

Biguanides

A single surviving drug, metformin, that lowers blood glucose mainly by cutting hepatic glucose output rather than by pushing the pancreas to secrete more insulin, and that remains the preferred first pharmacologic step for most adults with type 2 diabetes.

Online guide: <https://www.medguideglobal.com/pharmacology/endocrine-and-metabolic/biguanides>

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Quick revision

One Liner: Metformin is essentially the whole biguanide class: it lowers glucose by reducing hepatic gluconeogenesis and improving peripheral insulin sensitivity rather than by stimulating insulin secretion, which is why it does not cause hypoglycemia on its own and remains most guidelines' preferred first pharmacologic agent for type 2 diabetes.

1. Metformin is the only biguanide in routine current use; earlier biguanides (phenformin, buformin) were withdrawn decades ago after an unacceptable lactic acidosis rate, and that history is why the whole class still carries a lactic acidosis boxed warning today. [2]
2. Its mechanism is not insulin secretagogue: metformin activates AMP-activated protein kinase (AMPK), which suppresses hepatic gluconeogenesis, increases peripheral (mainly skeletal muscle) glucose uptake, and modestly reduces intestinal glucose absorption. [1][2]
3. The FDA label carries a boxed warning that postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension and resistant bradyarrhythmias. [1]
4. The label sets renal thresholds: metformin is contraindicated at eGFR below 30 mL/min/1.73 m², is not recommended to be started at eGFR 30 to 45 mL/min/1.73 m², and should be discontinued if eGFR later falls below 30 mL/min/1.73 m². [1]
5. Metformin should be discontinued at the time of, or before, iodinated contrast imaging in patients with eGFR 30 to 60 mL/min/1.73 m², a history of liver disease, alcoholism or heart failure, or those receiving intra-arterial contrast, with kidney function re-evaluated 48 hours later before restarting. [1]
6. Long-term use is associated with decreased vitamin B12 levels, reported in roughly 7% of trial patients; the label recommends periodic hematologic monitoring and B12 measurement every 2 to 3 years. [1]
7. Metformin is weight-neutral to modestly weight-reducing and does not itself cause hypoglycemia, which is why the ADA Standards of Care continue to favor it as the preferred initial pharmacologic agent for most adults with type 2 diabetes, alongside early add-on of an SGLT2 inhibitor or GLP-1 receptor agonist when cardiovascular, renal, hepatic or obesity risk is present. [4]
8. Gastrointestinal intolerance - diarrhea, nausea, flatulence, abdominal discomfort - is the most common reason patients stop metformin, and is the rationale for slow dose titration and extended-release formulations. [1]

Overview

1. Biguanides are, in current practice, a class of one drug. Metformin is the sole biguanide still marketed after its older relatives, phenformin and buformin, were withdrawn from most markets decades ago because they caused lactic acidosis at an unacceptable rate. Metformin's own lactic acidosis risk is far lower, but the mechanistic family resemblance is exactly why the boxed warning on metformin's own label still exists: the risk is a class property tied to how biguanides interact with mitochondrial and hepatic metabolism, not something unique to the withdrawn drugs alone. [2]
2. What separates metformin from the insulin secretagogues covered elsewhere in this hub is the mechanism itself. Metformin activates AMP-activated protein kinase inside hepatocytes and skeletal muscle cells, which suppresses hepatic gluconeogenesis (the liver's own glucose output), increases peripheral glucose uptake, and modestly reduces

intestinal glucose absorption. None of that requires the pancreas to secrete more insulin, which is the practical reason metformin monotherapy does not cause hypoglycemia and why it pairs cleanly with agents that work by a different mechanism. [1][2]

3. That mechanism also explains metformin's durable position as the preferred first pharmacologic step in most treatment algorithms. It is weight-neutral to modestly weight-reducing, inexpensive, and has decades of outcomes experience behind it. The ADA Standards of Care continue to describe it as the preferred initial agent for most adults with type 2 diabetes, while directing early addition of an SGLT2 inhibitor or a GLP-1 receptor agonist - independent of glycemic control - when the patient carries cardiovascular, renal, hepatic or obesity-related risk that those other classes specifically address. [4]

