Prescribing pearls: A guide to metformin

What and why

There is much focus on how to use newer diabetes drugs, such as SGLT2 inhibitors and GLP-1 receptor agonists, safely and effectively, including emerging evidence of their benefits beyond glucose lowering. However, the majority of people with diabetes are still treated with older drugs, often along with the newer ones.

The *Prescribing pearls* series focuses on practical prescribing of these older drugs, sharing insights from experienced prescribers on how to optimise benefits and minimise adverse effects. The guides are concise, current and contain information relevant to primary care teams.

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Initiating and monitoring

Check renal function prior to starting therapy
Do not start if eGFR is <30

Initiate at 500 mg once daily (taken during or after meals)

Titrate according to tolerability by 500 mg/day at weekly intervals; change to metformin M/R **at any time** if persisting gut symptoms

Increase dose up to 1000 mg twice daily or 850 mg three times daily

Combining metformin with an SGLT2 inhibitor

As per NICE NG28 recommendations[1]:

Assess CV risk:

- If chronic heart failure or established ASCVD, offer an SGLT2i*
- If high risk of developing CVD (QRISK >10%), consider an SGLT2i*

Introduce the SGLT2i **without delay** as soon as metformin tolerability is confirmed: do not wait to check HbA_{1c} at 3 months before doing so

*Use an SGLT2i with proven CV benefit. Only initiate if safe and according to the licence

During treatment, monitor renal function:

- At least once a year if normal renal function
- 3–6 monthly if additional risk factors for renal impairment (e.g. elderly patients), or if deterioration in renal function suspected

Reduce dose (usually to 1000 mg total) if eGFR falls below 45

Warn people of the small risk of **lactic acidosis** and to **pause metformin** if risk of dehydration; i.e. if vomiting, diarrhoea, fever or unable to take fluids (see How to advise on sick day rules):

- Warn to look out for laboured breathing, abdominal pain, muscle cramps, weakness or hypothermia, and to seek medical help if these occur

Stop metformin:

- If eGFR <30
- In people at risk of tissue hypoxia or sudden deterioration in renal function
- Pause if eGFR <60 and iodine-containing contrast medium is to be used (see **Contraindications and cautions** section)

Always consult the Summary of Product Characteristics before prescribing any drug. Visit https://www.medicines.org.uk/emc

Contraindications and cautions

Most contraindications are to prevent **lactic acidosis**, a very rare but serious metabolic complication which most often occurs in acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

Contraindications:

- Hypersensitivity to any components
- Acute conditions (dehydration, severe infection, shock)
- eGFR <30
- Advanced liver disease, acute intoxication, major alcohol abuse
- Acute unstable chronic HF
- Conditions associated with acidosis, including ketoacidosis

Cautions:

- eGFR 30–45: Reduce dose to 1000 mg total daily
- eGFR <60: Pause if iodine-containing contrast investigation or surgery planned. Check eGFR 48 hours later and restart if stable

Drug interactions

- Drugs which may affect renal function (e.g. NSAIDs, ACE inhibitors, ARBs and diuretics, especially loop diuretics): **monitor eGFR carefully**

Prescribing tips

- Start low, go slow when titrating dose.
- If high HbA_{1c} and osmotic symptoms, consider co-initiating rescue therapy with a sulfonylurea or insulin, which can then be reduced and stopped once control is achieved.
- Consider use of modified-release or combination tablets if on more than one glucose-lowering therapy, to reduce pill burden and help improve adherence.
- Undertake a practice search for people treated with metformin who have eGFR 30–45 and <30, and ensure appropriate dose reduction or cessation of metformin, as well as coding the chronic kidney disease.

What is metformin?[2]

Metformin is a biguanide drug for glucose lowering, available in the UK since 1957. It is available in two forms:

- Immediate-release (absorbed in the upper small bowel).
- Extended-release (absorbed more slowly in the upper gut).

Mechanisms of action[3]

Complex mechanisms of action are still under review. These may include:

- Reduced liver glucose production by gluconeogenesis or glycogenolysis.
- Increased insulin sensitivity in muscle, increasing peripheral glucose uptake.
- Delay in absorption or increased usage of glucose in the intestine.
- Alteration in the gut microbiome.
- Possible effects increasing secretion of GLP-1.

Indications

For treatment of type 2 diabetes when dietary management and exercise alone do not result in adequate glycaemic control:

- In adults, as monotherapy or in combination with other oral glucose-lowering agents, or with insulin.
- In children and adolescents aged ≥10 years, as monotherapy or in combination with insulin.

Positioning in guidelines

Metformin remains the first-line pharmacotherapy in most global guidelines, including NICE NG28[1] and the ADA/EASD consensus[4]. It is recommended as combination first-line therapy in some groups to ensure early benefits of other drug classes.

Glycaemic effects[3]

Efficacy is dose-dependent.

- 500 mg decreases HbA_{1c} by up to 9.8 mmol/mol.
- 1000 mg achieves >50% efficacy of 2000 mg.
- 2000 mg decreases HbA_{1c} by up to 21.9 mmol/mol.
- Although licensed for use up to 3000 mg daily in three divided doses, there is little additional glucose lowering at doses greater than 2000 mg, whereas side effects are increased.

Metformin is equipotent to sulfonylureas, thiazolidinediones and GLP-1 receptor agonists, and is more potent than DPP-4 inhibitors.

Using drugs with complementary mechanisms results in added glucose-lowering effects.

