a fasting blood glucose between 4 and 7 mmol/l on home monitoring
10. Advise the person to increase their insulin dose by approximately 2 units every 3-4 days if the average fasting blood glucose remains over 7 mmol/l
11. Advise the patient that it may take some time for insulin therapy to become established, depending on the individual’s sensitivity to treatment

Follow up

1. Following initiation agree telephone contact with person for the first few weeks of treatment
2. See for interim review after 3 months on treatment – check the HbA1c, review injection technique and sites, review diet and lifestyle, discuss any problems or concerns the person
may have in relation to treatment
3. Review every 6 months thereafter (incorporating annual review)
4. Refer to diabetes specialist nurse if particular problems with insulin therapy or if intensification of insulin regimen is required
5. Refer to diabetes consultant if no improvement on intensification of treatment

**Insulin intensification** (see Figure 3)
This may need to be considered if the dose of basal insulin reaches 40-50 units and the fasting blood glucose remains uncontrolled. It is not unusual to require large doses of insulin in people with Type 2 Diabetes who have high levels of insulin resistance. The aim is to optimise insulin dose and regimen to achieve target glycaemia while minimising the risk of hypoglycaemia and weight gain. To be fully successful insulin therapy must provide for both meal related and basal insulin requirements. When intensifying insulin therapy by addition of rapid-acting insulin or premixed insulin, sulphonylurea therapy should be stopped. The addition of prandial, short acting insulin results in the best combination of outcomes at the expense of weight gain and increased risk of hypoglycaemia. Using a premixed insulin in Type 2 diabetes does improve glycaemic control (by 4.26 mmol/mol (0.39%)) over basal bolus regimen alone but requires an increased dose of insulin compared to a basal bolus regimen more weight gain (0.6 kg) and hypoglycaemia.

Regular insulin is as effective as rapid-acting analogue insulin for HbA1c reduction, with no difference in rates of hypoglycaemia. Either can be used when intensifying insulin regimens

**TREATMENT STRATEGY** (see Figure 4)

**Step 1**
- **Lifestyle intervention** PLUS
  - Metformin – titrate dose OR
  - SU if symptomatic or Metformin not tolerated – titrate dose

**Step 2**
- **Lifestyle intervention** PLUS adding a second agent
  - Metformin + SU (no concern re hypo) OR
  - Metformin + TZD (if profile suggests insulin resistance and no CHF/oedema/renal carcinoma/haematuria) OR
  - Metformin + DPP4 inhibitor (‘gliptin) (if hypo/weight gain concerns)
  - Metformin + SGLT2 Inhibitor (if hypo/weight loss desirable – new class of treatment)

**Step 3**
- Consider referral to diabetes specialist depending on experience and expertise in practice
- **Lifestyle intervention** plus adding a third agent
  - Metformin + SU + TZD – titrate dose (if markers of insulin resistance and no CHF/oedema)
  - Metformin + SU + DPP4 (‘gliptin)
  - Metformin + TZD + DPP4 (‘gliptin)
  - Metformin + SU + GLP 1 (exenatide/liraglutide) (BMI >30, <10 years since diagnosis, weight loss beneficial) – half the dose of SU
  - Metformin + TZD + GLP 1 (exenatide/liraglutide) (BMI >30, <10 years since diagnosis, weight loss beneficial)
  - Metformin + SU + basal insulin (advise re hypoglycaemia and weight gain)
Step 4
- Intensify insulin regime
- Add pioglitazone if previous response to treatment

**Diabetes MCN endorsement**
May 2014

**Review date**
May 2017
Figure 1 - Pathophysiology of Type 2 Diabetes

- Hyperglycaemia → ↑ blood glucose
- ↓ glucose uptake in skeletal muscle
- ↓ incretin effect in the gastrointestinal tract
- ↑ hepatic glucose production
- ↑ lipolysis in adipose tissue
- ↑ glucagon secretion from pancreatic α cells
- ↓ insulin secretion from pancreatic β cells
Figure 2 – Mode of action of glucose lowering agents

↑ glucose uptake in skeletal muscle
Metformin
Pioglitazone

↓ hepatic glucose production
Metformin
Pioglitazone

↑ incretin effect in the gastrointestinal tract
DPP 4 inhibitor
GLP 1 analogue

↓ lipolysis in adipose tissue
Pioglitazone

↓ glucagon secretion from pancreatic α cells
DPP4 inhibitor
GLP 1 analogue

↓ absorption of glucose from the proximal tubule of the kidney
Dapagliflozin

↓ glucagon secretion from pancreatic β cells
Sulphonylurea
DPP 4 inhibitor
GLP 1 analogue

