RonanRx
PERSONALIZED MEDICINE

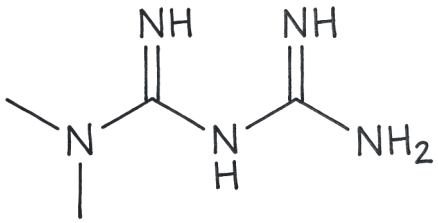
CLINICAL MONOGRAPH · METABOLIC & WEIGHT

Compounded Metformin

Metformin compounded for excipient sensitivity or alternative dosing

Metformin is the most widely prescribed oral medicine for type 2 diabetes. It lowers blood sugar mainly by reducing the amount of glucose the liver releases, with modest improvement in how the body's tissues respond to insulin. The FDA approved the brand-name tablet Glucophage in 1994. A liquid version, Riomet (100 mg/mL), is also FDA-approved for patients who cannot swallow tablets.

Because Glucophage, the extended-release versions, and Riomet liquid are already available, RonanRx does not compound metformin as a routine substitute for the manufactured products [fda_label_glucophage]. Compounded metformin is reserved for specific clinical situations: a documented allergy to a tablet excipient, a liquid formulation in a flavor or vehicle that commercial Riomet does not provide, or a custom low-strength capsule that the labeled tablet strengths cannot deliver [fda_label_riomet; fda_essentially_a_copy].



EVIDENCE POSTURE FDA APPROVED WELL STUDIED REVIEWED **2026-05-11**

State-licensed 503A | Pharmacist reviewed | Doctor led | Cold-chain ready | Patient choice preserved

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FOR CLINICIANS

Metformin is a biguanide oral antihyperglycemic agent that lowers fasting and post-prandial plasma glucose primarily through suppression of hepatic gluconeogenesis, with secondary improvement in peripheral insulin sensitivity. Mechanistic work has implicated AMP-activated protein kinase (AMPK) activation downstream of mild complex I inhibition and, more specifically, redox-mediated inhibition of mitochondrial glycerol-3-phosphate dehydrogenase as a unifying explanation for the suppression of glycerol-driven gluconeogenesis [madiraju2014, foretz2014]. Pharmacokinetically, metformin is not metabolized, is eliminated unchanged in the urine, and has an oral bioavailability of approximately 50, 60% with a plasma half-life of 4, 9 hours [graham2011] [fda_label_riomet].

Randomized evidence for the manufactured products is durable and clinically anchoring. UKPDS 34 [ukpds34_1998] demonstrated that intensive glycemic control with metformin in overweight adults with newly diagnosed type 2 diabetes reduced any diabetes-related endpoint and all-cause mortality compared with conventional dietary treatment, and the 10-year post-trial follow-up (UKPDS 80) [holman2008] showed persistence of macrovascular benefit (legacy effect). The Diabetes Prevention Program [knowler2002] randomized 3,234 adults with impaired glucose tolerance and demonstrated a 31% reduction in incident type 2 diabetes with metformin and a 58% reduction with intensive lifestyle vs placebo over a mean 2.8 years; the 10-year DPPOS follow-up [knowler2009] confirmed durable risk reduction, the long-term weight-loss analysis [aroda2019] documented sustained 2.0% mean weight reduction at 15 years among adherent metformin participants, and the 21-year long-term outcomes paper [dpp2025] reported continued separation in cumulative diabetes incidence. ADOPT [kahn2006] established glycemic durability of metformin monotherapy over sulfonylurea (and intermediate between metformin and thiazolidinedione) in newly diagnosed type 2 diabetes. Compounded metformin has no parallel efficacy program; its 503A role is narrow and patient-specific [fda_label_glucophage; fda_essentially_a_copy].

Why Personalized Compounded Metformin

Metformin's labeled tablet strengths (500 mg, 850 mg, 1000 mg immediate-release; 500 mg, 750 mg, 1000 mg extended-release) and Riomet's single 100 mg/mL solution were set to cover the average adult titrating toward 2,000 mg/day. Those strengths were not chosen for a 6-year-old with new-onset type 2 diabetes who cannot swallow tablets and reacts to Riomet's cherry flavoring, for an adult with an eGFR of 35 who needs to sit on 250 mg twice daily for weeks before any uptitration, or for a patient whose dye allergy rules out every commercial tablet on the shelf. The molecule does the same thing in all of them. The dosage form and the excipient profile do not.

That gap is the narrow, legitimate work a compounding pharmacy does for metformin. A prescriber who knows the chart can order a dye-free, lactose-free, gluten-free capsule for a patient with documented excipient sensitivity, a flavored aqueous suspension in a vehicle that commercial Riomet does not offer, or a 125 mg or 250 mg capsule that no labeled tablet provides for slow renal-impaired titration. The molecule is the same metformin hydrochloride the FDA reviewed for Glucophage in 1994. The strength, the vehicle, and the excipient list are built around the patient in front of the prescriber, not the average trial participant.

This is what pharmacy looked like before mass manufacturing arrived. A doctor wrote the prescription. A pharmacist prepared it for that named patient. Compounded metformin is that older arrangement, kept honest by modern oversight and reserved for the cases where the manufactured product genuinely cannot meet the clinical need.

Quick Facts About Compounded Metformin

Category: Biguanide oral antihyperglycemic

Active ingredient: Metformin hydrochloride, a small-molecule biguanide derived from the guanidine-rich plant Galega officinalis, with an oral bioavailability of approximately 50, 60% and renal excretion of unchanged drug as the dominant elimination pathway

FDA-approved branded forms: Glucophage (immediate-release tablet, 1994), Glucophage XR (extended-release tablet), Glumetza (extended-release tablet), Fortamet (extended-release tablet), and Riomet (oral solution, 100 mg/mL)

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

Evidence posture: Multi-decade randomized evidence supports the manufactured products for type 2 diabetes (UKPDS 34) and for delay of type 2 diabetes onset in adults at high risk (DPP/DPPOS); compounded preparations have no separate efficacy program

FDA-approval status: Manufactured Glucophage, Glumetza, Fortamet, and Riomet are FDA-approved. Compounded metformin is not FDA-approved.

Compounded under: 503A, patient-specific prescription only, where the manufactured FDA-approved product is not clinically appropriate

Honest framing: Metformin is widely available as immediate-release and extended-release tablets and as Riomet 100 mg/mL oral solution. The 503A role is therefore narrow: liquid suspensions for pediatric or dysphagia patients whose needs are not met by commercial Riomet, allergen-free formulations for documented excipient sensitivity, alternate vehicles, and custom-strength capsules for renal-impaired patients titrated below commercial tablet increments. Compounding is not appropriate for cost-driven substitution.

Drug shortage context: Metformin has appeared on FDA's drug shortage list intermittently, most recently for specific extended-release presentations linked to nitrosamine impurity recalls in 2020. During an active shortage of a specific presentation, 503A compounding of that presentation may be permitted under section 503A(b)(1)(D); outside shortage, the essentially-a-copy restriction applies.

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Compounded Metformin described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.

- **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
- **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
- **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
- **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
- **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Compounded Metformin?

Metformin (1,1-dimethylbiguanide) is a small-molecule biguanide oral antihyperglycemic [fda503a]. It is descended from guanidine, the active hypoglycemic principle of Galega officinalis (French lilac, goat's rue), a plant used in medieval European medicine for polyuria and characterized chemically in the early twentieth century. Metformin itself was first synthesized by Werner and Bell in 1922 and re-developed for diabetes by Jean Sterne in the 1950s under the trade name Glucophage in France [bailey2017].

Metformin is marketed in the United States as Glucophage (immediate-release tablet, FDA-approved 1994), Glucophage XR / Glumetza / Fortamet (extended-release tablet formulations), and Riomet (oral solution 100 mg/mL, FDA-approved for patients unable to swallow tablets) [fda_label_glucophage, fda_label_riomet] [fda503a]. Generic immediate-release and extended-release tablets are broadly available at all labeled strengths.

Compounded metformin is a pharmacy-prepared preparation dispensed under section 503A on a patient-specific prescription where the manufactured product cannot meet a documented clinical need [fda503a]. Compounded forms are typically a flavored oral suspension for pediatric or dysphagia patients whose needs commercial Riomet does not meet, an allergen-free or dye-free capsule for documented excipient sensitivity, or a custom low-strength capsule for renal-impaired patients titrated below the lowest commercial tablet.