4. The safety profile that actually limits metformin day to day is less dramatic than lactic acidosis but far more common: gastrointestinal intolerance. Diarrhea, nausea, vomiting, flatulence and abdominal discomfort are the most frequently reported adverse effects in the label's own trial data, and they are the reason clinicians titrate the dose slowly and often prefer an extended-release formulation. Two quieter, longer-horizon issues sit alongside that - the renal-function thresholds that gate who can safely take metformin at all, and a vitamin B12 deficiency signal that only becomes relevant with sustained, long-term use. [1]

Classification and drug examples

Intro: There is only one clinically relevant subclass here: the biguanide that survived. The distinction that matters in practice is formulation - immediate-release versus extended-release - not a family of related molecules the way other drug classes in this hub are organized.

Name: Biguanide (current use)

Note: Metformin is the only biguanide in routine clinical use; phenformin and buformin were withdrawn from most markets after an unacceptable lactic acidosis rate and are not covered here as active therapies.

Name: Metformin

1. Metformin hydrochloride

2. Glucophage

Route: Oral, immediate-release or extended-release

Note: Available as immediate-release tablets, extended-release tablets, and an oral solution; extended-release formulations are often better tolerated gastrointestinally. [1] [2]

Mechanism of action

Summary: Metformin's dominant glucose-lowering effect is reduced hepatic gluconeogenesis, with a secondary contribution from increased peripheral (chiefly skeletal muscle) glucose uptake and a modest reduction in intestinal glucose absorption. The unifying intracellular event is activation of AMP-activated protein kinase (AMPK), a cellular energy sensor, which shifts hepatocyte metabolism away from glucose production. Because none of this depends on stimulating additional insulin release from the pancreas, metformin is not classified as an insulin secretagogue and does not cause hypoglycemia when used alone.

Target: Hepatic and, to a lesser extent, skeletal-muscle AMP-activated protein kinase (AMPK) signalling; intestinal glucose absorption

Cidal Static: Not applicable - a metabolic and signalling effect on the patient's own hepatocytes and myocytes, not an action against a pathogen

Kill Kinetics: Onset over days to weeks with regular dosing; glucose-lowering effect is sustained only with continued therapy

1. Step: 1

1. Title: Metformin is absorbed and taken up by hepatocytes

1. Detail: Following oral absorption, metformin is taken up preferentially into the liver, its main site of pharmacologic action. [2]

2. Step: 2

2. Title: AMP-activated protein kinase (AMPK) is activated

2. Detail: Metformin activates AMPK, a cellular energy-sensing enzyme that responds to a shift in the cell's ATP-to-AMP ratio. [2]

3. Step: 3

3. Title: Hepatic gluconeogenesis is suppressed

3. Detail: AMPK activation reduces expression of the enzymes driving hepatic glucose production, decreasing hepatic glucose production, which is the mechanism the FDA label itself lists first for how metformin decreases blood glucose. [1]

4. Step: 4

4. Title: Peripheral glucose uptake improves

4. Detail: In skeletal muscle, metformin improves peripheral insulin sensitivity, increasing glucose uptake and utilization, so existing circulating insulin does more work rather than more insulin being secreted. [1]

5. Step: 5

5. Title: Intestinal glucose absorption is modestly reduced

5. Detail: A smaller contribution comes from decreased intestinal absorption of glucose, adding to the net glucose-lowering effect without an insulin secretagogue step anywhere in the pathway. [1]

Major clinical uses

1. Drug: Metformin

1. Organism: Not applicable

1. Indication: Adjunct to diet and exercise to improve glycemic control in adults, and in pediatric patients from age 10, with type 2 diabetes mellitus

1. Line: preferred first-line pharmacologic agent for most adults with type 2 diabetes

1. Note: Also used off-label for gestational diabetes, antipsychotic-associated weight gain, and polycystic ovary syndrome, though these are not the FDA-labelled indication. [1][2]

2. Drug: Metformin

2. Organism: Not applicable

2. Indication: Combination therapy alongside an SGLT2 inhibitor, GLP-1 receptor agonist, sulfonylurea, DPP-4 inhibitor or insulin when metformin monotherapy does not achieve glycemic targets