↑ insulin secretion from pancreatic β cells
Sulphonylurea
DPP 4 inhibitor
GLP 1 analogue
<table>
<thead>
<tr>
<th>Summary</th>
<th>Metformin</th>
<th>SU</th>
<th>Pioglitazone</th>
<th>DPP4</th>
<th>GLP 1</th>
<th>SGLT2</th>
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<tr>
<td>Mode of action</td>
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<td>↓insulin resistance</td>
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<td>Risk pancreatitis Injectable &gt;10 yrs Dx eGFR&lt;50</td>
<td>No long term CV data</td>
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Figure 3 Insulin Initiation and Intensification in Type 2 Diabetes

Isophane insulin* once daily – starting dose 8-16 units at bedtime (will be dependent on weight)

- check fasting levels daily; 2 hrs post-prandial levels twice a week
  - aim for fasting levels 4-7 mmol/l

If: fasting levels > 7 mmol/l, increase dose by 2 units every 3-4 days

If: fasting level 4-7 mmol/l and post-prandial levels < 8.5 mmol/l
  = continue with daily bedtime insulin

(NB If isophane insulin > 40 units and fasting levels remain > 7 mmol/l (with no evidence or Hx of hypos during the night or daytime), continue increasing daily dose by 2-4 units until fasting levels 4-7 mmol/l; recheck HbA1c at regular intervals; monitor weight gain; if concerns re dosage, discuss with DSN)

If: fasting levels 4-7 mmol/l, but post-prandial levels > 8.5 mmol/l
  - review lifestyle, dietary intake; recheck HbA1c
  - if HbA1c below target, no further action necessary

If HbA1c continues above target:
  - convert to a twice daily mixture **
    - start at 80% of current basal dose
    - give 60% before breakfast and 40% before evening meal
    - contact DSN/specialist health care professional for further advice re dose adjustment

If HbA1c continues above target:
  and regular meals and activity
  - consider addition of quick-acting insulin *** with meals
  - would be appropriate to discuss regime at this point with DSN/specialist staff as it may be necessary to review dose and/or timing of isophane or long-acting analogue at this stage

NB As per NHSL guidelines:-
  * Long-acting analogue may be appropriate in some circumstances - first line currently Lantus®
  ** First line mixture currently Humulin M3® (review date 6 months from publication)
  *** First line quick acting insulin Humulin S®
BLOOD GLUCOSE LOWERING THERAPY IN TYPE 2 DIABETES

If HbA1c > individually agreed target (typically 53-58mmol/mol) and after trial of lifestyle measures (e.g. for 3 months, and if appropriate i.e. person not unduly symptomatic; HbA1c/BGs not unduly raised), commence blood glucose lowering treatment as follows:

**STEP ONE (monotherapy)**

**SULPHONYLUREA (Gliclazide, Glipizide, Glimiperide)**
- Not overweight
- Metformin not tolerated or contraindicated
- Rapid response needed because of symptoms
- Provide education and advice on self monitoring blood glucose

**METFORMIN**
First line

**OR**

**SULPHONYLUREA NOT TOLERATED**

**STEP TWO (dual therapy)** If HbA1c > individually agreed target after 3-6 months & on maximum tolerated dose, add:

**SULPHONYLUREA**
First line

**PIOGLI TAZONE - consider if:**
- Risk of hypoglycaemia
- Marked insulin resistance
- No risk factors for bladder cancer
- Low fracture risk in post menopausal woman
- But avoid in heart failure

**OR**

**DPP-4 INHIBITOR (Saxa-/ Sita-/ Linagliptin Alogliptin) consider if:**
- Risk of hypoglycaemia
- Further weight gain undesirable
- But watch suitability of individual choice in renal impairment
- Check licence indications

**SGLT2 Inhibitor (Dapa-/ Cana-/ Empagliflozin)**
Consider if:
- Weight loss desirable
- Normal renal function
- Less than 75 years
- Low risk of UTI/genital infection

**STEP THREE (triple therapy)** If HbA1c > individually agreed target after 3-6 months & on maximum tolerated dose, continue dual therapy and add:

**INSULIN**
Once daily long acting human insulin, consider analogue insulin if risk of hypoglycaemia

**OR**

**PIOGLI TAZONE**

**DPP-4 INHIBITOR (Saxa-/ Sita-/ Linagliptin Alogliptin) Check License Indications**

**OR**

**GLP-1 MIMETIC (Lixisenatide/ Exenatide/ Exenatide MR/ Liraglutide) *6m trial***
- BMI 30-35 + weight loss desirable
- Insulin unacceptable
- May be less effective if Diabetes > 10 year duration

**SGLT2 Inhibitor (Dapa-/ Cana-/ Empagliflozin)**

**STEP FOUR** If HbA1c > individually agreed target after 3-6 months add:

Add or intensify insulin regime - once daily long-acting or twice daily mix regime, addition of quick-acting to once daily, basal bolus regime
Add Pioglitazone, DPP4 Inhibitor or SGLT2 Inhibitor to insulin therapy if inadequate control despite high doses of insulin
*consider referral to Diabetes Specialist Service for further advice*

**NHSL formulary choices per class at this link** [http://bit.ly/1ykXV29](http://bit.ly/1ykXV29)