How Compounded Metformin Works

Metformin lowers plasma glucose principally by suppressing hepatic gluconeogenesis. It is glucose-lowering without being insulin-secretagogue: it does not stimulate pancreatic insulin release and therefore does not produce hypoglycemia when used as monotherapy in non-fasted patients. Secondary mechanisms include modest improvement in peripheral (skeletal muscle and adipose) insulin sensitivity and a small decrease in intestinal glucose absorption.

At the molecular level, metformin produces mild inhibition of mitochondrial respiratory chain complex I, raising the cytosolic AMP:ATP ratio and activating AMP-activated protein kinase (AMPK). AMPK activation suppresses gluconeogenic gene expression and lipogenesis. More recently, Madiraju and colleagues [madiraju2014] identified mitochondrial glycerol-3-phosphate dehydrogenase (mGPDH) as a direct molecular target, and Foretz, Viollet and colleagues [foretz2014] integrated the redox and energy-charge models to explain how metformin suppresses gluconeogenesis from glycerol substrate independently of AMPK in some contexts. Rena, Hardie, and Pearson [rena2017] reviewed the parallel molecular and integrative mechanisms of metformin action in 2017.

Effects on the gut microbiome are increasingly recognized as a mechanistic contributor. Wu and colleagues [wu2017] demonstrated in treatment-naive adults with type 2 diabetes that metformin produces distinctive shifts in the gut microbiome and that microbiome-mediated changes in short-chain fatty acid production parallel its therapeutic glycemic effect.

Biological Role of Compounded Metformin

Hepatic glucose production is the dominant determinant of fasting hyperglycemia in type 2 diabetes and a major contributor to post-prandial hyperglycemia. Excess gluconeogenesis is driven by hepatic insulin resistance, elevated counter-regulatory hormones, and increased availability of gluconeogenic substrates (glycerol, lactate, alanine). Metformin acts on this pathway directly, distinct from agents that augment insulin secretion (sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists) or that act on renal glucose reabsorption (SGLT2 inhibitors).

The biguanide class also has effects outside the glucose axis. Long-term observational and randomized data have explored signals for body-weight neutrality or modest weight loss [aroda2019], reduced incidence of microvascular and macrovascular complications [ukpds34_1998, holman2008], reduced cancer incidence in observational cohorts [evans2005, currie2009] (with substantial methodologic caveats), and proposed effects on aging biology [justice2018, justice2022]. These extended biological roles motivate compound interest in metformin as a candidate geroscience agent and underlie the TAME (Targeting Aging with Metformin) trial program.

Detailed Mechanism of Compounded Metformin

Metformin is a small (165 Da) hydrophilic cationic molecule. It enters hepatocytes principally through organic cation transporter 1 (OCT1, SLC22A1) and accumulates in mitochondria along the electrochemical gradient. Within mitochondria it produces a mild, reversible inhibition of respiratory chain complex I, which lowers the ATP:ADP ratio, raises cytosolic AMP, and activates AMP-activated protein kinase (AMPK). AMPK activation suppresses transcription of gluconeogenic enzymes (PEPCK, G6Pase) and inhibits SREBP-1c-driven lipogenesis [foretz2014].

Madiraju and colleagues [madiraju2014] identified mitochondrial glycerol-3-phosphate dehydrogenase (mGPDH) as a non-AMPK-dependent molecular target of metformin. mGPDH inhibition raises cytosolic NADH and lowers the conversion of glycerol-3-phosphate to dihydroxyacetone phosphate, thereby suppressing glycerol-driven gluconeogenesis. This redox-based mechanism reconciles earlier observations that metformin can suppress gluconeogenesis at clinically relevant doses without sufficient AMPK activation in hepatocytes [foretz2014].

Microbiome-mediated mechanisms add a third layer. Wu and colleagues [wu2017] performed shotgun metagenomic and metabolomic analyses of treatment-naive adults with type 2 diabetes randomized to

metformin vs placebo and demonstrated reproducible shifts in microbial taxa (notably Escherichia and Akkermansia muciniphila) and short-chain fatty acid production that paralleled glycemic response. Metformin's high gut concentrations relative to plasma support direct microbiome activity as a clinically meaningful component of its effect.

In skeletal muscle and adipose tissue, metformin produces transcriptomic and proteomic changes consistent with improved fuel handling. Kulkarni and colleagues [kulkarni2018] characterized parallel metabolic and non-metabolic pathway regulation in older adults' skeletal muscle and subcutaneous adipose tissue, with effects on mitochondrial respiration and insulin signaling. Konopka and colleagues [konopka2019], however, demonstrated that metformin attenuates the mitochondrial adaptations to aerobic exercise training in older adults, a clinically relevant observation when metformin is used in combination with exercise-based interventions, including for prediabetes.

Compounded Metformin Research History

Galega officinalis (French lilac) was used in medieval European herbal medicine for polyuria. Its guanidine and galegine content was identified as the active hypoglycemic principle in the early twentieth century, and metformin (1,1-dimethylbiguanide) was first synthesized by Werner and Bell in 1922. Jean Sterne re-developed metformin clinically in the 1950s in Paris and introduced it under the trade name Glucophage in 1959 for type 2 diabetes; the historical arc is reviewed by Bailey (2017) [bailey2017] [konopka2019]. Metformin was approved by the FDA for type 2 diabetes in the United States in December 1994 (Glucophage).

The pivotal randomized evidence is UKPDS 34 [ukpds34_1998]: 1,704 overweight adults with newly diagnosed type 2 diabetes were randomized to intensive control with metformin, intensive control with sulfonylurea or insulin, or conventional dietary treatment [kulkarni2018]. Metformin reduced any diabetes-related endpoint by 32%, diabetes-related death by 42%, and all-cause mortality by 36% vs conventional treatment, with less weight gain and less hypoglycemia than sulfonylurea or insulin. The 10-year post-trial monitoring (UKPDS 80) [holman2008] demonstrated persistence of macrovascular benefit despite convergence of glycemic control after the trial, the so-called legacy effect.

The Diabetes Prevention Program (DPP) [knowler2002] randomized 3,234 adults with impaired glucose tolerance to placebo, metformin 850 mg twice daily, or intensive lifestyle intervention. Over a mean of 2.8 years, lifestyle reduced incident type 2 diabetes by 58% and metformin by 31% relative to placebo. The Diabetes Prevention Program Outcomes Study (DPPOS) followed the cohort: at 10 years [knowler2009] the cumulative incidence of diabetes remained lower in the metformin and lifestyle arms; at 15 years the long-term weight-loss analysis [aroda2019] documented sustained mean 2.0% weight reduction among adherent metformin participants; and the 21-year long-term effects paper [dpp2025] reported continued separation in cumulative diabetes incidence with notable effect heterogeneity by baseline BMI and fasting glucose. Aroda and colleagues [aroda_b12_2016] additionally identified an increased prevalence of biochemical and

clinical vitamin B12 deficiency in long-term metformin-treated participants, the most clinically actionable long-term safety signal of the cohort.

ADOPT [kahn2006] randomized 4,360 adults with newly diagnosed type 2 diabetes to rosiglitazone, metformin, or glyburide monotherapy. Cumulative incidence of monotherapy failure was lower with rosiglitazone (15%) than with metformin (21%) and glyburide (34%); however, the safety profile of rosiglitazone subsequently shifted prescribing back toward metformin as the first-line agent, a position cemented by Kahn 2006, UKPDS, and DPP and reflected in successive ADA Standards of Care.

Beyond diabetes, metformin has been studied in polycystic ovary syndrome [moll2006, legro2007, tang2012], gestational diabetes [rowan2008], cancer-incidence epidemiology [evans2005, currie2009] (with confounding caveats), aging biology and geroscience, and altered gut microbiome composition [wu2017]. The TAME (Targeting Aging with Metformin) trial program [justice2018] proposes metformin as a candidate intervention for biological aging endpoints; results have not yet been reported [justice2022].