2. Line: background agent onto which other classes are added

2. Note: Fixed-dose combination products pairing metformin with several of these classes exist to reduce pill burden. [4]

3. Drug: Metformin

3. Organism: Not applicable

3. Indication: Off-label use in polycystic ovary syndrome to improve insulin resistance and, secondarily, ovulatory and metabolic features

3. Line: adjunct, not an FDA-labelled indication

3. Note: Prescribed for its insulin-sensitising effect rather than a glucose-lowering indication in this population. [2]

4. Drug: Metformin

4. Organism: Not applicable

4. Indication: Off-label use in gestational diabetes as an alternative or adjunct to insulin

4. Line: adjunct/alternative, not an FDA-labelled indication

4. Note: Practice varies by guideline and region; insulin remains the labelled standard in pregnancy. [2]

Pharmacokinetics

Drug: Metformin

Route: Oral, immediate-release, extended-release, or oral solution

Absorption: Absolute bioavailability roughly 50 to 60% under fasting conditions; food modestly decreases and delays absorption

Csf Penetration: Not clinically relevant to this drug's mechanism

Metabolism: Not metabolized; excreted unchanged

Elimination: Renal, via tubular secretion and glomerular filtration; elimination half-life is prolonged as renal function declines

Dose Adjust: eGFR is the dominant dose-adjustment variable: not recommended to start below 45 mL/min/1.73 m², contraindicated below 30 mL/min/1.73 m², and discontinued if eGFR later falls below 30 [1]

1. This page gives no dose regimens by design. Starting dose, titration schedule and maximum dose depend on the specific formulation, renal function and concomitant therapy, and belong in a current prescribing reference used by the treating clinician.

2. Because metformin is renally cleared unchanged rather than hepatically metabolized, kidney function is the single most consequential pharmacokinetic variable governing both dosing and the drug's central safety concern, lactic acidosis, in a way that has no real parallel among the insulin secretagogues. [1]

3. Extended-release formulations slow the rate of absorption rather than changing the elimination pathway, and are used mainly to improve gastrointestinal tolerability rather than to alter renal dosing thresholds. [1]

Adverse effects

1. Effect: Diarrhea

1. Detail: The single most frequently reported adverse effect in the label's clinical trial data, reported in roughly half of treated patients at some point. [1]

2. Effect: Nausea and vomiting

2. Detail: Common, particularly with rapid dose escalation; slower titration and extended-release formulations reduce the incidence. [1]

3. Effect: Flatulence, abdominal discomfort and indigestion

3. Detail: Reported across trial populations and, together with diarrhea and nausea, account for most treatment discontinuations attributable to metformin. [1]

4. Effect: Metallic taste and asthenia

4. Detail: Reported less frequently than the gastrointestinal effects above but documented in the label's adverse-reaction tables. [1]

1. Effect: Lactic acidosis

1. Detail: The subject of metformin's boxed warning: postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension and resistant bradyarrhythmias. Risk increases with renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment and conditions causing tissue hypoperfusion or hypoxemia.

1. Action: Metformin is withheld in patients with these risk factors and in the eGFR ranges specified in the label; new symptoms such as malaise, myalgia, respiratory distress, unusual somnolence or abdominal distress during treatment warrant prompt medical evaluation rather than waiting. [1][3]

2. Effect: Vitamin B12 deficiency

2. Detail: Long-term use is associated with a biochemical decrease in serum vitamin B12, reported in roughly 7% of clinical trial patients, through a mechanism related to altered small-intestinal calcium-dependent B12 absorption.

2. Action: The label recommends measurement of hematologic parameters annually and vitamin B12 levels every 2 to 3 years during long-term therapy, with evaluation and management if deficiency or anemia is detected. [1]

Drug: Metformin

Effect: As the only biguanide in current use, every listed adverse effect in this section is specific to metformin by default; there is no second drug in the class to contrast it against. [2]