Other benefits and cardiovascular safety[5]

- Reduced diabetes complications, diabetes-related mortality and all-cause mortality have been demonstrated in overweight adults in the small UKPDS metformin study[6].
- Cardiovascular safety demonstrated over more than 60 years of use. Uncertainty about whether metformin reduces cardiovascular risk, mainly due to absence of evidence. It is unlikely that a cardiovascular outcome trial will be undertaken in future.
- Reduces total and LDL-cholesterol and triglyceride levels.
- Weight loss up to 4 kg demonstrated in short-term studies. Possible modes of action include increased carbohydrate utilisation in the gut, less absorption and anorexia causing decreased food intake. Weight-neutral in longer-term studies.
- Ongoing research is exploring potential benefits for cancer and ageing.

Adverse effects

- **No hypoglycaemia** unless combined with drugs that cause hypoglycaemia themselves (e.g. sulfonylureas, insulin).
- **Gastrointestinal intolerance** (nausea, bloating, loose stools) is common when initiating therapy (but may occur at any time) and is dose-dependent, and may be more likely if IBS or IBD. Slow titration advised if significant side effects. Switch to modified-release, which causes fewer side effects, if immediate-release not tolerated.
- **Vitamin B12 deficiency** is more common than previously thought and is mainly due to malabsorption. It is important to diagnose and manage megaloblastic anaemia and neuropathy due to B12 deficiency.
  - ➤ Check B12 in those on long-term metformin, especially if anaemia, peripheral neuropathy or other symptoms (e.g. mental disturbances, glossitis, mouth ulcers).[7]
  - ➤ See updated MHRA guidance – June 2022.[7]
- **Lactic acidosis** is rare, occurring in 3–10 per 100 000 person-years, but serious.
  - ➤ More likely in states which increase lactate production (e.g. sepsis and severe infections, cardiogenic shock, major alcohol abuse).
  - ➤ Iodine-containing contrast medium can cause nephropathy and increased risk of metformin accumulation, and thus lactic acidosis. Pause metformin at time of investigation, or 48 hours before investigation if eGFR is <60. Check eGFR two days later and restart if stable.
  - ➤ Discontinue metformin if undergoing surgery and restart after ≥48 hours if eGFR stable.
- **Taste disturbance** can occur.
- Rare adverse effects include **skin erythema**, **pruritus**, **urticaria**, and **hepatitis or abnormal liver function tests**.

Key summary table

Hypoglycaemia risk	Weight impact	Renal concerns	Hepatic concerns	CV safety/ benefit	Use in elderly
Not unless combined with drugs causing hypoglycaemia	Neutral	Reduce dose if eGFR <45 and stop if <30	Do not use in **severe** liver disease	CV-neutral, possible benefits in overweight	Safe if eGFR criteria met

CV=cardiovascular; eGFR=estimated glomerular filtration rate (in mL/min/1.73 m^2).

Available brands

Immediate-release requires twice-daily or three-times-daily dosing. Extended-release is absorbed more slowly and so can be given once daily. **Both formulations are equally effective**.

Dosing should start with 500 mg daily, building up by 500 mg at weekly intervals, if tolerated, up to 1000 mg twice daily. If immediate-release metformin is not tolerated despite slower titration, extended-release preparations are better tolerated.

Metformin immediate-release is also available in combination with pioglitazone or with each of the DPP-4 inhibitors and SGLT2 inhibitors. Combination tablets reduce pill burden but a restricted range of fixed-dose combinations is available. Extended-release metformin is not available in fixed-dose combinations.

Drug contents	Strengths available	Brand examples	Dosing
Metformin immediate-release (tablet, caplet, oral solution)	100 mg, 500 mg, 850 mg, 1000 mg	Glucophage	Twice daily
Metformin extended-release	500 mg, 750 mg, 1000 mg	Glucophage SR	Once daily
Metformin + Pioglitazone	850 mg + 15 mg	Competact	Twice daily
Metformin + Alogliptin	1000 mg + 12.5 mg	Vipdomet	Twice daily
Metformin + Saxagliptin	850 mg, 1000 mg + 2.5 mg	Kombiglyza	Twice daily
Metformin + Sitagliptin	1000 mg + 50 mg	Janumet	Twice daily
Metformin + Vildagliptin	850 mg, 1000 mg + 50 mg	Eucreas	Twice daily
Metformin + Canagliflozin	850 mg, 1000 mg + 50 mg	Vokanamet	Twice daily
Metformin + Empagliflozin	1000 mg + 5 mg, 12.5 mg	Synjardy	Twice daily
Metformin + Dapagliflozin	850 mg, 1000 mg + 5 mg	Xigduo	Twice daily

References

1. NICE (2015) *Type 2 diabetes in adults: management* [NG28]. Updated March 2022. Available at: www.nice.org.uk/guidance/ng28

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3. Rena G, Hardie DG, Pearson ER (2017) The mechanisms of action of metformin. *Diabetologia* **60**: 1577–85

4. Buse JB, Wexler DJ, Tsapas A et al (2020) 2019 update to: Management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **43**: 487–93

5. Griffin SJ, Leaver JK, Irving GJ (2017) Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia* **60**: 1620–9

6. UKPDS Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**: 854–65

7. MHRA (2022) *Metformin and reduced vitamin B12 levels: new advice for monitoring patients at risk*. Available at: https://bit.ly/39W7y4U