Compounded Metformin Timeline

- **1922** • Werner and Bell synthesize 1,1-dimethylbiguanide (metformin) [bailey2017]
- **1957** • Jean Sterne publishes the first clinical use of metformin for type 2 diabetes in Paris under the name Glucophage [bailey2017]
- **1994** • FDA approves Glucophage (metformin hydrochloride) immediate-release tablet for type 2 diabetes in the United States (December 30, 1994) [fda_label_glucophage]
- **1998** • UKPDS 34 (Lancet), metformin in overweight adults with newly diagnosed type 2 diabetes reduces any diabetes-related endpoint and all-cause mortality vs conventional dietary treatment [ukpds34_1998]
- **2002** • Diabetes Prevention Program (Knowler et al., NEJM), metformin reduces incident type 2 diabetes by 31% in adults with impaired glucose tolerance [knowler2002]
- **2005** • Evans et al [evans2005]. (BMJ), observational signal of reduced cancer incidence among adults with type 2 diabetes treated with metformin
- **2006** • Kahn et al [kahn2006]. (NEJM), ADOPT trial establishes glycemic durability of metformin monotherapy in newly diagnosed type 2 diabetes
- **2006** • Moll et al [moll2006]. (BMJ), clomifene plus metformin vs clomifene plus placebo for ovulation induction in newly diagnosed PCOS
- **2007** • Legro et al [legro2007]. (NEJM), clomiphene, metformin, or both for infertility in PCOS demonstrates clomiphene-superior live-birth rate

2008 • Holman et al [holman2008]. (NEJM), UKPDS 10-year post-trial monitoring (UKPDS 80) demonstrates persistent macrovascular benefit of metformin (legacy effect)

2008 • Rowan et al [rowan2008]. (NEJM), MIG trial: metformin vs insulin for gestational diabetes, non-inferior on perinatal composite

2009 • Knowler et al [knowler2009]. (Lancet), DPPOS 10-year follow-up confirms durable reduction in diabetes incidence with metformin and lifestyle

2009 • Currie et al [currie2009]. (Diabetologia), influence of glucose-lowering therapies on cancer risk in type 2 diabetes

2010 • Salpeter et al [salpeter2010]. (Cochrane), systematic review finds no excess fatal or nonfatal lactic acidosis with metformin use in type 2 diabetes

2011 • Graham et al [graham2011]. (Clin Pharmacokinet), comprehensive review of metformin clinical pharmacokinetics

2012 • Tang et al [tang2012]. (Cochrane), insulin-sensitising drugs (metformin and others) for PCOS-related oligo-amenorrhoea and subfertility

2014 • Bannister et al [bannister2014]. (Diabetes Obes Metab), observational cohort comparing mortality of adults with type 2 diabetes on metformin or sulfonylurea monotherapy with matched non-diabetic controls

2014 • Madiraju et al [madiraju2014]. (Nature), metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase

2014 • Foretz, Guigas, Bertrand, Pollak, Viollet (Cell Metab), review integrating redox- and energy-charge-based mechanisms of metformin's gluconeogenic suppression [foretz2014]

2014 • Inzucchi et al [inzucchi2014]. (JAMA), systematic review of metformin in patients with type 2 diabetes and kidney disease, supporting safer use at lower eGFR than the historical creatinine-based cut-off

2016 • FDA revises the metformin label to use eGFR instead of serum creatinine for renal contraindication thresholds (eGFR <30 mL/min/1.73 m² as the absolute contraindication; eGFR 30, 45 as caution) [fda_label_glucophage]

2016 • Aroda et al [aroda_b12_2016]. (J Clin Endocrinol Metab), long-term metformin use is associated with increased prevalence of biochemical and clinical vitamin B12 deficiency in DPPOS participants

2017 • Bailey (Diabetologia), historical overview of metformin from Galega officinalis to clinical use [bailey2017]

2017 • Wu et al [wu2017]. (Nature Medicine), metformin alters the gut microbiome of treatment-naive adults with type 2 diabetes in a manner that contributes to its glycemic effect

2018 • Kulkarni et al [kulkarni2018]. (Aging Cell), metformin regulates metabolic and non-metabolic pathways in skeletal muscle and adipose tissue of older adults

2018 • Justice et al [justice2018]. (Cardiovasc Endocrinol Metab), design and rationale for the TAME (Targeting Aging with Metformin) trial program

2019 • Aroda et al [aroda2019]. (Ann Intern Med), long-term weight loss with metformin in DPPOS participants; sustained ~2% mean weight reduction at 15 years among adherent participants

2019 • Konopka et al [konopka2019]. (Aging Cell), metformin inhibits mitochondrial adaptations to aerobic exercise training in older adults

2020 • FDA recalls multiple metformin extended-release products due to N-nitrosodimethylamine (NDMA) impurity exceeding the acceptable daily intake limit; specific presentations added to FDA drug shortage list [fda_shortage_list]

2022 • Justice et al [justice2022]. (Aging Cell), geroscience-guided repurposing of FDA-approved drugs to target aging, including the prioritization framework that places metformin among lead candidates

2025 • DPP/DPPOS long-term outcomes (Lancet Diabetes Endocrinol), 21-year cumulative diabetes incidence and effect heterogeneity of lifestyle and metformin interventions [dpp2025]

Clinical Contexts for Compounded Metformin

Type 2 diabetes mellitus in adults FDA APPROVED

FDA-approved indication for manufactured metformin (Glucophage, Glucophage XR, Glumetza, Fortamet, Riomet) and generics.

Metformin is FDA-approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, alone or in combination with other antihyperglycemic agents and insulin. UKPDS 34 [ukpds34_1998] demonstrated in overweight adults with newly diagnosed type 2 diabetes that intensive control with metformin reduced any diabetes-related endpoint, diabetes-related death, and all-cause mortality compared with conventional dietary treatment. The 10-year post-trial monitoring (UKPDS 80) [holman2008] showed persistent macrovascular benefit (legacy effect). ADOPT [kahn2006] established glycemic durability of metformin monotherapy in newly diagnosed type 2 diabetes [fda_label_glucophage; fda_label_riomet]. Bannister and colleagues [bannister2014] reported in a large observational cohort that adults with type 2 diabetes initiated on metformin had lower mortality than matched non-diabetic controls, a hypothesis-generating finding that has motivated the geroscience research program around metformin [justice2018, justice2022].

Branded product: Glucophage / Glucophage XR / Glumetza / Fortamet / Riomet (metformin hydrochloride)

Type 2 diabetes mellitus in pediatric patients ages 10 years and older FDA APPROVED

FDA-approved indication for manufactured metformin immediate-release and oral solution (Riomet).

Metformin immediate-release tablets and Riomet oral solution (100 mg/mL) are FDA-approved for type 2 diabetes in pediatric patients ages 10 years and older [fda_label_riomet; fda_label_glucophage]. The pediatric labeled indication is the primary clinical scenario where a liquid formulation is requested; commercial Riomet covers most needs. Compounded oral suspensions may be appropriate when commercial Riomet's flavor, excipient profile, or container closure cannot meet a documented patient-specific need.

Branded product: Riomet (metformin hydrochloride oral solution, 100 mg/mL)

Prevention or delay of type 2 diabetes in adults at high risk WELL STUDIED

Off-label use supported by strong randomized evidence (DPP/DPPOS); endorsed by ADA Standards of Care but not an FDA-labeled indication.

The Diabetes Prevention Program [knowler2002] randomized 3,234 adults with impaired glucose tolerance to placebo, metformin 850 mg twice daily, or intensive lifestyle intervention. Over a mean 2.8 years, metformin reduced incident type 2 diabetes by 31% and lifestyle by 58% vs placebo. The DPPOS 10-year follow-up [knowler2009] confirmed durable risk reduction. The DPPOS long-term weight analysis [aroda2019] documented sustained ~2% mean weight reduction among adherent metformin participants at 15 years, and the 21-year long-term effects paper [dpp2025] reported continued separation in cumulative diabetes incidence. The use of metformin for diabetes prevention in adults with prediabetes is recommended by ADA Standards of Care but is not an FDA-labeled indication; it is off-label in the United States.

