



## 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.

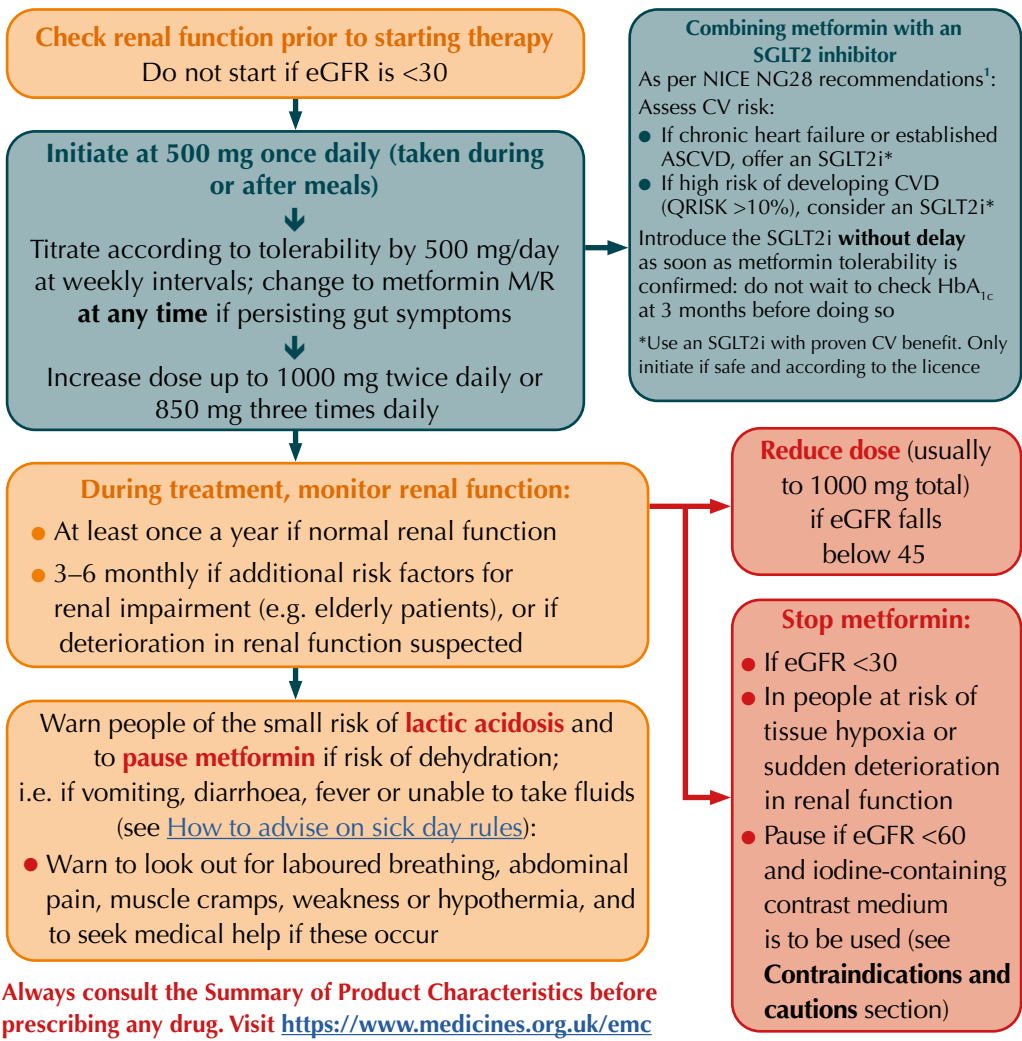
The *Prescribing pearls* series focuses on practical prescribing of these older drugs, sharing insights from experienced prescribers on how to optimise benefits and minimise adverse effects. The guides are concise, current and contain information relevant to primary care teams.

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### Initiating and monitoring



### 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<sub>1c</sub> 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?<sup>2</sup>

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<sup>3</sup>

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  $\geq 10$  years, as monotherapy or in combination with insulin.

### Positioning in guidelines

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

### Glycaemic effects<sup>3</sup>

Efficacy is dose-dependent.

- 500 mg decreases HbA<sub>1c</sub> by up to 9.8 mmol/mol.
- 1000 mg achieves >50% efficacy of 2000 mg.
- 2000 mg decreases HbA<sub>1c</sub> 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<sup>5</sup>

- Reduced diabetes complications, diabetes-related mortality and all-cause mortality have been demonstrated in overweight adults in the small UKPDS metformin study<sup>6</sup>.
- 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).<sup>7</sup>
  - See [updated MHRA guidance – June 2022](#).<sup>7</sup>
- **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  $\geq 48$  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 <b>severe</b> 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<sup>2</sup>).

**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**

- NICE (2015) *Type 2 diabetes in adults: management* [NG28]. Updated March 2022. Available at: [www.nice.org.uk/guidance/ng28](http://www.nice.org.uk/guidance/ng28)
- Sanchez-Rangel E, Inzucchi SE (2017) Metformin: clinical use in type 2 diabetes. *Diabetologia* **60**: 1586–93
- Rena G, Hardie DG, Pearson ER (2017) The mechanisms of action of metformin. *Diabetologia* **60**: 1577–85
- 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
- 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
- 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
- MHRA (2022) *Metformin and reduced vitamin B12 levels: new advice for monitoring patients at risk*. Available at: <https://bit.ly/39W7y4U>