Contraindications, precautions and interactions

1. Severe renal impairment, eGFR below 30 mL/min/1.73 m². [1]
2. Known hypersensitivity to metformin. [1]
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. [1]
1. Initiation is not recommended at eGFR 30 to 45 mL/min/1.73 m²; treatment is stopped if eGFR later falls below 30. [1]
2. Discontinue at the time of, or before, iodinated contrast imaging in patients with eGFR 30 to 60 mL/min/1.73 m², a history of liver disease, alcoholism or heart failure, or those receiving intra-arterial contrast; re-evaluate eGFR 48 hours after the procedure before restarting. [1]
3. Hepatic impairment, excess alcohol intake, sepsis, dehydration, surgery or any condition producing tissue hypoperfusion or hypoxemia raise lactic acidosis risk and warrant temporary discontinuation. [1]
4. Long-term use warrants periodic monitoring for vitamin B12 deficiency, particularly in patients with pre-existing anemia or peripheral neuropathy. [1]
1. With: Iodinated contrast media
1. Effect: Can acutely reduce renal function and precipitate lactic acidosis in susceptible patients; temporary discontinuation around the procedure is directed by the prescribing information. [1]
2. With: Alcohol
2. Effect: Potentiates the effect of metformin on lactate metabolism, increasing lactic acidosis risk, particularly with acute excess intake or chronic alcoholism. [1]
3. With: Carbonic anhydrase inhibitors (for example, topiramate)
3. Effect: Concomitant use has been associated with metabolic acidosis and may increase the risk of lactic acidosis when combined with metformin. [1]

High-yield exam pearls

1. Pearl: Metformin decreases hepatic glucose output; it does not stimulate insulin secretion.
1. Why: This single mechanistic fact explains why metformin monotherapy does not cause hypoglycemia and why it is not an insulin secretagogue, distinguishing it sharply from the sulfonylureas covered elsewhere in this hub. [1]
2. Pearl: The lactic acidosis boxed warning traces back to the older, withdrawn biguanides phenformin and buformin, not to metformin's own trial data alone.
2. Why: It explains why a rare but serious warning persists on a drug whose actual reported lactic acidosis rate in appropriately selected patients is low. [2]
3. Pearl: eGFR 30 and 45 mL/min/1.73 m² are the two numbers to memorize: below 30 is an absolute contraindication, and 30-45 means do not start (though continuing an existing, tolerated regimen may be reasonable under clinician judgement).
3. Why: Renal-threshold questions are one of the most reliably tested specifics in this class. [1]
4. Pearl: Iodinated contrast is a temporary hold, not a permanent stop.
4. Why: The label directs discontinuation around the imaging procedure in at-risk patients with re-evaluation of kidney function 48 hours later, not indefinite discontinuation. [1]
5. Pearl: Vitamin B12 deficiency is a long-term-use finding, not an acute adverse effect.
5. Why: It becomes relevant only with sustained therapy and is why periodic B12 monitoring, not baseline-only testing, is recommended. [1]

Common exam traps

1. Trap: Assuming metformin causes hypoglycemia the way a sulfonylurea does.
1. Correction: Metformin does not stimulate insulin secretion and does not cause hypoglycemia when used alone;

hypoglycemia with metformin therapy usually reflects a concurrent insulin secretagogue or insulin itself. [1]

2. Trap: Treating the lactic acidosis boxed warning as evidence that metformin is uniquely dangerous compared with other diabetes drugs.

2. Correction: The warning reflects a class-mechanism risk inherited from older, withdrawn biguanides; metformin remains the preferred first-line agent in most guidelines precisely because its real-world risk, in appropriately selected patients, is low. [2][4]

3. Trap: Believing metformin is contraindicated in all chronic kidney disease.

3. Correction: The contraindication is specifically eGFR below 30 mL/min/1.73 m²; metformin can still be used, often at reduced exposure, above that threshold with appropriate monitoring. [1]

4. Trap: Forgetting that metformin needs to be stopped only temporarily, not permanently, around iodinated contrast imaging.