Polycystic ovary syndrome (PCOS), ovulation induction and metabolic features WELL STUDIED

Off-label; supported by randomized evidence [moll2006] and Cochrane review [tang2012]. Not an FDA-labeled indication.

Moll et al. [moll2006] randomized 228 women with newly diagnosed PCOS to clomifene citrate plus metformin vs clomifene citrate plus placebo and found no significant difference in ovulation rate, with a non-significant trend toward more ovulation on the metformin arm. Legro et al. [legro2007] subsequently randomized 626 infertile women with PCOS to clomiphene, metformin, or both for up to six months: live-birth rate was 22.5% with clomiphene alone, 7.2% with metformin alone, and 26.8% with combination, clomiphene was superior to metformin and not significantly improved by adding metformin. The Cochrane review by Tang and colleagues [tang2012] integrated these and other trials. Metformin is appropriately positioned for PCOS as a metabolic adjunct rather than a first-line ovulation-induction agent.

Gestational diabetes mellitus WELL STUDIED

Off-label; supported by the MIG randomized trial [rowan2008]. Not an FDA-labeled indication; obstetric guideline positioning varies.

The Metformin in Gestational Diabetes (MIG) trial [rowan2008] randomized 751 women with gestational diabetes between 20 and 33 weeks of gestation to metformin (with supplemental insulin if required) or insulin alone. The primary composite perinatal outcome (neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar <7, or prematurity) occurred in 32.0% of the metformin group and 32.2% of the insulin group, non-inferiority. Maternal preference favored metformin. Long-term offspring follow-up of MIG and subsequent trials has been mixed; obstetric society positioning on metformin for GDM varies internationally and the indication is not FDA-labeled.

Aging biology and healthspan endpoints (TAME program) EMERGING

Investigational. The Targeting Aging with Metformin (TAME) trial program positions metformin as a candidate intervention for biological aging endpoints; results have not yet been reported. This is not an FDA-approved indication and remains an active research question.

Justice and colleagues [justice2018] described the design and rationale for the TAME (Targeting Aging with Metformin) trial program, which positions metformin as a candidate intervention for composite aging endpoints (incident cardiovascular events, cancer, dementia, mortality) in adults aged 65, 79 without diabetes. The geroscience repurposing framework [justice2022] places metformin among lead candidates on the basis of its safety profile, mechanism, and observational signals such as the Bannister cohort [bannister2014]. The Konopka observation [konopka2019] that metformin attenuates mitochondrial adaptations to aerobic exercise training is a relevant caveat for healthspan-oriented use in older adults engaged in exercise interventions, and the Kulkarni skeletal-muscle and adipose study [kulkarni2018] characterizes the broader pathway regulation. No phase III aging-endpoint trial of metformin has yet reported.

Cancer incidence and mortality in adults with type 2 diabetes EMERGING

Hypothesis-generating observational signal only; randomized evidence does not support a clinical claim. Not an FDA-labeled indication.

Evans and colleagues [evans2005] reported in a Tayside, Scotland record-linkage study a 23% reduction in incident cancer among adults with type 2 diabetes treated with metformin compared with non-metformin antihyperglycemic therapy. Currie and colleagues [currie2009] extended this analysis in a UK General Practice Research Database cohort and found differential cancer-incidence signals across glucose-lowering therapies, including a directionally favorable signal for metformin vs insulin. Both studies are subject to immortal-time bias, time-related confounding, and indication-related confounding, and subsequent randomized analyses have not confirmed a cancer-prevention effect. The cancer-incidence literature is therefore positioned as hypothesis-generating, not actionable.

Off-Label Uses of Compounded Metformin

Prevention or delay of type 2 diabetes in adults at high risk WELL STUDIED

Off-label in the U.S.; recommended by ADA Standards of Care on the basis of DPP/DPPOS.

Metformin 850 mg twice daily reduced incident type 2 diabetes by 31% over a mean 2.8 years in DPP [knowler2002]; benefit persisted at 10 [knowler2009], 15 [aroda2019], and 21 [dpp2025] years. ADA Standards of Care recommend metformin for diabetes prevention in selected adults with prediabetes; FDA labeling does not include this indication.

Polycystic ovary syndrome (PCOS) WELL STUDIED

Off-label.

Off-label use is well documented in PCOS for ovulation adjunct, menstrual regularity, and metabolic features [moll2006, legro2007, tang2012]; metformin is not a first-line ovulation-induction agent (clomiphene and letrozole are superior on live-birth endpoints).

Gestational diabetes mellitus WELL STUDIED

Off-label.

MIG [rowan2008] randomized 751 women with GDM and reported non-inferiority of metformin vs insulin on a composite perinatal outcome; obstetric positioning varies internationally.

Aging biology and healthspan (TAME program) EMERGING

Investigational off-label.

Hypothesis-generating; TAME trial design [justice2018] and geroscience prioritization [justice2022] frame metformin as a candidate aging-intervention agent. No phase III aging-endpoint trial has yet reported.

FDA-Approved Uses of Compounded Metformin

Brand	Indication	Year	Route
Glucophage / Glucophage XR	Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ages 10 years and older with type 2 diabetes mellitus	1994	Oral (immediate-release and extended-release tablet)
Glumetza	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	2005	Oral (extended-release tablet)
Fortamet	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	2004	Oral (extended-release tablet)
Riomet	Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ages 10 years and older with type 2 diabetes mellitus	2003	Oral solution, 100 mg/mL

Metformin hydrochloride is FDA-approved in the United States as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ages 10 years and older with type 2 diabetes mellitus. Manufactured products include Glucophage (immediate-release tablet, December 1994), Glucophage XR / Glumetza / Fortamet (extended-release tablet formulations), and Riomet (oral solution, 100 mg/mL) [fda_label_riomet]. Multiple generic immediate-release and extended-release tablet products are available at standard strengths.

Metformin labeling carries a Boxed Warning regarding lactic acidosis, a rare but serious metabolic complication [fda_label_riomet]. The 2016 label revision changed the renal contraindication from serum-creatinine-based thresholds to estimated glomerular filtration rate (eGFR), with eGFR <30 mL/min/1.73 m² as the absolute contraindication and eGFR 30, 45 mL/min/1.73 m² as the caution zone where initiation is not recommended and continuation is at lower dose with closer monitoring [fda_label_glucophage, inzucchi2014].

Compounded Compounded Metformin (503A)

Compounded metformin under 503A occupies a narrow and honest role. Metformin is widely available as immediate-release tablets (500, 850, 1000 mg), extended-release tablets (Glucophage XR, Glumetza, Fortamet, and generics), and as Riomet 100 mg/mL oral solution [fda_label_glucophage, fda_label_riomet]. The commercial Riomet liquid covers most non-tablet clinical needs, including pediatric patients ages 10 and older [dpp2025]. Compounding under section 503A is therefore appropriate only when a documented patient-specific clinical need cannot be met by the manufactured products, and routine compounding of essentially-a-copy preparations is not permitted [fda_essentially_a_copy] [fda503a] [holman2008].

RonanRx limits 503A compounded metformin to four documented patient-specific scenarios: (1) liquid oral suspensions in flavor, vehicle, or excipient profiles that commercial Riomet cannot provide, typically for pediatric patients or adults with dysphagia or enteral-feeding access; (2) allergen-free or dye-free capsules for patients with documented sensitivity to a Glucophage / Glucophage XR / generic tablet excipient (e.g., povidone, polyethylene glycol, hypromellose, a colorant, or a lactose-containing filler); (3) alternate vehicle preparations for documented sensitivity to a commercial liquid excipient; and (4) custom low-strength capsules (e.g., 100 mg or 250 mg) for renal-impaired patients (eGFR 30, 45 mL/min/1.73 m²) titrated below the lowest commercial tablet strength on a prescriber-documented basis [fda_label_glucophage, inzucchi2014] [fda503a].

The regulatory context for metformin compounding differs from the recent GLP-1 receptor agonist shortage situation. Metformin has appeared on FDA's drug shortage list only intermittently, most recently for specific extended-release presentations associated with NDMA nitrosamine impurity recalls in 2020 [fda_shortage_list] [aroda2019]. Outside an active shortage of a specific presentation, the essentially-a-copy restriction applies in full and compounding cannot be used as a price-driven substitute for the manufactured products [fda_essentially_a_copy] [fda503a].

Compounded metformin preparations are not bioequivalent to the manufactured products [fda503a]. Clinicians and patients should understand that absorption, glycemic response, and tolerability of a compounded oral suspension or capsule may differ from published Glucophage, Glucophage XR, or Riomet data, particularly when excipients, concentration, vehicle, or container closure differ from the reference product [kahn2006]. The published efficacy and safety evidence base for metformin is generated with

manufactured product and does not transfer to compounded preparations without separate stability and patient-specific tolerability evaluation [ukpds34_1998; knowler2002; knowler2009].

Compounded Metformin Formulations and Routes

Form	Concentration	Description
Compounded oral suspension	Custom, commonly 100 mg/mL matched to commercial Riomet, or alternate strength on prescriber order	Nonsterile oral liquid prepared under USP <795> standards in a flavored, dye-free, or excipient-free vehicle as documented by the prescriber's patient-specific clinical need. Beyond-use dating is assigned per pharmacy stability data.
Compounded capsule (allergen-free / dye-free / custom-strength)	Custom, commonly 100, 250, 500, 750, or 1000 mg per capsule	Nonsterile capsule preparation under USP <795> for documented excipient sensitivity to a commercial tablet, or for custom low-strength titration below the lowest commercial tablet (500 mg IR; 500 mg or 750 mg XR).
Manufactured immediate-release tablet (reference product)	500, 850, or 1000 mg	Glucophage and generic metformin hydrochloride immediate-release tablets, FDA-approved 1994. Multiple manufacturers.
Manufactured extended-release tablet (reference product)	500, 750, or 1000 mg	Glucophage XR, Glumetza, Fortamet, and generic metformin hydrochloride extended-release tablets. Once-daily dosing typical.
Manufactured oral solution (reference product)	100 mg/mL	Riomet oral solution, FDA-approved 2003 for adults and pediatric patients ages 10 and older. Cherry-flavored, sugar-free.

Routes used in published literature: oral.

Compounded Metformin Dosing

Route	Population	Range	Duration	Study type
Oral	Adults with type 2 diabetes (immediate-release labeled regimen)	Start 500 mg twice daily with meals, or 850 mg once daily, and titrate in 500 mg weekly increments (or 850 mg every two weeks) to a maintenance dose of 2,000 mg/day.	Indefinite while clinically beneficial and renal function is preserved	FDA-approved labeled regimen

Route	Population	Range	Duration	Study type
		Maximum 2,550 mg/day in divided doses.		
Oral	Adults with type 2 diabetes (extended-release labeled regimen)	Start 500 mg once daily with the evening meal; titrate in 500 mg weekly increments to a maintenance dose of 1,500, 2,000 mg/day. Maximum 2,000 mg/day (Glucophage XR) or 2,500 mg/day (Fortamet).	Indefinite while clinically beneficial and renal function is preserved	FDA-approved labeled regimen
Oral	Pediatric patients ages 10, 16 years with type 2 diabetes	Start 500 mg twice daily with meals; titrate in 500 mg weekly increments to a maximum of 2,000 mg/day in divided doses. Extended-release formulations are not approved for pediatric use.	Indefinite while clinically beneficial and renal function is preserved	FDA-approved labeled regimen
Oral	Adults with prediabetes (DPP regimen, off-label)	850 mg twice daily as studied in DPP	Long-term; sustained risk reduction at 10, 21 years among adherent participants	Randomized controlled trial regimen (DPP/DPPOS), off-label
Oral	Adults with renal impairment (eGFR 30, 45 mL/min/1.73 m²)	Initiation not recommended; in patients already on metformin, reduce dose to ~half-maximum (typically 1,000 mg/day in divided doses) and monitor renal function more frequently. Contraindicated at eGFR <30.	Until eGFR falls below 30 mL/min/1.73 m² or until clinical contraindication develops	FDA labeling (post-2016 revision)

Doctor-prescribed and titrated. Metformin titration is paced to gastrointestinal tolerability, diarrhea, nausea, and abdominal discomfort are dose- and rate-dependent and are concentrated in the first weeks of therapy. Slow titration (500 mg per week) and administration with the largest meal are the primary tolerability levers; switching to extended-release reduces GI events in many patients.

Compounded metformin preparations should mirror the manufactured-product dosing intent unless the prescriber documents a patient-specific reason for variance [inzucchi2014]. A custom low-strength capsule for an eGFR 30, 45 patient, for example, is appropriate when the patient cannot reliably split a 500 mg tablet and a commercial 250 mg presentation is unavailable; the prescribing intent should be documented in the chart and the pharmacy record [fda_label_glucophage].

Compounded Metformin Safety

Metformin's safety profile is favorable relative to most antihyperglycemic agents. The dominant adverse events are gastrointestinal: diarrhea, nausea, abdominal discomfort, and metallic taste, concentrated in the first weeks of therapy and dose-dependent. Across UKPDS 34 [1], DPP [3], ADOPT [7], and clinical practice, metformin does not cause hypoglycemia as monotherapy and is associated with weight neutrality or modest weight loss [5]. Hypoglycemia risk emerges when metformin is combined with insulin or insulin secretagogues [27].

Lactic acidosis carries a Boxed Warning in U.S. labeling on the basis of historical phenformin-era data and isolated case reports. The Cochrane systematic review by Salpeter and colleagues [12] pooled 347 prospective comparative trials and cohort studies (70,490 patient-years on metformin) and found no cases of fatal or nonfatal lactic acidosis attributable to metformin; the pooled upper confidence limit was 4.3 cases per 100,000 patient-years, indistinguishable from non-metformin therapy [27]. Risk is concentrated in patients with acute or chronic renal impairment, decompensated heart failure, hepatic impairment, acute illness with reduced perfusion, or recent iodinated contrast exposure. The 2016 FDA label revision moved the renal threshold from creatinine to eGFR (absolute contraindication at eGFR <30, caution at 30, 45), informed by the Inzucchi systematic review [22].

Vitamin B12 deficiency is the most clinically actionable long-term safety signal. Aroda and colleagues [13] analyzed DPPOS participants on long-term metformin and reported increased prevalence of biochemical (serum B12 <298 pg/mL) and clinical B12 deficiency vs placebo, with the risk increasing with cumulative metformin exposure. Annual or biennial B12 monitoring is appropriate for patients on multi-year metformin therapy, particularly older adults and those with neuropathy [27].

Cardiovascular safety is supported by UKPDS 34 [1] and the 10-year post-trial monitoring [2], and is reinforced by the REACH registry analysis by Roussel and colleagues [34], which reported lower 2-year all-cause mortality among adults with diabetes and established atherothrombosis treated with metformin. Pancreatitis, hepatotoxicity, and hypersensitivity are not characteristic of metformin. The Bannister observational cohort [14] reported that adults with type 2 diabetes initiated on metformin had lower all-cause mortality than matched non-diabetic controls, a hypothesis-generating signal that has driven the geroscience research program [25][26] but does not on its own justify a healthspan claim [27]. Compounded preparations may differ from manufactured products in absorption, tolerability, and excipient profile; safety data summarized here from manufactured products cannot be assumed to translate without modification to compounded preparations.

Contraindications

Metformin is contraindicated in: severe renal impairment (eGFR <30 mL/min/1.73 m²); acute or chronic metabolic acidosis, including diabetic ketoacidosis; and known hypersensitivity to metformin hydrochloride

[27]. Per the 2016 label revision, initiation of metformin is not recommended at eGFR 30, 45 mL/min/1.73 m²; patients already on metformin in this range may continue at a reduced dose with closer renal monitoring [2722].

Temporary discontinuation is recommended before iodinated contrast procedures in patients with eGFR 30, 60, in patients with a history of liver disease, alcoholism, or heart failure, or in any patient who will receive intra-arterial iodinated contrast; metformin should be withheld at the time of, or before, the procedure and restarted only after renal function has been re-evaluated and found stable. Metformin should be withheld during acute illness that may impair renal function (sepsis, dehydration, severe gastrointestinal illness).