4. Correction: The label describes a hold at the time of, or before, the procedure with renal re-evaluation 48 hours afterward before restarting, not permanent discontinuation. [1]

Self-test questions

1. Question: What is metformin's primary mechanism of lowering blood glucose?

1. Stimulating pancreatic insulin secretion
2. Reducing hepatic gluconeogenesis and improving peripheral insulin sensitivity
3. Blocking intestinal disaccharidases
4. Inhibiting renal glucose reabsorption

1. Explanation: Metformin activates AMPK, which reduces hepatic glucose production and improves peripheral (mainly skeletal muscle) glucose uptake; it is not an insulin secretagogue. [1]

2. Question: Below what eGFR is metformin absolutely contraindicated?

1. 60 mL/min/1.73 m²
2. 45 mL/min/1.73 m²
3. 30 mL/min/1.73 m²
4. 15 mL/min/1.73 m²

2. Explanation: The FDA label states metformin is contraindicated at eGFR below 30 mL/min/1.73 m², and it is not recommended to be started at eGFR 30 to 45. [1]

3. Question: What is the correct management of metformin around iodinated contrast imaging in an at-risk patient?

1. Permanently discontinue metformin
2. No action is needed regardless of renal function
3. Discontinue at the time of or before the procedure and re-evaluate eGFR 48 hours later before restarting
4. Double the metformin dose before the procedure

3. Explanation: The label directs a temporary hold around the procedure in patients with eGFR 30-60, liver disease, alcoholism, heart failure, or intra-arterial contrast, with renal re-evaluation 48 hours afterward. [1]

4. Question: Which long-term deficiency is specifically monitored during metformin therapy?

1. Vitamin D
2. Vitamin B12
3. Folate
4. Iron

4. Explanation: Metformin is associated with decreased vitamin B12 levels with long-term use, and the label recommends periodic hematologic and B12 monitoring. [1]

5. Question: Why does the biguanide class carry a lactic acidosis boxed warning even though metformin's own risk is low?

1. Because metformin caused a major lactic acidosis outbreak in trials
2. Because the warning is a regulatory holdover from earlier biguanides, phenformin and buformin, that were

withdrawn for this reason

3. Because metformin is metabolized to a toxic lactate compound

4. There is no lactic acidosis warning on metformin's label

5. Explanation: Phenformin and buformin were withdrawn from most markets due to an unacceptable lactic acidosis rate; the mechanistic family resemblance is why the warning persists on metformin's label despite its own much lower reported risk. [2]

6. Question: According to the ADA Standards of Care, what typically prompts early addition of an SGLT2 inhibitor or GLP-1 receptor agonist alongside metformin?

1. Any elevation in HbA1c above target alone

2. Presence of cardiovascular, renal, hepatic or obesity-related risk, independent of glycemic control

3. Patient preference for injectable therapy only

4. Metformin intolerance is required first

6. Explanation: The ADA Standards of Care direct early addition of these classes based on cardiovascular, renal, hepatic or obesity risk rather than waiting for glycemic control alone to fail. [4]

Frequently asked questions

1. Question: Why is metformin still first-line if it carries a lactic acidosis warning?

1. Answer: The warning reflects a mechanistic family risk inherited from older biguanides (phenformin, buformin) that were withdrawn because their own lactic acidosis rate was unacceptable. Metformin's real-world risk, in patients selected according to the label's renal and clinical criteria, is low, and its long track record, weight-neutral profile and lack of intrinsic hypoglycemia risk are why the ADA Standards of Care continue to favor it as the preferred initial pharmacologic agent for most adults with type 2 diabetes. [2][4]

2. Question: Can metformin be used in someone with reduced kidney function?

2. Answer: It depends on the exact eGFR. The label contraindicates metformin below 30 mL/min/1.73 m² and advises against starting it between 30 and 45. Above 45, it can generally be used with appropriate monitoring, since metformin is cleared by the kidney unchanged and reduced clearance is the main driver of lactic acidosis risk. [1]

3. Question: Does metformin cause weight gain like some other diabetes drugs?

3. Answer: No - metformin is weight-neutral to modestly weight-reducing, which is one of the properties that distinguishes it from insulin secretagogues such as sulfonylureas, which commonly cause weight gain. [1]

4. Question: Why does metformin need to be stopped before a contrast CT scan?

4. Answer: Iodinated contrast can acutely reduce kidney function in susceptible patients, and reduced renal clearance of metformin is the key risk factor for lactic acidosis. The label directs a temporary hold at the time of or before the procedure in at-risk patients, with kidney function re-checked 48 hours later before restarting - it is a precaution, not a sign the drug itself reacts with the contrast agent. [1]

References

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