Drug interactions

Metformin is not metabolized by cytochrome P450 enzymes and does not participate in CYP-mediated drug-drug interactions. The dominant pharmacokinetic interactions involve renal cation-transporter substrates: cimetidine, dolutegravir, ranolazine, vandetanib, trimethoprim, and isavuconazole can increase metformin plasma exposure by inhibiting renal tubular secretion through OCT2 / MATE1. Carbonic anhydrase inhibitors (topiramate, acetazolabide) increase the risk of metabolic acidosis when combined with metformin [2720].

Pharmacodynamic interactions include: increased risk of hypoglycemia when metformin is combined with insulin, sulfonylureas, or meglitinides (consider down-titration of the insulin-secretagogue or insulin dose); attenuation of glycemic effect with chronic corticosteroids, thiazide and loop diuretics, or sympathomimetics; and risk of lactic acidosis with concurrent ethanol misuse. Iodinated contrast: see contraindications section.

Adverse events

The most common adverse events are gastrointestinal: diarrhea, nausea, abdominal pain, flatulence, and metallic taste, concentrated in the first 2, 4 weeks of therapy and during dose escalation. In UKPDS 34, DPP, and ADOPT, GI adverse-event-driven discontinuation occurred in approximately 5, 10% of metformin-initiating participants [137]. Hypoglycemia does not occur with metformin monotherapy [27]. Weight is neutral to slightly favorable [5]. Asthenia, headache, and rhinitis are reported at low incidence.

Serious adverse events are uncommon. Lactic acidosis is the most consequential reported event; the Cochrane review [12] found no cases attributable to metformin across 347 trials and 70,490 patient-years. Risk concentrates in patients with renal, hepatic, or cardiac failure or with acute illness. Vitamin B12 deficiency emerges with long-term exposure [13]; clinical sequelae include macrocytic anemia and peripheral neuropathy that may be confounded with diabetic neuropathy. Hepatotoxicity, hematologic toxicity, and hypersensitivity are not characteristic of metformin [27]. Pharmacovigilance signals from compounded preparations are formulation-specific and cannot be inferred from the manufactured-product evidence base.

Monitoring Compounded Metformin Therapy

Baseline assessment should include weight, blood pressure, HbA1c, fasting plasma glucose, hepatic transaminases, complete blood count, serum vitamin B12, and a comprehensive metabolic panel with calculated eGFR [inzucchi2014]. Renal function should be reassessed at least annually, more frequently in older adults, in patients with eGFR <60, or in patients on concurrent renally cleared drugs.

On therapy: HbA1c every 3 months until at glycemic target and at least every 6 months thereafter; eGFR at least annually (more frequently as above); serum vitamin B12 every 1, 2 years for patients on multi-year metformin therapy, with measurement of methylmalonic acid or homocysteine in patients with low-normal B12 and neurologic symptoms [aroda_b12_2016]. Hold metformin during acute illness that risks dehydration or hypotension and before iodinated contrast procedures per labeling [fda_label_glucophage] [inzucchi2014].

Compounded Metformin in Special Populations

Compounded Metformin Evidence Quality

Evidence supporting the manufactured metformin products is among the strongest in endocrinology [fda_essentially_a_copy] [roussel2010; madiraju2014]. UKPDS 34 [ukpds34_1998] and the 10-year post-trial monitoring [holman2008] anchor the type-2-diabetes indication with reductions in any diabetes-related endpoint and all-cause mortality and a persistent macrovascular legacy effect. The Diabetes Prevention Program [knowler2002] and its long-term follow-up [knowler2009, aroda2019, dpp2025] support the diabetes-prevention rationale across 21 years. ADOPT [kahn2006] established glycemic durability of metformin monotherapy, and the Maruthur AHRQ comparative-effectiveness systematic review [maruthur2016] integrated metformin into the broader oral and injectable antihyperglycemic landscape and supported its first-line position [salpeter2010]. The pharmacokinetic, mechanistic, and microbiome evidence base provides a coherent molecular explanation for the clinical effect [graham2011; wu2017; justice2018]. The safety evidence frames the lactic-acidosis, B12, and cardiovascular risks at clinically actionable resolution [foretz2014; rena2017; konopka2019].

Off-label evidence is heterogeneous [fda_essentially_a_copy]. For PCOS [moll2006, legro2007, tang2012] and gestational diabetes [rowan2008], randomized evidence is strong enough to support clinical use but does not extend to FDA labeling in the U.S. For cancer-incidence reduction [evans2005, currie2009], evidence is observational, subject to immortal-time and indication bias, and not actionable. For aging biology and healthspan endpoints, evidence is hypothesis-generating; the TAME trial program is the appropriate test bed, and no phase III aging-endpoint trial has yet reported [justice2022].

Evidence specifically supporting compounded preparations is absent, there is no parallel efficacy program for compounded metformin oral suspensions or capsules [salpeter2006_lacticacidosis; inzucchi2014; aroda_b12_2016]. Compounded use is an extrapolation from the manufactured-product evidence base, justified case by case by documented patient-specific factors that the manufactured product cannot accommodate. Compounded preparations may differ from manufactured products in excipient profile, vehicle, concentration, and container closure; absorption and tolerability cannot be assumed equivalent without local data [fda_essentially_a_copy] [bannister2014; kulkarni2018].

Major Compounded Metformin Clinical Studies

Study	Design	Participants	Duration	Finding
UKPDS 34 (UK Prospective Diabetes Study Group 1998, Lancet)	Randomized controlled trial of intensive blood-glucose control with metformin vs sulfonylurea/insulin vs conventional dietary treatment in overweight adults with newly diagnosed type 2 diabetes	1704	Median 10.7 years	Metformin reduced any diabetes-related endpoint by 32%, diabetes-related death by 42%, and all-cause mortality by 36% vs conventional treatment; less weight gain and less hypoglycemia than sulfonylurea or insulin [ukpds34_1998]
UKPDS 80 (Holman 2008, NEJM)	Ten-year post-trial monitoring of the original UKPDS cohort	3277	10 years post-trial	Persistence of metformin's macrovascular benefit despite convergence of glycemic control after the trial, the legacy effect [holman2008]
Diabetes Prevention Program (Knowler 2002, NEJM)	Phase III, randomized, placebo-controlled trial of metformin 850 mg twice daily vs intensive lifestyle vs placebo in adults with impaired glucose tolerance	3234	Mean 2.8 years	Metformin reduced incident type 2 diabetes by 31% and lifestyle by 58% vs placebo [knowler2002]
DPPOS 10-year follow-up (Knowler 2009, Lancet)	Long-term observational follow-up of the DPP cohort	2766	10 years	Cumulative incidence of diabetes remained lower in the metformin and lifestyle arms; risk reduction relative to placebo was 18%

Study	Design	Participants	Duration	Finding
				(metformin) and 34% (lifestyle) at 10 years [knowler2009]
Aroda DPPOS long-term weight loss (2019, Ann Intern Med)	Pre-specified long-term weight-loss analysis of DPPOS participants	2776	15 years	Adherent metformin participants sustained mean ~2.0% weight reduction at 15 years; weight loss was greater with higher baseline fasting glucose and BMI [aroda2019]
DPP 21-year long-term effects (Lancet Diabetes Endocrinol 2025)	Twenty-one-year long-term effects and effect-heterogeneity analysis of the DPP/DPPOS cohort	—	21 years	Continued separation in cumulative diabetes incidence with effect heterogeneity by baseline BMI and fasting glucose; durable benefit for both metformin and lifestyle vs placebo [dpp2025]
ADOPT (Kahn 2006, NEJM)	Randomized double-blind active-comparator trial of rosiglitazone, metformin, or glyburide monotherapy in newly diagnosed type 2 diabetes	4360	Median 4.0 years	Cumulative incidence of monotherapy failure was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide; metformin durable and superior to glyburide [kahn2006]
Moll PCOS trial (2006, BMJ)	Randomized double-blind trial of clomifene citrate plus metformin vs clomifene citrate plus placebo in newly diagnosed PCOS	228	Up to 6 ovulation cycles	No significant difference in ovulation rate; non-significant trend favoring metformin co-administration [moll2006]
Legro PCOS (2007, NEJM)	Randomized double-blind multi-arm trial of clomiphene, metformin, or both for infertility in PCOS	626	Up to 6 months	Live-birth rates: 22.5% clomiphene, 7.2% metformin, 26.8% combination; clomiphene superior to metformin and not significantly improved by metformin addition [legro2007]

Study	Design	Participants	Duration	Finding
Tang PCOS Cochrane review (2012)	Systematic review and meta-analysis of insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for PCOS-related oligo-amenorrhoea and subfertility	—	—	Metformin improves ovulation and pregnancy rates vs placebo but is inferior to clomiphene for live-birth endpoints [tang2012]
MIG (Rowan 2008, NEJM)	Open-label randomized trial of metformin (with supplemental insulin if needed) vs insulin alone for gestational diabetes	751	From 20, 33 weeks gestation through delivery	Composite perinatal outcome 32.0% metformin vs 32.2% insulin, non-inferiority; maternal preference favored metformin [rowan2008]
Salpeter Cochrane lactic acidosis review (2010)	Systematic review of 347 comparative trials and cohort studies for fatal and nonfatal lactic acidosis with metformin in type 2 diabetes	70,490 patient-years on metformin	—	No cases of fatal or nonfatal lactic acidosis attributable to metformin; pooled upper confidence limit 4.3 cases per 100,000 patient-years, indistinguishable from non-metformin therapy [salpeter2010]
Aroda DPPOS B12 (2016, J Clin Endocrinol Metab)	Long-term analysis of DPPOS participants for biochemical and clinical vitamin B12 deficiency	—	Up to ~13 years on metformin	Increased prevalence of biochemical (B12 <298 pg/mL) and clinical B12 deficiency with long-term metformin use vs placebo, with risk increasing as cumulative metformin exposure rises [aroda_b12_2016]
Bannister observational cohort (2014, Diabetes Obes Metab)	Observational cohort comparing all-cause mortality of adults with type 2 diabetes initiated on metformin or sulfonylurea	Approximately 78,000 metformin initiators, 12,000 sulfonylurea initiators, and	—	Adults with type 2 diabetes initiated on metformin had lower all-cause mortality than matched non-diabetic controls; sulfonylurea initiators had higher

Study	Design	Participants	Duration	Finding
	monotherapy with matched non-diabetic controls	matched non-diabetic controls		mortality, hypothesis-generating signal motivating geroscience research [bannister2014]
Inzucchi metformin / kidney disease (2014, JAMA)	Systematic review of metformin use in patients with type 2 diabetes and chronic kidney disease	—	—	Available evidence supported safer metformin use at lower eGFR than the historical serum-creatinine-based cut-off; informed the 2016 FDA label revision to eGFR-based thresholds [inzucchi2014]
Madiraju mGPDH mechanism (2014, Nature)	Preclinical mechanistic study using rodent hepatocytes and in vivo models	—	—	Metformin suppresses gluconeogenesis through redox-mediated inhibition of mitochondrial glycerol-3-phosphate dehydrogenase (mGPDH), independent of AMPK in this pathway [madiraju2014]
Graham metformin PK review (2011, Clin Pharmacokinet)	Comprehensive review of metformin clinical pharmacokinetics	—	—	Bioavailability ~50, 60%, renal excretion of unchanged drug as the dominant elimination pathway, plasma half-life 4, 9 hours, OCT1/OCT2/ MATE-mediated transport [graham2011]
Wu microbiome (2017, Nature Medicine)	Randomized placebo-controlled trial with shotgun metagenomic and metabolomic analysis in treatment-naive adults with type 2 diabetes	—	—	Metformin produces reproducible shifts in microbial taxa (Escherichia, Akkermansia muciniphila) and short-chain fatty acid production that parallel glycemic response and contribute to therapeutic effect [wu2017]
Kulkarni metformin in	Randomized controlled trial of metformin vs	—	—	Metformin regulates parallel metabolic and non-

Study	Design	Participants	Duration	Finding
older adults (2018, Aging Cell)	placebo with skeletal muscle and subcutaneous adipose biopsies in older adults			metabolic pathways in skeletal muscle and adipose tissue, with effects on mitochondrial respiration and insulin signaling [kulkarni2018]
Konopka metformin and exercise (2019, Aging Cell)	Randomized controlled trial in older adults of aerobic exercise training with or without metformin	—	—	Metformin attenuates skeletal muscle mitochondrial adaptations and cardiorespiratory fitness gains from aerobic exercise training in older adults [konopka2019]
Justice TAME design (2018, Cardiovasc Endocrinol Metab)	Design and rationale paper for the TAME (Targeting Aging with Metformin) trial program	—	—	Frames metformin as a candidate intervention for composite biological-aging endpoints (CV events, cancer, dementia, mortality) in adults aged 65, 79 without diabetes; results not yet reported [justice2018]
Evans cancer epidemiology (2005, BMJ)	Record-linkage observational cohort in Tayside, Scotland	—	—	23% reduction in incident cancer among adults with type 2 diabetes on metformin vs non-metformin antihyperglycemic therapy; hypothesis-generating, subject to immortal-time and time-related confounding [evans2005]
Currie cancer therapies (2009, Diabetologia)	UK General Practice Research Database observational cohort	—	—	Differential cancer-incidence signals across glucose-lowering therapies; directionally favorable signal for metformin vs insulin [currie2009].

Study	Design	Participants	Duration	Finding
				Subject to confounding-by-indication.
Roussel REACH registry (2010, Arch Intern Med)	Observational analysis of the international Reduction of Atherothrombosis for Continued Health (REACH) registry	19691	2-year follow-up	Metformin use was associated with lower 2-year all-cause mortality in adults with diabetes and established atherothrombosis vs no metformin [roussel2010]
Maruthur AHRQ comparative-effectiveness review (2016, Ann Intern Med)	Systematic review and network meta-analysis of monotherapy and metformin-based combination therapy for type 2 diabetes	—	—	Integrated metformin into the broader oral and injectable antihyperglycemic landscape; supported metformin as first-line monotherapy on the basis of glycemic efficacy, weight, and safety profile [maruthur2016]

Compounded Metformin Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Metformin is a small hydrophilic cationic molecule (165 Da). Oral bioavailability of the immediate-release tablet is 50, 60% under fasting conditions and is reduced by ~25% with food in some studies; the extended-release formulation has comparable systemic exposure with a flatter Cmax profile. Plasma half-life is 4, 9 hours. Metformin is not metabolized; it is eliminated as unchanged drug in the urine, principally by tubular secretion via the renal organic cation transporters OCT2 and MATE1/MATE2-K, with glomerular filtration as a secondary route [graham2011] [fda_label_glucophage].

Hepatocellular uptake is mediated by OCT1 (SLC22A1); intracellular accumulation in mitochondria along the membrane potential drives the mechanistic effects on complex I and mGPDH [madiraju2014, foretz2014] [fda_label_glucophage]. Genetic variation in OCT1 influences hepatic exposure and glycemic response, though clinically actionable pharmacogenetic testing is not in routine use.

Compounded oral suspensions and capsules may differ from the manufactured products in absorption rate, peak concentration, and food effect, particularly when vehicle viscosity, particle size, or excipient composition differs from the reference [fda_label_riomet]. The PK data summarized above are generated

with manufactured Glucophage, Glucophage XR, and Riomet products and should not be assumed to translate to compounded preparations without local stability and absorption data.

Pharmacodynamics

Pharmacodynamic effects include reduction of fasting plasma glucose and post-prandial glucose, primarily through suppression of hepatic gluconeogenesis with secondary improvement in peripheral insulin sensitivity. HbA1c reduction is typically 1.0, 1.5% from baseline in adults with type 2 diabetes at therapeutic doses (1,500, 2,000 mg/day) [ukpds34_1998; knowler2002]. Weight is neutral to modestly favorable; sustained ~2% weight reduction is documented in long-term DPPOS analyses [aroda2019]. Effects on lipids are modest (small decreases in LDL-C and triglycerides). The Wu microbiome work [wu2017] documents reproducible gut-microbiome shifts and short-chain fatty acid changes that parallel glycemic response.

↓↑ Comparing Compounded Metformin Formulations

The manufactured U.S. products are Glucophage (immediate-release tablet, 500/850/1000 mg), Glucophage XR / Glumetza / Fortamet (extended-release tablets, 500/750/1000 mg with formulation-specific release profiles), and Riomet (oral solution 100 mg/mL) [fda_label_glucophage; fda_label_riomet]. Generic immediate-release and extended-release tablets are widely available. The drug substance is identical across products; differences are formulation-level (release rate, vehicle, container closure, excipient profile).

Compounded oral suspensions and capsules vary in vehicle, flavor, excipient profile, and concentration. They are not bioequivalent to the manufactured products; clinicians should anticipate that local absorption and tolerability may differ from manufactured-product published data, particularly when switching between commercial Riomet and a compounded suspension or between a commercial tablet and a custom-strength capsule.

🌡 Compounded Metformin Storage and Handling

Manufactured Glucophage, Glucophage XR, Glumetza, and Fortamet tablets are stored at controlled room temperature (20, 25°C, with excursions permitted to 15, 30°C) in a tightly closed container, protected from moisture [fda_label_glucophage]. Riomet oral solution is stored at controlled room temperature in the original container [fda_label_riomet].

Compounded oral suspensions and capsules are stored per the pharmacy's stability data and beyond-use-date assignment under USP <795>. Suspensions are typically refrigerated to preserve flavor and chemical stability; capsules at controlled room temperature [usp_795].

Compounded Metformin Compounding & Operations

503A compounding

Compounded metformin is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares nonsterile oral suspensions and capsules per USP General Chapter <795>, the official compendial standard for nonsterile pharmaceutical compounding, with documented active ingredient sourcing, gravimetric verification, content-uniformity assessment for capsule batches, and full lot traceability [fda503a; usp_795]. Suspension stability is assigned per pharmacy-validated stability data or referenced compendial data.

Beyond-use dating, ingredient identity verification, and stability assessment follow USP <795> requirements. Each compounded batch is documented per state board of pharmacy retention rules with full traceability from API lot through dispensing.

Pharmacist review

Each prescription for compounded metformin undergoes pharmacist review prior to dispensing [inzucchi2014]. The review confirms: a documented patient-specific clinical reason that the manufactured Glucophage, Glucophage XR, Glumetza, Fortamet, or Riomet product is not appropriate (documented excipient sensitivity, need for a vehicle or flavor that commercial Riomet does not provide, custom low-strength capsule for renal-impaired patients in the eGFR 30, 45 band, or an active shortage of a specific presentation); current eGFR and the absence of contraindications including eGFR <30 mL/min/1.73 m², decompensated heart failure, or hepatic impairment [fda_label_glucophage]; appropriate concomitant medication review including hypoglycemia risk if combined with insulin or sulfonylureas, and renal cation-transporter interactions; and a prescribed regimen consistent with FDA-label titration unless the prescriber documents a patient-specific reason.

RonanRx does not fill prescriptions that read as routine substitution of compounded for manufactured product without documented clinical rationale, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy]. Because Riomet oral solution and a wide range of tablet strengths are commercially available, the bar for a documented patient-specific need is meaningful and the routine cases at other compounds (e.g., adult preference for a sweetened liquid where Riomet is acceptable) do not qualify [fda_label_riomet].

Quality and traceability

Active pharmaceutical ingredients are sourced from FDA-registered facilities with documented certificates of analysis. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, content-uniformity result (for capsules), and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

Compounded metformin oral suspensions are typically refrigerated to preserve flavor and chemical stability; capsules are stored at controlled room temperature [fda_label_riomet]. Manufactured Glucophage, Glucophage XR, Glumetza, Fortamet, and Riomet are room-temperature products and do not require a cold chain in transit [fda_label_glucophage]. Patients receiving a refrigerated suspension are educated on refrigeration on arrival and inspection for temperature excursions.

Frequently Asked Questions About Compounded Metformin

Is compounded metformin the same as Glucophage or Riomet?

No. Glucophage, Glucophage XR, Glumetza, Fortamet, and Riomet are the FDA-approved manufactured metformin products [fda_label_glucophage; fda_label_riomet]. Compounded metformin is pharmacy-prepared on a patient-specific prescription and is not bioequivalent to the manufactured products. Compounded drugs are not FDA-approved [fda503a].

Why would anyone compound metformin when Glucophage and Riomet are widely available?

The 503A role is narrow and patient-specific. Reasons that qualify include: documented sensitivity to an excipient in the manufactured tablet or commercial Riomet; need for a flavor or vehicle that commercial Riomet does not provide for a pediatric or dysphagia patient; or a custom low-strength capsule for renal-impaired patients (eGFR 30, 45) titrated below the lowest commercial tablet [fda_label_riomet]. Cost or general preference does not qualify under FDA's essentially-a-copy guidance [fda_label_glucophage; fda_essentially_a_copy; inzucchi2014].

What does the diabetes-prevention evidence say?

The Diabetes Prevention Program randomized 3,234 adults with impaired glucose tolerance and reported a 31% reduction in incident type 2 diabetes with metformin and a 58% reduction with intensive lifestyle vs placebo over a mean 2.8 years [knowler2002; aroda2019; dpp2025]. Long-term follow-up at 10, 15, and 21 years continues to show separation in cumulative diabetes incidence with metformin [knowler2009]. ADA Standards of Care recommend metformin for diabetes prevention in selected adults with prediabetes, but this is off-label in the United States.

How serious is the lactic acidosis warning?

Metformin labeling carries a Boxed Warning for lactic acidosis, inherited from the phenformin era. The Cochrane systematic review by Salpeter and colleagues pooled 347 trials and 70,490 patient-years on metformin and found no cases of lactic acidosis attributable to metformin; the pooled upper confidence limit was 4.3 cases per 100,000 patient-years, indistinguishable from non-metformin therapy

[salpeter2010; inzucchi2014; fda_label_glucophage]. Risk is concentrated in patients with severe renal impairment, decompensated heart failure, or acute illness with reduced perfusion.

Does long-term metformin cause vitamin B12 deficiency?

Aroda and colleagues analyzed DPPOS participants on long-term metformin and reported increased prevalence of biochemical and clinical vitamin B12 deficiency vs placebo, with risk rising as cumulative metformin exposure increased [aroda_b12_2016]. Annual or biennial serum B12 monitoring is appropriate for patients on multi-year metformin therapy, especially older adults and those with neuropathy symptoms.

What is the role of metformin in PCOS and gestational diabetes?

For PCOS, randomized evidence positions metformin as a metabolic adjunct rather than a first-line ovulation-induction agent (clomiphene is superior on live-birth endpoints; letrozole is the current preferred first-line) [legro2007]. For gestational diabetes, the MIG trial demonstrated non-inferiority of metformin vs insulin on a composite perinatal outcome; obstetric society positioning varies internationally [moll2006; tang2012; rowan2008]. Both uses are off-label in the U.S.

Can metformin slow aging?

The TAME (Targeting Aging with Metformin) trial program positions metformin as a candidate intervention for composite biological-aging endpoints in adults aged 65, 79 without diabetes [justice2022]. Justification rests on the favorable safety profile, mechanistic plausibility, and observational signals such as the Bannister cohort (where adults with type 2 diabetes on metformin had lower all-cause mortality than matched non-diabetic controls) [bannister2014]. No phase III aging-endpoint trial of metformin has yet reported, so a clinical claim is not currently supported [justice2018].

Who should not take metformin?

Contraindicated at eGFR <30 mL/min/1.73 m², in acute or chronic metabolic acidosis (including diabetic ketoacidosis), and in known hypersensitivity. Initiation is not recommended at eGFR 30, 45. Hold metformin during acute illness that may impair renal function and before iodinated contrast procedures per labeling [fda_label_glucophage; inzucchi2014].

Does RonanRx sell compounded metformin directly to patients?

No. Compounded metformin requires a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that the manufactured Glucophage, Glucophage XR, Glumetza, Fortamet, or Riomet product is not appropriate, plus pharmacist review before dispensing [fda_essentially_a_copy]. RonanRx is not a direct-to-consumer storefront [fda503a].

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How to Access Compounded Metformin

Compounded Compounded Metformin is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Compounded Metformin, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)